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On the Origin of Dolabriferol: Total Synthesis via Its Putative Contiguous Precursor

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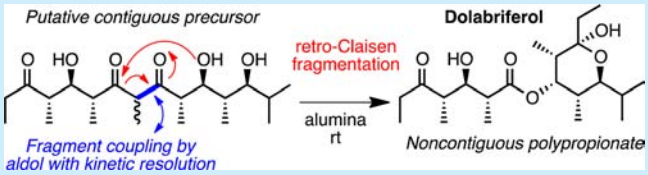
Supporting Information

ABSTRACT: The putative contiguous polypropionate precursor of dolabriferol was synthesized using as the key step a rationally designed enantiomer-selective aldol coupling (i.e., with kinetic resolution) of a racemic C1−C8 ketone fragment with an enantiopure C9−C15 aldehyde fragment. When exposed to alumina, the precursor was cleanly transformed into dolabriferol via a regioselective retro-Claisen fragmentation, providing the first experimental evidence for the proposed origin of dolabriferol and demonstrating that it is a plausible isolation artifact.



Dolabriferol (**1**), isolated from the anaspidean mollusk *Dolabrifera dolabrifera*,[1] belongs to a small family of marine natural products known as noncontiguous polypropionates. In contrast to most polypropionates found in nature, members of this group have structures composed of a polypropionate carboxylic acid fragment joined to a polypropionate alcohol fragment via an ester linkage and hence possess noncontiguous carbon skeletons.[2] These structures are generally believed to result from retro-Claisen fragmentations of hemiacetals formed by cyclization of 5-hydroxy-1,3-dione motifs embedded in biosynthetically derived polypropionate chains.[3] For example, Gavagnin et al. proposed a hypothetical biosynthesis of **1** involving retro-Claisen rearrangement of hemiacetal **3**, a ring−chain tautomer of the putative contiguous polypropionate precursor **2** (Scheme 1).[1] Although such processes might be enzyme-mediated, the natural product status of noncontiguous polypropionates is uncertain, and they are often viewed as plausible isolation artifacts.[3] Evidence for such hypotheses is largely circumstantial and includes the failure to detect the expected noncontiguous polypropionates after a careful extraction procedure[2d] and the observation[2a,d,4−8] of several related retro-Claisen transformations in vitro. Nonetheless, only two examples of conversion of a contiguous polypropionate "natural product" into an isomeric noncontiguous "natural product" are known. The hemiacetal **5** and isomeric ester **6** were isolated[2a] from *Siphonaria australis*, and transformation of the former into the latter by retro-Claisen rearrangement was accomplished under relatively mild conditions (DBU/benzene/rt[2a,5b] or chromatography over alumina[5a]). Similarly, treatment of siphonarin B (**7**)[4] with alumina in refluxing ethanol gave baconipyrone C (**8**),[2b] both previously isolated from *S. zelandica*.[8]

Using a reaction prediction program, Goodman et al. conducted a computational study of Gavagnin's proposed pathway from **2** to **1** via **3** and **4** assuming thermodynamic control.[9] The relevant structures of lowest relative energy (RHF/3-21G/water basis set) among the >200 found were 12-*epi*-**1** (−12.3 kJ/mol), the 13→9 (9*S*)-hemiacetal of (8*R*)-**2** (0.0 kJ/mol), and **1** (2.3 kJ/mol) from which it was concluded that the Gavagnin pathway was feasible. However, the question of whether **1** is a biosynthetic product or a plausible isolation artifact cannot be addressed by this approach. Moreover, if retro-Claisen fragmentations are irreversible, the pathway from **2** to **1** will be under kinetic control and therefore depend on the relative concentration and retro-Claisen reactivity of **3** (the 11→7 hemiacetal of **2**) compared to those of the regioisomeric 13→9 and 5→9 hemiacetals of **2** and other tautomers or intermediates capable of competing irreversible reactions (e.g., retro-aldol, elimination). If hemiacetal equilibration is much faster than retro-Claisen fragmentation, product distribution will be governed by reactivity (Curtin−Hammett principle); otherwise, the relative concentrations of the hemiacetals will increasingly dominate product formation. For example, in contrast to the alumina-mediated transformation of **7** into **8** noted above, analogous treatment of **9**, a complex mixture of ring−chain and keto−enol tautomers containing both 11→7 and 5→9 hemiacetals gave a 1:1.5 mixture of **8** and **10** suggesting that retro-Claisen fragmentation was faster than hemiacetal equilibration under these conditions.[8] In this context, an additional complication in the proposed transformation of **2** into **1** arises from Goodman's calculations[9] that suggest the formation of the 13→9 hemiacetal regioisomer is very strongly favored (>99.8% at rt) for both (8*R*)-**2** and (8*S*)-**2**.[10] In light of the above ambiguities, we set out to prepare the putative contiguous precursor **2** and to evaluate its propensity to undergo the proposed rearrangement to dolabriferol (**1**). In this paper, we report a concise total synthesis of **2** and its remarkably facile conversion into **1**.

Several groups have reported synthetic studies on dolabriferol (**1**), and all approaches envisaged an esterification or retro-

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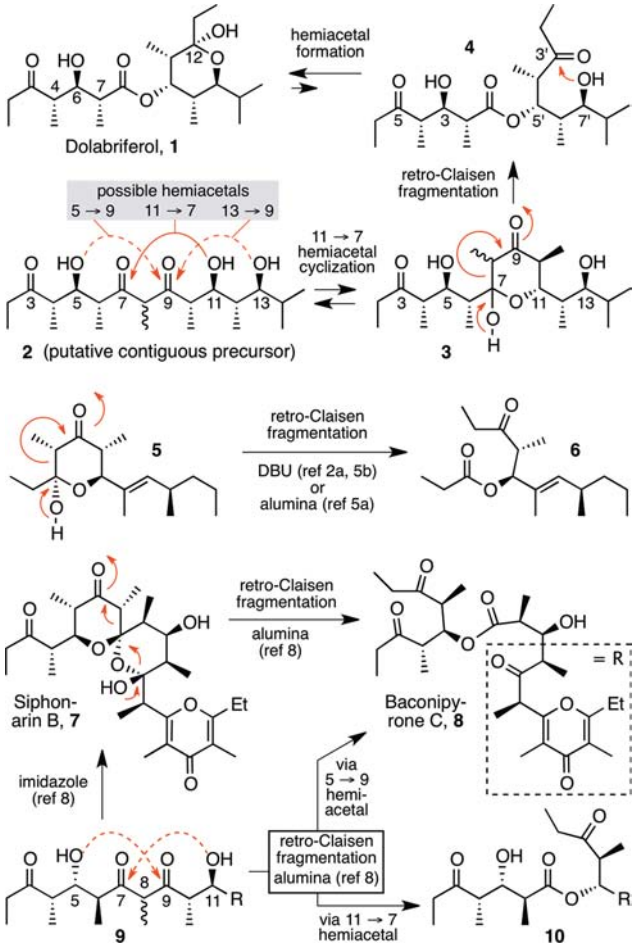
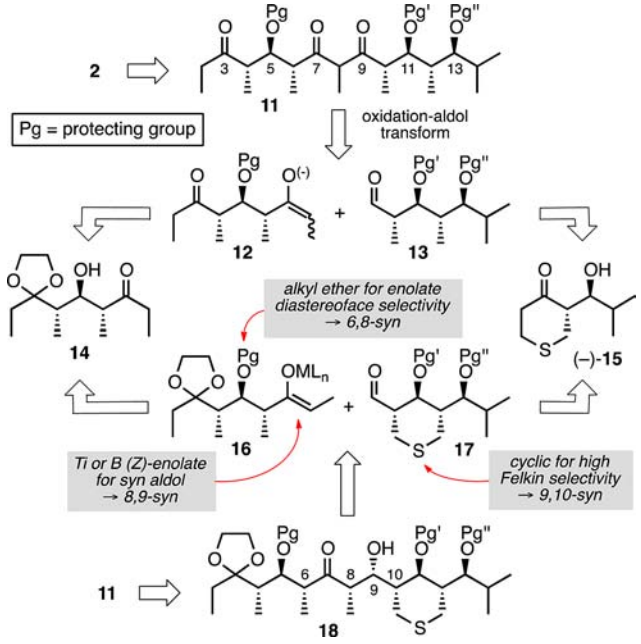
Scheme 1. Proposed Origin of Dolabriferol and Related in Vitro Retro-Claisen Fragmentations of Contiguous Polypropionates



Claisen fragmentation to construct the key ester linkage in a hydroxy-protected intermediate followed by deprotection.[6,7,11−14] Vogel et al.[13] used the esterification approach to complete the first total synthesis of **1** establishing its absolute configuration. The choice of an Alloc ($-C(=O)OCH_2CH=CH_2$) protecting group for the C-7′ OH group proved crucial for success and underscores the sensitivity of **1**. Toste et al.,[14] also using the esterification strategy, prepared several 7′-*O*-protected derivatives of **4** (SEM = $CH_2OC_2H_4SiMe_3$; TES = $SiEt_3$; TBS = $SiMe_2$-*t*-Bu; BOM = CH_2OCH_2Ph) via esterification but were unable to remove the protecting group without decomposition in the final step. Lister and Perkins,[6] the first to use the retro-Claisen approach, obtained the 7′-*O*-TBS derivative of *ent*-**4** by fragmentation of *ent*-13-*O*-TBS-**2** in the presence of DBU; however, advancing to *ent*-**1** was thwarted as the TBS protecting group could not be removed. Following a closely related route, Currie and Goodman[7] successfully obtained **1** by retro-Claisen fragmentation of a triply protected derivative of **2** (functionalities at C-3, C-5, and C-13 blocked) followed by removal of the protecting groups (from 7′-*O*-PMB-**4** in the final step). Although these synthetic studies clearly demonstrated the feasibility of obtaining the dolabriferol skeleton via a retro-Claisen fragmentation, the origin of **1** was not addressed because the presence of protecting groups on **2** serves to block various competing reactions along Gavagnin's proposed pathway (Scheme 1).

Our retrosynthesis of **2** is presented in Scheme 2. Previous synthetic studies[6,8,15] have amply demonstrated the sensitivity

Scheme 2. Retrosynthetic Analysis of Putative Precursor 2



of 5,11-dihydroxy 3,7,9-triones toward both acidic and basic reaction conditions and underscore the need to reveal the corresponding functionality in **2** under mild conditions. Accordingly, we selected **11** as the intermediate objective with protecting groups (Pg) carefully selected to permit its transformation into **2**. Disconnection of **11** at the C8−C9 bond via an oxidation/directed−aldol transform generates enolate **12** and aldehyde **13**, and suitably protected synthetic equivalents of each should be available by straightforward transformations of known compounds **14**[16] and (−)-**15**,[17] respectively. Although both new stereocenters generated in the anticipated aldol coupling are absent in **2**, a highly stereoselective reaction was desirable. Among the four possible diastereomers, 6,8-*syn*-8,9-*syn*-9,10-*syn*-**18** was particularly attractive as previous work has shown that aldol reactions of (*Z*)-enolates **16** [ML_n = B(*c*-Hex)$_2$ or Ti(O*i*Pr)$_3$; Pg = CH_2OMe but not $SiEt_3$] with *i*PrCHO give 6,8-*syn*-8,9-*syn* adducts with excellent diastereoselectivity[15] and aldol additions to tetrahydrothiopyran-3-carbaldehydes related to **17** are highly Felkin selective[18] even with (*Z*)-enolates.[19,20] Moreover, we have demonstrated synthetically useful levels of kinetic resolution (i.e., $s > 10$) in related aldol reactions rationally designed to have the three stereocontrol elements (i.e., enolate and aldehyde diastereoface selectivities and relative topicity) highly biased.[21] All previous examples have involved couplings of enantiopure (or achiral) ketones with racemic aldehydes; however, because (±)-**14** was in hand, aldol coupling of the derived (±)-**16** with enantiopure **17** provided an opportunity to test this design with the reactant roles reversed.

The synthesis commenced with the preparation of (−)-**15** (77%, 92% ee) on a decagram scale by L-proline catalyzed aldol reaction of **19** with *i*PrCHO using a modification of the published protocols[17] to achieve higher yield with respect to the more valuable **19** (Scheme 3).[22] The triethylsilyl ether derivative of (−)-**15** was prepared under standard conditions

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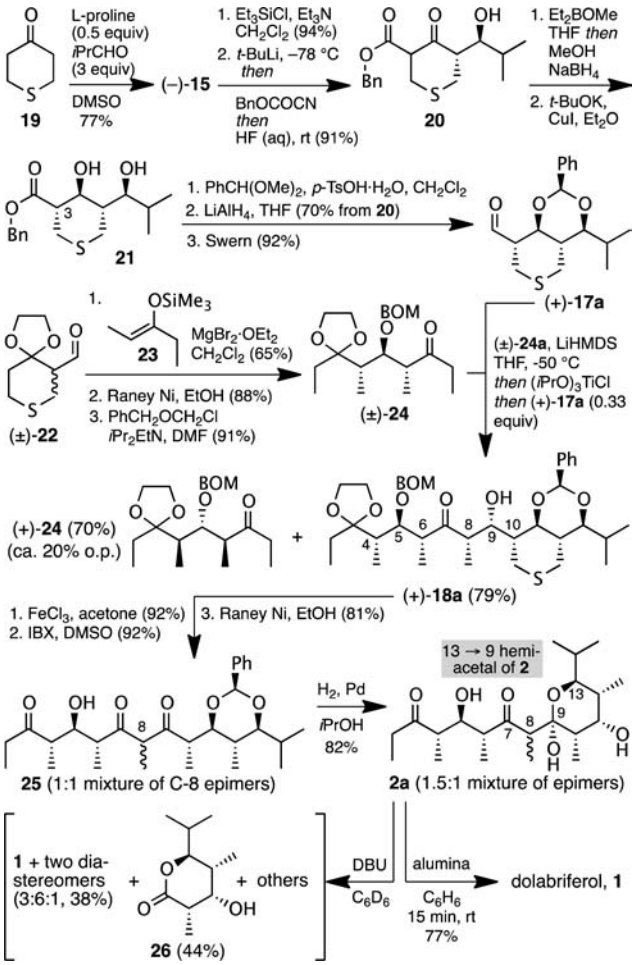
Scheme 3. Synthesis of Dolabriferol (1)



and treated with *t*-BuLi followed by BnO_2CCN to afford *β*-ketoester **20** in 82% yield over two steps. Hydroxy-directed reduction[23] of **20** gave a separable 1:1 mixture of 1,3-*syn* diols **21** and 3-*epi*-**21**. During attempted benzylation of 3-*epi*-**21** by reaction with KH and BnBr, a rapid isomerization to **21**, presumably via a retroaldol−aldol mechanism, was noted. After extensive optimization, subjecting the crude 1:1 mixture of diols to *t*-BuOK (2 equiv) and CuI (0.3 equiv) in Et_2O at 0 °C for 5 min produced **21** (dr >19:1; ca. 80% yield over two steps) on decagram scale. A three-step sequence involving formation of the benzylidene acetal, reduction of the ester, and oxidation of the resulting primary alcohol transformed **21** into aldehyde (+)-**17a** in 80% yield.

The reported procedure for the synthesis of (±)-**14** gave a separable 1:1 mixture of diastereomers.[16] In an improved route, (±)-**14** was obtained by $MgBr_2{\cdot}Et_2O$-mediated Mukaiyama aldol reaction of **23**[16] with (±)-**22**[21c] (dr = 4:1) followed by Raney Ni desulfurization and was subsequently converted to the BOM derivative (±)-**24** under standard conditions (Scheme 3). Conversion of (±)-**24** into its Ti(IV) (*Z*)-enolate by transmetalation[16,24] of the corresponding Li enolate followed by addition of (+)-**17a** (0.33 equiv) gave a 7:1 mixture of aldol adducts from which (+)-**18a** (79%) and (+)-**24** (70%, ca. 20% optical purity) were isolated. The recovery of **24** enriched in the dextrorotatory enantiomer confirms that (+)-**18a** results from preferential reaction of (+)-**17a** with (−)-**24**, as expected. The C-8 and C-9 configurations in (+)-**18a** are assigned based on the known diastereoselectivities of aldol reactions of **16** [Pg = CH_2OMe; ML_n = $Ti(O\text{-}i\text{-}Pr)_3$][16] and of additions to aldehydes related to **17**;[18] the 8,9-*syn* relative configuration in **18a** is supported by NMR ($^3J_{H8-H9}$ = 3.5 Hz; δ_C CH_3C-8 = 10.2; δ_C C-9 = 69.5).[16] The minor aldol adduct presumably results from the mismatched reaction of (+)-**17a** with (+)-**24** but was not isolated in pure form or characterized.

Following $FeCl_3$-mediated removal of the ethylene ketal protecting group and IBX oxidation of the alcohol in (+)-**18a**, desulfurization of the resulting trione with Raney Ni occurred with concomitant hydrogenolysis of the BOM group to afford **25** (68%) that was a 1:1:0.1 mixture of two keto and enol tautomeric forms, respectively, in $CDCl_3$ solution (Scheme 3).[25] The benzylidene acetal in **25** was surprisingly resistant to hydrogenolysis.[26] After considerable experimentation, stirring a suspension of excess freshly prepared Pd black and **25** in *i*PrOH under a H_2 atmosphere (4 bar) afforded **2** in good yield. Among the plethora of possible keto−enol and ring−chain tautomeric forms, in C_6D_6 solution **2** was predominantly a 1.5:1 mixture of hemiacetals **2a** [(9*S*) 13→9; epimeric at C-8] consistent with Goodman's calculations.[9,10] Treatment of **2a** with DBU in C_6D_6 slowly produced a mixture of products including a 3:6:1 mixture of **1** and two unidentified diastereomers,[27] respectively (38%), and **26**[28] (ca. 44%), among others. Presumably **1** (and its diastereomers) results from retro-Claisen fragmentation of the C7−C8 bond in the 11→7 hemiacetal **3** (and its diastereomers)[27] and **26** arises from fragmentation of C8−C9 bond in the 13→9 hemiacetal **2a** (or perhaps by fragmentation of the same bond in the 5→9 hemiacetal of **2** followed by lactonization). To improve the retro-Claisen regioselectivity and reduce base-mediated epimerization, we subjected **2a** to alumina.[5a,8] Although **2a** was stable to neutral alumina in hot EtOH, brief exposure to neutral alumina in benzene cleanly produced dolabriferol (**1**) in excellent yield. This remarkably selective retro-Claisen process presumably results from a much higher reactivity of hemiacetal **3** (compared to its regioisomers) under conditions (alumina/benzene) where hemiacetal equilibration is rapid. The facile conversion of **2** into **1** clearly establishes the latter as a plausible artifact of isolation.

In summary, the first total synthesis of **2**, the putative contiguous precursor of dolabriferol (**1**), was achieved via a rationally designed enantioselective aldol coupling of (±)-**24** with (+)-**17a** as the key step.[29] A unique feature of this "fragment coupling with kinetic resolution" strategy is that the stereocenters in the racemic fragment are set under substrate-control, thereby allowing syntheses of either enantiomer or racemic product from the identical reactants via the same convergent route by simply changing the catalyst used in the initial preparation of **15**. Although **2** existed predominantly in the undesired hemiacetal form **2a**, exposure to neutral alumina resulted in a highly regioselective retro-Claisen fragmentation via hemiacetal **3** to efficiently afford **1**. These results cannot rule out an enzyme-mediated retro-Claisen process in vivo; however, they demonstrate for the first time that **2** is a competent biosynthetic end product capable of in vitro transformation into dolabriferol (**1**) under very mild conditions.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01798.

Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all reported compounds; comparison of NMR data for natural and synthetic **1**; structure assignments for 7-*epi*-**1** (tentative) and **26** (PDF)

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Notes

The authors declare no competing financial interest.

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