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A Retro-Claisen Approach to Dolabriferol

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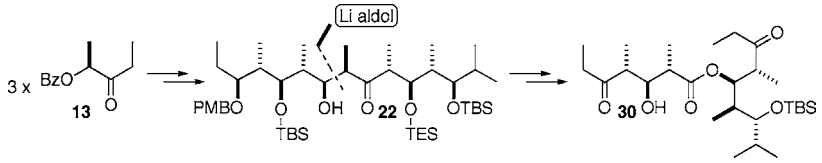
ABSTRACT



The protected precursor 30 to dolabriferol was generated by a DBU-induced, ester-forming, retro-Claisen process. The required linear carbon chain present in 22 was synthesized by a stereoselective lithium aldol reaction. The necessary aldehyde and ketone fragments were synthesized using stereocontrolled aldol reactions with the ethyl (*S*)-lactate derived ketone 13.

Dolabriferol (**1**) was isolated from the ether-soluble acetone extracts of specimens of *Dolabrifera dolabrifera* by Ciavatta and co-workers in 1996[1] in the first chemical study of an opisthobranch belonging to the Dolabriferidae family. Found off the coast of Cuba, *D. dolabrifera* is readily distinguishable from other members of the *Aplysia* genus by the presence of small and asymmetrical parapodia, a flattened body, and a calcified internal shell. The structure of dolabriferol (**1**) was elucidated by extensive NMR studies, and the complete relative stereochemistry was confirmed by single crystal X-ray analysis. Without proof of the absolute stereochemistry, a comparison to the seemingly related baconipyrones (**2**−**5**)[2] suggests the absolute configuration drawn for **1** as a candidate for synthesis. Dolabriferol (**1**) is a polypropionate featuring a highly substituted hemiketal tethered to a β-hydroxy ketone via an unusual ester linkage. The presence of a noncontiguous carbon backbone assigns dolabriferol (**1**) to a group of marine polypropionates that includes the baconipyrones A−D (**2**−**5**)[2], siserrone A (**6**),[3] and ester **7** (isolated from *S. australis*)[4] (Figure 1). This structural motif appears to be the result of rupture of an intermediate hemiacetal via a retro-Clasien fragmentation. As such, the natural product status of dolabriferol can be questioned.[2]

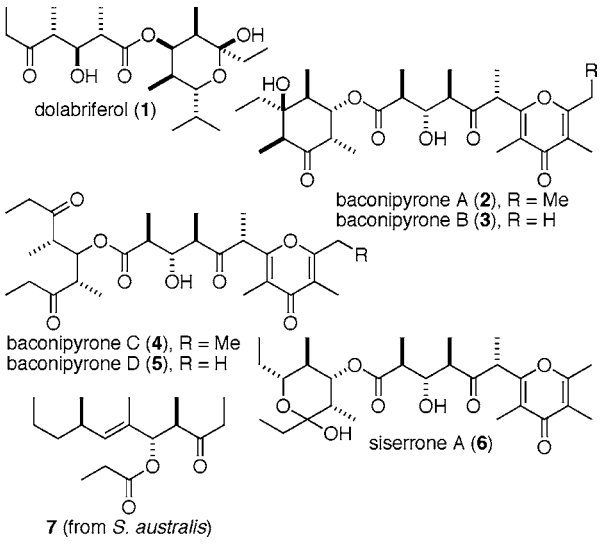


Figure 1. Selected noncontiguous marine polypropionates.

(1) Ciavatta, M. L.; Gavagnin, M.; Puliti, R.; Cimino, G.; Martinez, E.; Ortea, J.; Mattia, C. A. *Tetrahedron* **1996**, *52*, 12831−12838.
(2) Manker, D. C.; Faulkner, D. J.; Stout, T. J.; Clardy, J. *J. Org. Chem.* **1989**, *54*, 5371−5374.
(3) (a) Hochlowski, J. E.; Faulkner, D. J. *J. Org. Chem.* **1984**, *49*, 3838−3840. (b) Sundram, U. N.; Albizati, K. F. *Tetrahedron Lett.* **1992**, *33*, 437−440. (c) Lister, T., Perkins, M. V. *Aust. J. Chem.* **2004**, *57*, 787−797.
(4) Brecknell, D. J.; Collett, L. A.; Davies-Coleman, M. T.; Garson, M. J.; Jones, D. D. *Tetrahedron* **2000**, *56*, 2497−2502.

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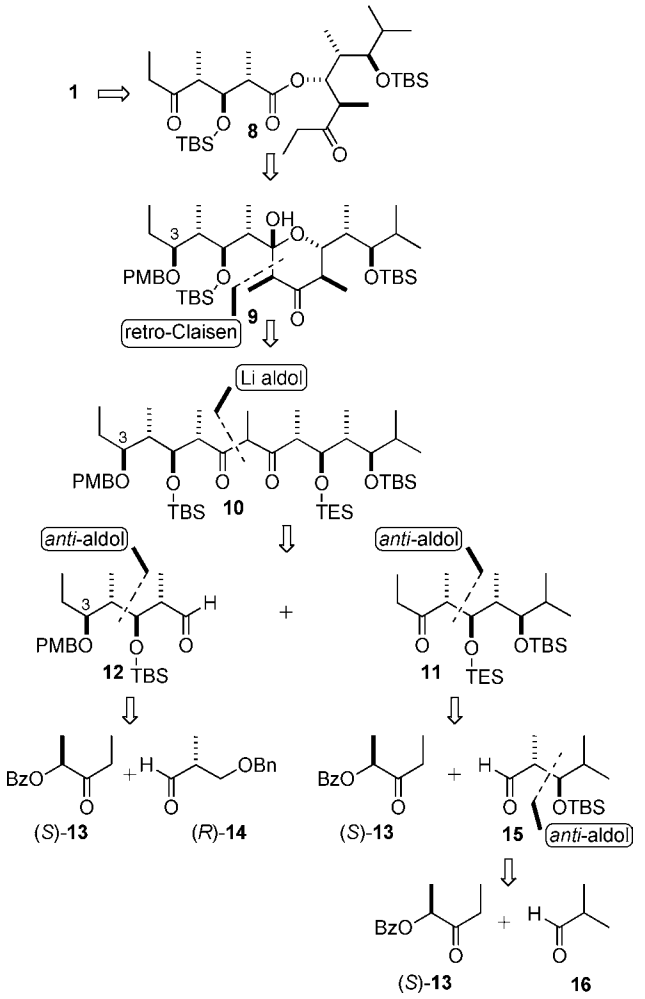
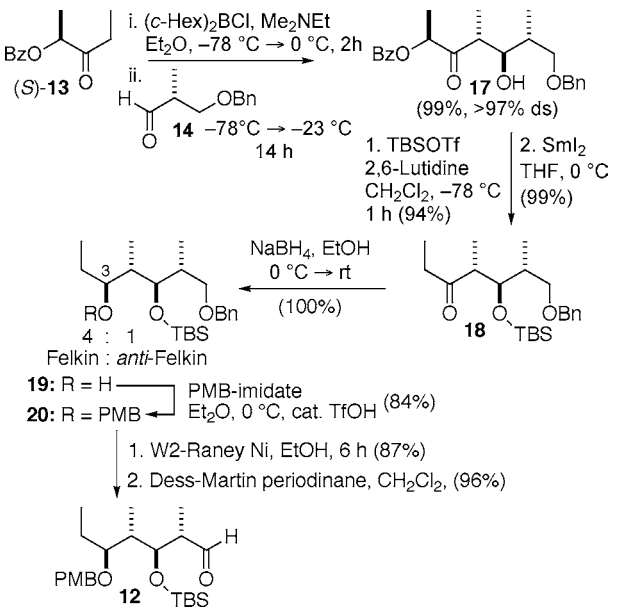
While dolabriferol (**1**) has attracted some synthetic interest,[5] its total synthesis has yet to be reported. Our[6] and others'[5] previous attempts to prepare the ester linkage in dolabriferol (**1**) by coupling acid and alcohol equivalents have not proved successful. We now report the synthesis of the direct precursor to dolabriferol (**1**) using a "biomimetic" retro-Claisen reaction to install this ester linkage.

Scheme 1



Retrosynthetic analysis (Scheme 1) revealed that compound **8**, the protected precursor to dolabriferol (**1**), is formed by retro-Claisen reaction of hemiketal **9** and deprotection/oxidation of C3. The pseudosymmetrical acyclic precursor **10** to hemiacetal **9** should be available from an aldol coupling of ketone **11** with *β*-silyloxy-*δ*-alkoxy aldehyde **12** followed by oxidation. Substrate-directed aldol reactions of the lactate-derived (*S*)-2-benzoyloxypentan-3-one ((*S*)-**13**) with aldehydes **14**−**16** were proposed for the preparation of both aldehyde **12** and ketone **11**. Noticeably, these sequences install all but one of the stereocenters present in dolabriferol (**1**). Adjustment of the C3 oxidation state and protection of the formed hydroxyl in **12** was proposed to avoid potential hemiketalization at various stages of the synthesis.

Scheme 2



The synthesis of aldehyde **12** is shown in Scheme 2. The (*E*)-enol dicyclohexylborinate of known[7] ketone (*S*)-**13** was reacted with an excess of freshly prepared[8] α-methyl chiral aldehyde (*R*)-**14** to give **17** in excellent yield (99%) and diastereoselectivity (>97% ds). The generated alcohol was masked as a TBS ether (TBSOTf), and subsequent reductive removal of the α-benzoate[7] using SmI_2 gave **18** in high yield (93%, two steps). At this stage, temporary C3 reduction and protection was required to avoid cyclization upon liberation of the primary benzyl ether. To this end, carbonyl reduction with $NaBH_4$ gave a 4:1 ratio of Felkin isomer **19** and its C-3 epimer that could be readily separated by flash chromatography.

While both epimers could be used in the synthesis, as this center is ultimately at the carbonyl oxidation state, the major epimer **19** was taken forward to simplify subsequent spectral analysis. Protection of alcohol **19** using PMB-trichloroacetimidate under modified conditions[9] gave the *p*-methoxybenzyl ether **20** in good yield (84%). Selective debenzylation of **20** with Raney nickel[10] followed by Dess−Martin oxidation[11] furnished aldehyde **12** in 84% overall yield.

(5) (a) Dias, L. C.; de Sousa, M. A. *Tetrahedron Lett.* **2003**, *44*, 5625−5628. (b) Chenevert, R.; Courchesne, G.; Caron, D. *Tetrahedron: Asymmetry* **2003**, *14*, 2567−2571.

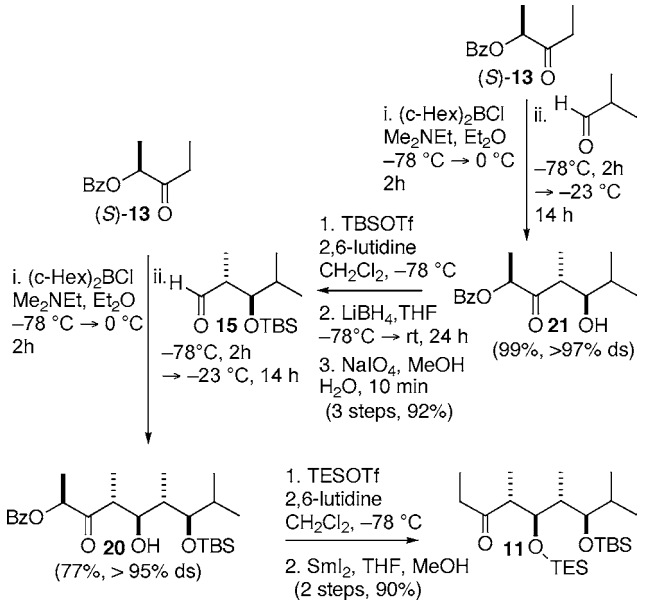
(6) Our attempts to access an analogue of ester **8** by coupling alcohol **20** with the acid derived from **18** using various protocols proved unsuccessful due to unfavorable steric interactions and facile dehydration of compound **20**. Lister, T. Unpublished results.

(7) (a) Paterson, I.; Wallace, D. J.; Velázquez, S. M. *Tetrahedron Lett.* **1994**, *35*, 9083−9886. (b) Paterson, I.; Wallace, D. J. *Tetrahedron Lett.* **1994**, *35*, 9087−9090. (c) Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639−652.

(8) (a) Paterson, I.; Yeung, K.-S.; Watson, C.; Ward, R. A.; Wallace, P. A. *Tetrahedron* **1998**, *54*, 11935−11954. (b) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc.* **2001**, *123*, 9535−9544.

(9) Paterson, I.; Lombart, H.; Allerton, C. *Org. Lett.* **1999**, *1*, 19−22.

Scheme 3



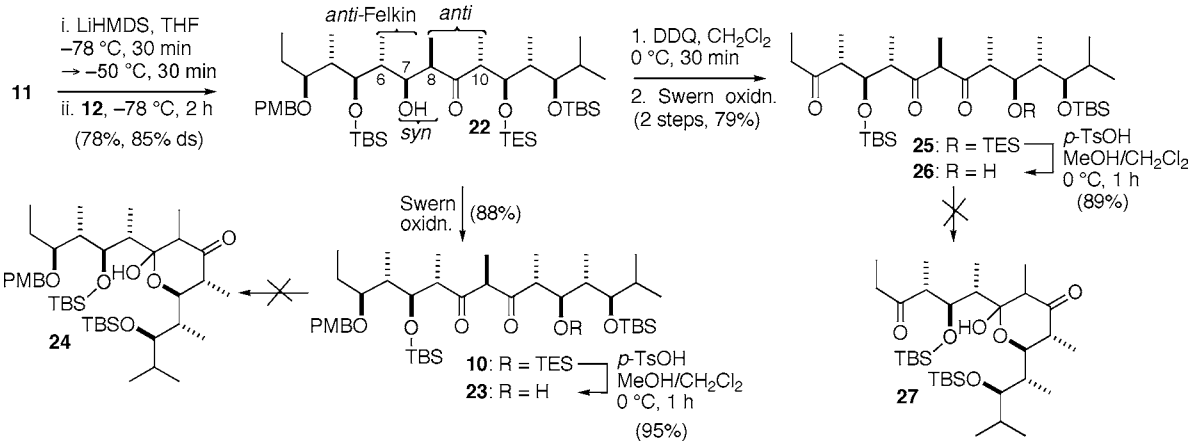
The synthesis of ketone **11** is shown in Scheme 3. Reaction of the (*E*)-enol dicyclohexylborinate of ketone (*S*)-**13** with 2-methyl propanal (**16**) gave ketone **21** with high selectivity (99%, >95% ds). Protection (TBS ether), conversion to the diol with $LiBH_4$, and oxidative cleavage gave aldehyde **15** (91% over 3 steps). In an iterative process, the (*E*)-enol dicyclohexylborinate ketone (*S*)-**13** was now reacted with 1.5 equiv of aldehyde **15** giving a single detectable isomer of adduct **20** in 77% yield. This level of diastereoselectivity highlights the high π-facial selectivity exhibited by (*S*)-**13** considering its dominance over any facial preference of aldehyde **15**. Protection of the free hydroxyl as a triethylsilyl ether, followed by benzoate cleavage[7] (SmI_2) gave ketone **11** in good yield (90%, 2 steps).

With the key aldol fragments in hand, our attention was focused on their coupling (Scheme 4). In an optimized procedure, lithium hexamethyldisilyl azide (LiHMDS) was used to generate the enolate of **11** (30 min at −78 °C followed by 30 min at −50 °C), which smoothly reacted with aldehyde **12** at −78 °C to give adduct **22** in good yield (78%) as a separable mixture of just two diastereomers (85% ds). The stereocenters formed in this coupling are lost in the subsequent oxidation, but the formation of one major isomer allows the progression of stereochemically pure material. The dominant isomer was tentatively assigned as the 6,7-*anti*-Felkin-7,8-*syn*-8,10-*anti* product **22** (Scheme 4) based on literature precedent for similar double stereodifferentiating lithium aldol reactions.[12] In preliminary experiments, Swern oxidation[13] of β-hydroxy ketone **22** gave the corresponding dione **10**, which surprisingly existed exclusively as a single epimer of the β-diketone with no enol form present. Selective desilylation proceeded smoothly under either acidic conditions (*p*-TSOH) or the action of fluoride ion (HF·pyr/pyr) giving the deprotected acyclic dione **23**, but this compound did not cyclize to give the hemiacetal **24** required for retro-Claisen reaction.[14] Failure of this cyclization caused us to abandon this fully protected approach.

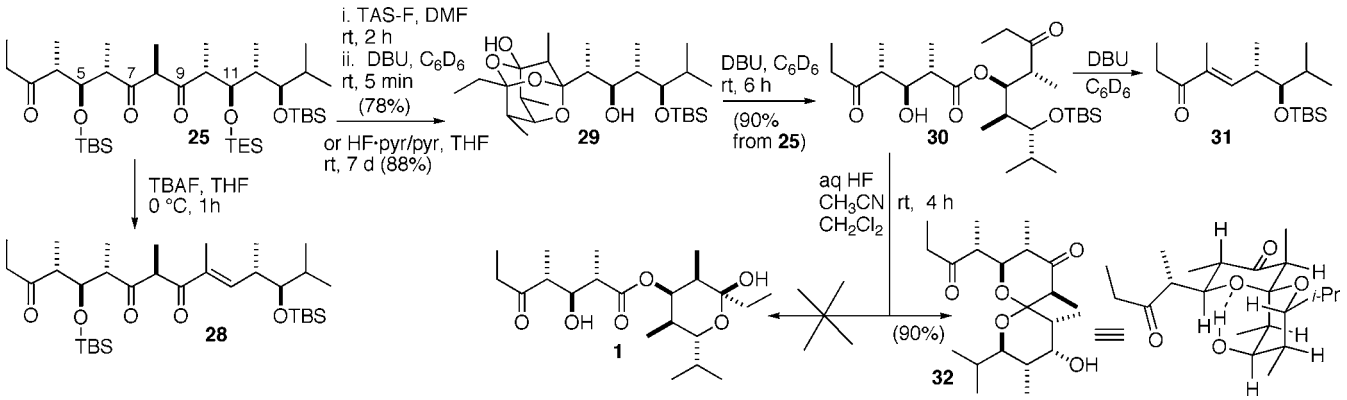
Assuming that the cyclization was inhibited by steric hindrance, we chose to change our strategy and now adjust the oxidation state of C3 to that required in dolabriferol. To this end, adduct **22** was treated with DDQ in moist CH_2Cl_2, followed by double Swern oxidation[13] to give trione **25** in good yield (79%, two steps). This species proved similarly stable to epimerization and selective desilylation gave compound **26**. Again, this compound failed to cyclize[15] to the desired hemiacetal **27**, indicating that the bulky TBS protecting groups were the cause of the problem. Removal of one or both of these TBS groups introduces a variety of competing cyclization modes but still seemed a viable path forward.

The base sensitivity of dione **25** was highlighted during attempted deprotection with TBAF which lead only to the formation of enone **28** (Scheme 5). However, controlled desilylation could be achieved (5 equiv of TAS-F,[16] 2 h, or HF·pyr/pyr, 7 days) with the removal of the C-5 TBS and C-11 TES ethers. The product from the HF·pyr/pyr reaction was identified as the unusual trioxaadamantane **29**.[17] The

Scheme 4



Scheme 5



TAS-F[16] reaction initially produced a mixture of hemiacetal products and brief exposure to DBU[4c] rapidly gave trioxaadamantane **29**. Compound **29** was found to be very acid sensitive and decomposed to a mixture of dihydropyrones[18] upon exposure to $CDCl_3$. After some experimentation it was discovered that extended exposure of **29** to DBU facilitated retro-Claisen to give the desired ester **30**. Under these reaction conditions the product **30** slowly underwent β-elimination of the carboxylate giving enone **31**, which although undesirable, helped to confirm the formation of ester **30**.

With a direct precursor to dolabriferol (**1**) in hand we began searching for a means to cleave the final silyl ether. Notably this final TBS ether had already endured, in previous steps, the conditions commonly used for silyl protecting group removal on sensitive systems.

Disappointingly, none of our attempts at this final TBS removal gave dolabriferol, with the reactions either returning starting material, complex mixtures or in the case of TBAF and TAS-F[16] enone **31**. The one exception to this was treatment of **30** with aqueous $HF/CH_3CN/CH_2Cl_2$ which gave spiroacetal **32** as the only product. Formation of this product can only occur by acid-catalyzed Claisen reaction to reform the linear carbon backbone followed by spirocyclization.[19] The TBS cleavage may occur before or after the Claisen reaction.

It appears that the combination of an overly robust TBS protecting group coupled with a highly sensitive (acid and base) substrate prevented the current approach from yielding synthetic dolabriferol (**1**). Despite this recalcitrant situation, our synthesis affords **30** as a single isomer in 35% yield after 11 linear steps from ketone **13**. We are hopeful that replacement of the troublesome TBS ether will ultimately prove successful.

Acknowledgment. We thank the Australian Research Council for funding and Flinders University for its support and facilities. We are also grateful to Dr. Maria Ciavatta for providing copies of the original NMR spectra for dolabriferol.

Supporting Information Available: Experimental procedures and data for compounds **17**−**23**, **25**, **26**, and **29**−**32** and NMR spectra for compounds **10**−**12**, **22**, **25**, **29**, **30**, and **32**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL060347S

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(14) Attempted acid-catalyzed cyclizations were not successful, and treatment with TFA resulted in decomposition with apparent formation of the dihydropyrone corresponding to dehydration of compound **24**.

(15) Again, acid-catalyzed cyclizations were not successful, and treatment with TFA resulted in decomposition with apparent formation of the dihydropyrone corresponding to dehydration of compound **27**.

(16) (a) Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. J. *Org. Chem.* **1998**, *63*, 6436−6437. (b) Scheidt, K. A.; Bannister, T. D.; Tasaka, A.; Wendt, M. D.; Savall, B. M.; Fegley, G. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 6981−6990.

(17) This trioxaadamantane ring system has been observed in a number of polypropionate natural products. See: (a) Roll, D. M.; Biskupiak, J. E.; Mayne, C. L.; Ireland, C. M. *J. Am. Chem. Soc.* **1986**, *108*, 6680−6682. (b) Paterson, I.; Perkins, M. V. *J. Am. Chem. Soc.* **1993**, *115*, 1608−1610. (c) Blanchfield, J. T.; Brecknell, D. J.; Brereton, I. M.; Garson, M. J.; Jones, D. D. *Aust. J. Chem.* **1994**, *47*, 2255−2269.

(18) Dihydropyrones resulting from the dehydration of two hemiacetals (formed from cyclisation of the C5 hydroxyl onto the C9 carbonyl and from cyclisation of the C11 hydroxyl onto the C7 carbonyl) appeared to be formed.

(19) The energy levels of various cyclization and retro-Claisen products of the unprotected linear precursor to dolabriferol have been reported in: Socorro, I. M.; Taylor, K.; Goodman, J. M. *Org. Lett.* **2005**, *7*, 3541−3544. The energy (at RHF/3-21G/water) of compound **32,** −1183.94750 + −75.60402 (for water) = −1259.55077 hartrees, is comparable to that of dolabriferol, (**1**) −1259.54938 hartrees (calculated by Goodman at RHF/3-21G/water, personal communication).