

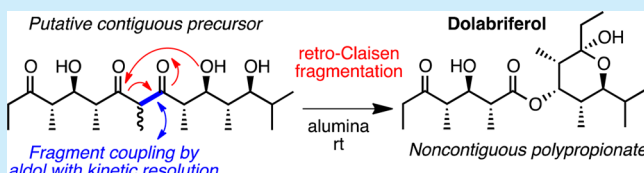
On the Origin of Dolabriferol: Total Synthesis via Its Putative Contiguous Precursor

Athanasios Karagiannis, Naveen Diddi, and Dale E. Ward*

Department of Chemistry, University of Saskatchewan, 110 Science Place, Saskatoon, SK S7N 5C9, Canada

S 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 baconipyron 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 calculations⁹ 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-

Received: June 20, 2016

The reaction scheme illustrates the biosynthesis of Dolabriferol (1) from a putative precursor 2. The sequence of reactions is as follows:

- Structure 2 (putative contiguous precursor)** is converted to **Structure 3** via **11 → 7 hemiacetal cyclization**.
- Structure 3** undergoes **retro-Claisen fragmentation** to form **Structure 4**.
- Structure 4** undergoes **hemiacetal formation** to form **Dolabriferol (1)**.
- Structure 2** is also converted to **Structure 5** via **retro-Claisen fragmentation**.
- Structure 5** is converted to **Structure 6** using **DBU (ref 2a, 5b) or alumina (ref 5a)**.
- Structure 6** is converted to **Structure 7 (Siphonarin B)** via **retro-Claisen fragmentation** using **alumina (ref 8)**.
- Structure 7** is converted to **Structure 8 (Baconipyron C)** via **retro-Claisen fragmentation** using **alumina (ref 8)**.
- Structure 8** is converted to **Structure 9** via **imidazole (ref 8)**.
- Structure 9** is converted to **Structure 10** via **retro-Claisen fragmentation** using **alumina (ref 8)**.
- Structure 9** is also converted to **Structure 10** via **5 → 9 hemiacetal** and **retro-Claisen fragmentation** using **alumina (ref 8)**.

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

2 \Rightarrow 11

Pg = protecting group

oxidation-aldol transform

12 + 13

alkyl ether for enolate diastereoface selectivity \rightarrow 6,8-syn

14

15 (-)

Ti or B (Z)-enolate for syn aldol \rightarrow 8,9-syn

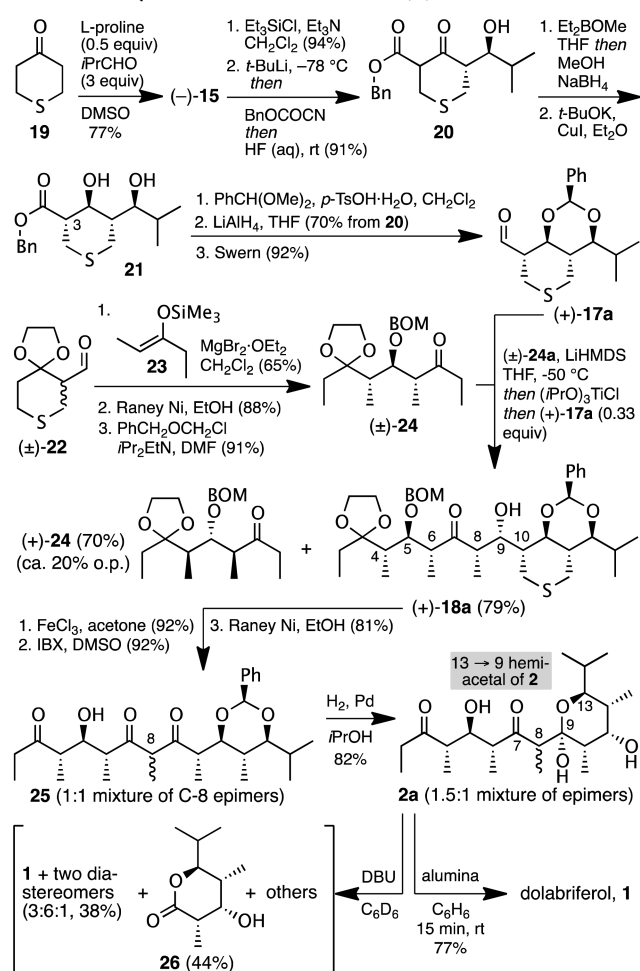
cyclic for high Felkin selectivity \rightarrow 9,10-syn

16 + 17

18

The synthesis commenced with the preparation of (–)-**15** (77%, 92% ee) on a decagram scale by L-proline catalyzed aldol reaction of **19** with iPrCHO using a modification of the published protocols¹⁷ 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

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 reduction²³ 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 (\pm)-**14** gave a separable 1:1 mixture of diastereomers.¹⁶ In an improved route, (\pm)-**14** was obtained by $\text{MgBr}_2\cdot\text{Et}_2\text{O}$ -mediated Mukaiyama aldol reaction of **23**¹⁶ with (\pm)-**22**^{21c} (dr = 4:1) followed by Raney Ni desulfurization and was subsequently converted to the BOM derivative (\pm)-**24** under standard conditions (Scheme 3). Conversion of (\pm)-**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** [$\text{Pg} = \text{CH}_2\text{OMe}$; $\text{ML}_n = \text{Ti}(\text{O}-i\text{-Pr})_3$]¹⁶ and of additions to aldehydes related to **17**;¹⁸ the 8,9-*syn* relative configuration in **18a** is supported by NMR ($^3J_{\text{H8-H9}} = 3.5 \text{ Hz}$; $\delta_{\text{C}} \text{CH}_3\text{C-8} = 10.2$; $\delta_{\text{C}} \text{C-9} = 69.5$).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** [(9S) 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 (\pm)-**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.

■ 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 ^1H 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)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dale.ward@usask.ca.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Pramod Jadhav and Sushital Jana (University of Saskatchewan) for preliminary experiments on the synthesis of **21** and the improved route to (\pm)-**14**, respectively. Financial support from the Natural Sciences and Engineering Research Council (Canada) (RGPIN 1536-2013) and the University of Saskatchewan is gratefully acknowledged.

■ REFERENCES

- (1) Ciavatta, M. L.; Gavagnin, M.; Puliti, R.; Cimino, G.; Martinez, E.; Ortea, J.; Mattia, C. A. *Tetrahedron* **1996**, *52*, 12831–12838.
- (2) (a) Ester **6** (unnamed): Hochlowski, J. E.; Faulkner, D. J. *J. Org. Chem.* **1984**, *49*, 3838–3840. (b) Baconipyrone A–D: Manker, D. C.; Faulkner, D. J.; Stout, T. J.; Clardy, J. *J. Org. Chem.* **1989**, *54*, 5371–5374. (c) Membrenones A and B: Ciavatta, M. L.; Trivellone, E.; Villani, G.; Cimino, G. *Tetrahedron Lett.* **1993**, *34*, 6791–6794. (d) Sisserone A: Brecknell, D. J.; Collett, L. A.; Davies-Coleman, M. T.; Garson, M. J.; Jones, D. D. *Tetrahedron* **2000**, *56*, 2497–2502. (e) Micromelones A and B: Napolitano, J. G.; Souto, M. L.; Fernandez, J. J.; Norte, M. *J. Nat. Prod.* **2008**, *71*, 281–284. (f) Dolabriferols B and C: Jimenez-Romero, C.; Gonzalez, K.; Rodriguez, A. D. *Tetrahedron Lett.* **2012**, *53*, 6641–6645.
- (3) Davies-Coleman, M. T.; Garson, M. J. *Nat. Prod. Rep.* **1998**, *15*, 477–493.
- (4) Hochlowski, J.; Coll, J.; Faulkner, D. J.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *106*, 6748–6750.
- (5) (a) Sundram, U. N.; Albizzati, K. F. *Tetrahedron Lett.* **1992**, *33*, 437–440. (b) Lister, T.; Perkins, M. V. *Aust. J. Chem.* **2004**, *57*, 787–797.
- (6) (a) Lister, T.; Perkins, M. V. *Org. Lett.* **2006**, *8*, 1827–1830. (b) Lister, T. Ph.D. Thesis, Flinders University, Adelaide, Australia, 2006.
- (7) Currie, R. H.; Goodman, J. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 4695–4697.
- (8) Beye, G. E.; Ward, D. E. *J. Am. Chem. Soc.* **2010**, *132*, 7210–7215.
- (9) Socorro, I. M.; Taylor, K.; Goodman, J. M. *Org. Lett.* **2005**, *7*, 3541–3544.
- (10) The relative energies for all possible 6-membered ring hemiacetal tautomers of **2** have been calculated (kJ/mol) (RHF/3-21G/water basis set; ref 9). From (8R)-**2**: 13→9, 0.0; 11→7, 37.7; 5→9, 25.5. From (8S)-**2**: 13→9, 6.7; 11→7, 23.0; 5→9, 27.1.
- (11) (a) Chênevert, R.; Courchesne, G.; Caron, D. *Tetrahedron: Asymmetry* **2003**, *14*, 2567–2571. (b) Pelchat, N.; Caron, D.; Chênevert, R. *J. Org. Chem.* **2007**, *72*, 8484–8488.
- (12) Dias, L. C.; de Sousa, M. A. *Tetrahedron Lett.* **2003**, *44*, 5625–5628.
- (13) (a) Laclef, S.; Turks, M.; Vogel, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 8525–8527. (b) Laclef, S. Ph.D. Thesis, École Polytechnique Fédérale de Lausanne, Switzerland, 2010.
- (14) Gesinski, M. R.; Brenzovich, W. E., Jr.; Staben, S. T.; Srinilta, D. J.; Toste, F. D. *Tetrahedron Lett.* **2015**, *56*, 3643–3646.
- (15) (a) Paterson, I.; Chen, D. Y.-K.; Franklin, A. S. *Org. Lett.* **2002**, *4*, 391–394. (b) Beye, G. E.; Goodman, J. M.; Ward, D. E. *Org. Lett.* **2009**, *11*, 1373–1376.
- (16) Ward, D. E.; Kundu, D.; Biniiaz, M.; Jana, S. *J. Org. Chem.* **2014**, *79*, 6868–6894.
- (17) (a) Ward, D. E.; Jheengut, V. *Tetrahedron Lett.* **2004**, *45*, 8347–8350. (b) Pihko, P. M.; Laurikainen, K. M.; Usano, A.; Nyberg, A. I.; Kaavi, J. A. *Tetrahedron* **2006**, *62*, 317–328.
- (18) Ward, D. E.; Sales, M.; Man, C. C.; Shen, J.; Sasmal, P. K.; Guo, C. *J. Org. Chem.* **2002**, *67*, 1618–1629.
- (19) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151–4157.
- (20) Ward, D. E. In *Modern Methods in Stereoselective Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2013; Chapter 6, pp 377–429.
- (21) (a) Ward, D. E.; Jheengut, V.; Akinnusi, O. T. *Org. Lett.* **2005**, *7*, 1181–1184. (b) Ward, D. E.; Becerril-Jimenez, F.; Zahedi, M. M. *J. Org. Chem.* **2009**, *74*, 4447–4454. (c) Ward, D. E.; Jheengut, V.; Beye, G. E.; Gillis, H. M.; Karagiannis, A.; Becerril-Jimenez, F. *Synlett* **2011**, *2011*, 508–512. (d) Becerril-Jimenez, F.; Ward, D. E. *Org. Lett.* **2012**, *14*, 1648–1651. (e) Ward, D. E.; Kazemini, A. *J. Org. Chem.* **2012**, *77*, 10789–10803.
- (22) On a per mole basis, iPrCHO is ca. 3 orders of magnitude less expensive than **19** (ca. \$4K/mol). The latter is readily available in two simple steps (>70% yield; 50 g scale) from dimethyl 3,3'-thiodipropionate (ca. \$25/mol): Ward, D. E.; Rasheed, M. A.; Gillis, H. M.; Beye, G. E.; Jheengut, V.; Achonduh, G. T. *Synthesis* **2007**, *2007*, 1584–1586.
- (23) Chen, K. M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155–158.
- (24) (a) Reetz, M. T.; Peter, R. *Tetrahedron Lett.* **1981**, *22*, 4691–4694. (b) Siegel, C.; Thornton, E. R. *J. Am. Chem. Soc.* **1989**, *111*, 5722–5728.
- (25) Perkins (ref 6) and Goodman (ref 7) reported 1,3-diones related to **25** as single keto tautomers (but with opposite relative configurations at C-8); however, under their retro-Claisen conditions (DBU, benzene), epimerization at C-8 is likely. For selected examples of kinetically stable chiral 1,3-diones that epimerize under mild conditions, see refs 8 and 21d and: (a) Paterson, I.; Perkins, M. V. *Tetrahedron* **1996**, *52*, 1811–1834. (b) De Brabander, J.; Oppolzer, W. *Tetrahedron* **1997**, *53*, 9169–9202. (c) Calter, M. A.; Liao, W. S. *J. Am. Chem. Soc.* **2002**, *124*, 13127–13129. (d) Ward, D. E.; Zahedi, M. M. *Org. Lett.* **2012**, *14*, 6246–6249.
- (26) For a related example, see: Muri, D.; Carreira, E. M. *J. Org. Chem.* **2009**, *74*, 8695–8712.
- (27) The major diastereomer was tentatively assigned as 7-*epi*-**1** by comparison of its NMR data with those of **1** and **10**. Because 7-*epi*-**1** was unchanged when re-subjected to the reaction conditions, epimerization presumably occurs prior to retro-Claisen fragmentation.
- (28) Exner, C. J.; Laclef, S.; Poli, F.; Turks, M.; Vogel, P. *J. Org. Chem.* **2011**, *76*, 840–845.
- (29) For the use of this strategy in the total synthesis of caloundrin B, see ref 21d.