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Enantioselective Total Synthesis of (−)-Dactylolide

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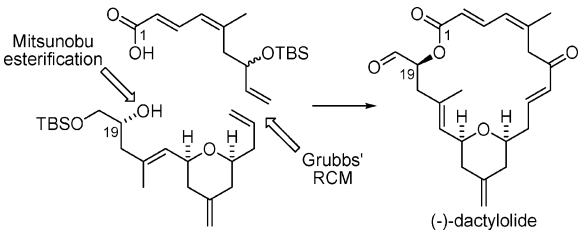
ABSTRACT



The enantioselective total synthesis of (−)-dactylolide is reported. The absolute stereochemistry of the tetrahydropyran was established by catalytic asymmetric Jacobsen hetero-Diels−Alder reaction. The remote C19 stereocenter was introduced by a sequence of chelation-controlled Grignard addition and Ireland−Claisen rearrangement.

In 2001, Riccio and co-workers[1] reported the isolation of dactylolide **1** (Figure 1) from a marine sponge belonging to

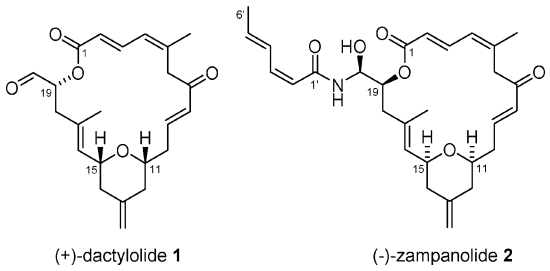


Figure 1. (+)-Dactylolide **1** and (−)-zampanolide **2**.

the genus *Dactylospongia* found off the coast of Vanuatu. It exhibited cytotoxicity against L1210 and SK-OV-3 tumor cell lines, with 63% and 40% inhibition, respectively, at 3.2 μg mL^{-1}.[1] Structurally, dactylolide **1** posesses an unsaturated 18-membered lactone ring containing a 2,6-*cis*-substituted tetrahydropyran and an aldehyde side chain. However, the relative stereochemistry at the aldehyde-bearing C19-stereocenter was not reported on isolation. The complete relative stereochemistry was assigned by Smith[2] in the first total synthesis of (+)-dactylolide **1** in studies that were also directed toward the total synthesis of the structurally related and more potent natural product (−)-zampanolide **2**.[3,4] Since this first report there have been four other total syntheses of dactylolide disclosed by the groups of Hoye, Jennings, Floreancig, and Keck.[5]

Key aspects of the retrosynthetic analysis applied in this study are outlined in Scheme 1. The final stages of the synthesis involve the convergent coupling of acid **3** and tetrahydropyran fragment **4** using a sequence of Mitsunobu esterification followed by Grubbs' ring-closing metathesis (RCM) to form the lactone ring, which could then be elaborated to (−)-dactylolide **1** by global deprotection and oxidation. The key tetrahydropyran fragment **4**, containing the remote C19 stereocenter, was to be obtained from

(1) Cutignano, A.; Bruno, I.; Bifulco, G.; Casapullo, A.; Debitus, C.; Gomez-Paloma, L.; Riccio, R. *Eur. J. Org. Chem.* **2001**, 775.

(2) (a) Smith, A. B., III; Safonov, I. G. *Org. Lett.* **2002**, *4*, 635. (b) Smith, A. B., III; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 11102.

(3) Tanaka, J.; Higa, T. *Tetrahedron Lett.* **1996**, *37*, 5535.

(4) Smith, A. B., III; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2001**, *123*, 12426.

(5) (a) Hoye, T. R.; Hu, M. *J. Am. Chem. Soc.* **2003**, *125*, 9576. (b) Ding, F.; Jennings, M. P. *Org. Lett.* **2005**, *7*, 2321. (c) Aubele, D. L.; Wan, S.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2005**, *44*, 3485. (d) Sanchez, C. C.; Keck, G. E. *Org. Lett.* **2005**, *7*, 3053.

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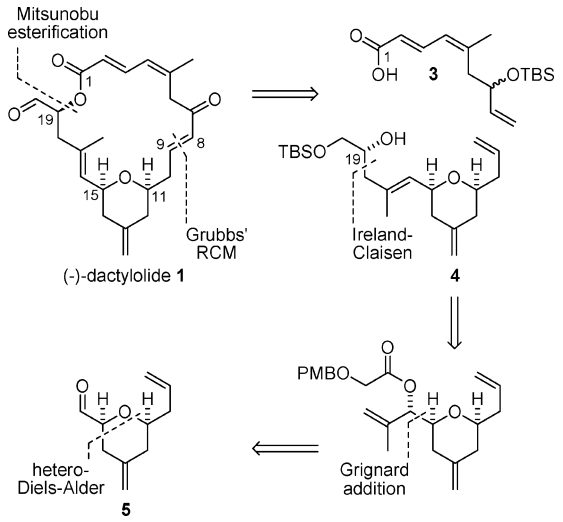
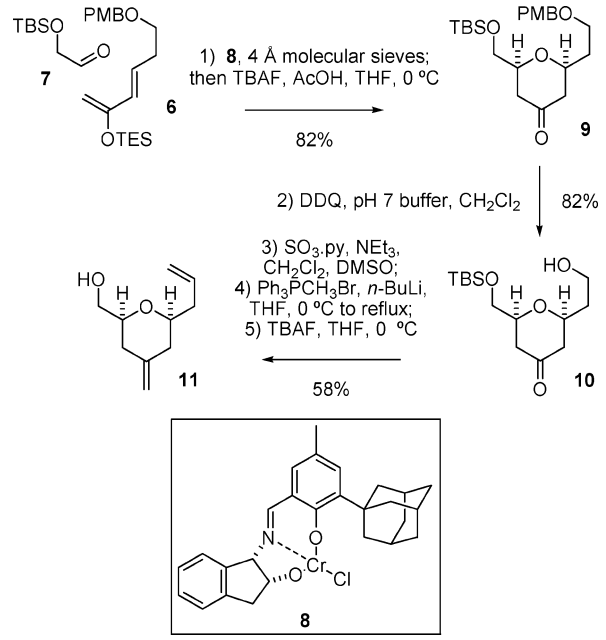
Scheme 1. Retrosynthetic Analysis



aldehyde **5** by a judicious sequence of substrate-controlled reactions including Grignard addition and Ireland−Claisen rearrangement. The stereochemistry of aldehyde **5** would itself be established by a Jacobsen catalytic asymmetric hetero-Diels−Alder reaction. Herein, we report the successful execution of this strategy for the efficient enantioselective synthesis of (−)-dactylolide **1**.

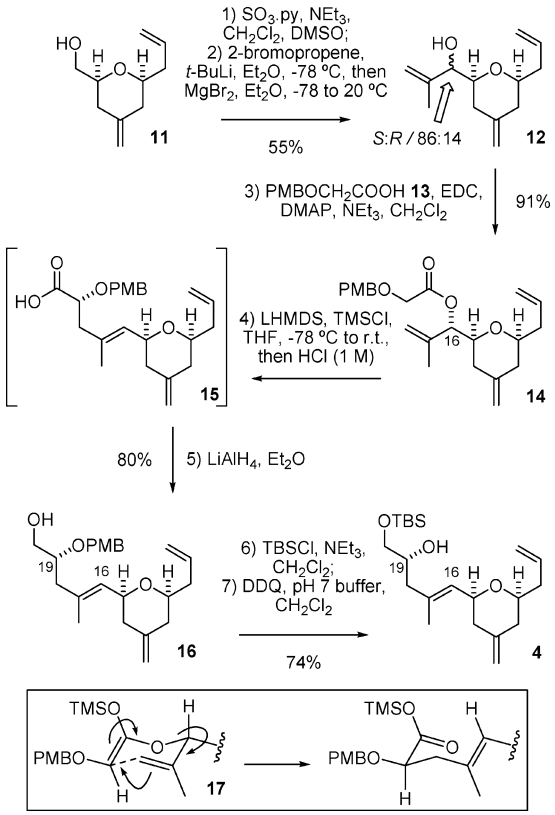
The synthesis of tetrahydropyran **4** began with the union of triethylsilyl enol ether **6** and aldehyde **7** in the presence of Jacobsen's chiral tridentate chromium(III) catalyst **8** (Scheme 2).[6,7] Careful workup of the resulting silyl enol ether

Scheme 2



afforded the *cis*-tetrahydropyranone **9** in 82% yield and 99% ee[8,9] *via* an endo-selective hetero-Diels−Alder cycloaddition pathway, allowing for the synthesis of compound **9** on a multigram scale. Removal of the PMB protecting group with DDQ provided alcohol **10** in 82% yield. Parikh−Doering oxidation[10] of the hydroxyl group then furnished the dicarbonyl compound, which was subjected to Wittig methylenation of the carbonyl groups and silyl ether deprotection to provide diene **11** in 58% yield. Oxidation of the primary alcohol **11** provided the corresponding aldehyde in good yield, which was used directly in the subsequent Grignard addition (Scheme 3). It was envisaged that addition of

Scheme 3



isopropenyl Grignard to the aldehyde would proceed with chelation control to favor formation of **12** with the (16*S*)-configuration at the newly formed stereocenter.[11] The Grignard addition was best achieved by lithium−halogen exchange of 2-bromopropene with *tert*-butyllithium followed by a transmetalation with magnesium bromide. Grignard addition to the aldehyde provided allylic alcohol **12** in 63% yield as an inseparable 86:14 mixture in favor of the desired

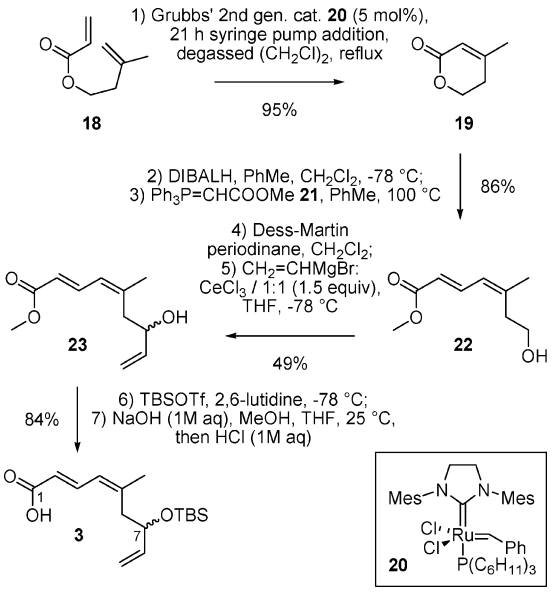
(6) Paterson, I.; Tudge, M. *Tetrahedron* **2003**, *59*, 6833.
(7) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398.
(8) The enantiomeric excess was determined using chiral HPLC (Chiralcel AD-H, 5% isopropyl alcohol/hexane) by comparison with both enantiomers of the tetrahydropyran **9**.
(9) An attempted hetero-Diels−Alder reaction of TBS-protected analogue of enol ether **6** and PMB-protected analogue of aldehyde **7** gave the corresponding pyran in 77% yield but only 66% ee.
(10) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
(11) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033.

(16*S*)-diastereomer.[12] The alcohol **12** was then esterified with PMB protected glycolic acid **13** to give the glycolate ester in 91% yield. At this stage, the two diastereomers resulting from the preceding Grignard addition were easily separable by HPLC to afford ester **14** (76%) as a single diastereomer.

The Ireland−Claisen [3,3] sigmatropic rearrangement[13] of ester **14** afforded polar carboxylic acid **15**, which was not isolated but immediately reduced to give the primary alcohol **16** (80%) as a single diastereomer. Protection of primary alcohol **16** as the TBS ether and removal of the PMB group provided alcohol **4** (74%). In this sequence, the (16*S*)-configuration of the starting ester **14**[11] and the chelation-controlled generation of the (*Z*)-ketene silyl acetal intermediate **17**[14] (see box, Scheme 3) leads ultimately, *via* a chairlike transition state, to the formation of tetrahydropyran **4** with the (19*R*,16*E*)-configuration depicted.[15,16]

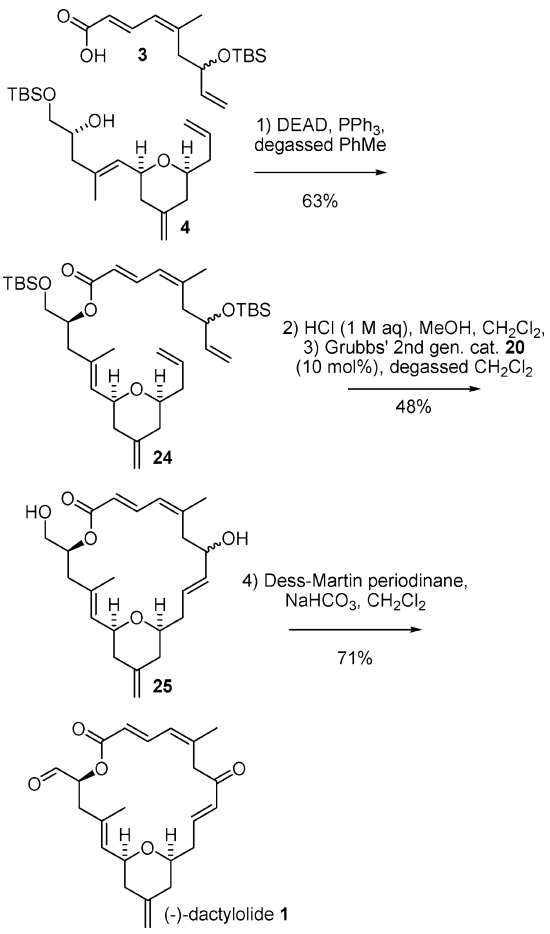
A concise synthesis of the C1−C9 coupling fragment, trienoic acid **3**, was completed from acrylate ester **18**, as shown in Scheme 4, with the trisubstituted *Z*-alkene estab-

Scheme 4



lished *via* a six-membered lactone intermediate **19**. Treatment of the ester **18**[17] with Grubbs' second-generation catalyst

Scheme 5



20,[18] using the RCM protocol of Buchwald,[19] afforded lactone **19** in excellent yield (95%). Partial reduction of the lactone **19** gave the corresponding lactol as a latent hydroxyaldehyde, and direct reaction of this intermediate with stabilized ylide **21** afforded the desired (2*E*,4*Z*)-diene ester **22** in 86% yield (over two steps) after chromatographic separation of the 94:6 2*E*/*Z* mixture. Oxidation of the primary alcohol **22** with Dess−Martin periodinane[20] afforded the aldehyde, but its elaboration to trienol **23** with vinyl Grignard reagent proved problematic due to the acidity of the α-proton in the β,γ-unsaturated aldehyde, a finding also reported by Jennings *et al.*[5b] In an attempt to reduce any competing enolization of the aldehyde, advantage was taken of the reduced basicity of organocerium reagents.[21] Generation of the vinylcerium reagent *via* transmetalation at −78 °C and addition of the aldehyde gave the desired trienol **23** in 56% yield. Finally, protection of the allylic alcohol **23** as the TBS ether and hydrolysis of the methyl ester afforded

(12) Assigned by analogy to the literature (ref 11). Confirmation of this stereochemical assignment was obtained on the synthesis of pyran **4** (see below, refs 15 and 16).

(13) (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (b) Martin-Castro, A. M. *Chem Rev.* **2004**, *104*, 2939.

(14) (a) Rozners, E.; Xu, Q. *Org. Lett.* **2003**, *5*, 3999. (b) Hong, J. H.; Oh, C.-H.; Cho, J.-H. *Tetrahedron* **2003**, *59*, 6103. (c) Mulzer, J.; Mohr, J.-T. *J. Org. Chem.* **1994**, *59*, 1160. (d) Burke, S. D.; Pacofsky, G. J.; Piscopio, A. D. *J. Org. Chem.* **1992**, *57*, 2228. (e) Burke, S. D.; Pacofsky, G. J. *Tetrahedron Lett.* **1986**, *27*, 445. (f) Burke, S. D.; Fobare, W. F.; Pacofsky, G. J. *J. Org. Chem.* **1983**, *48*, 5221.

(15) The (19*R*)-configuration of the secondary alcohol **4** was confirmed using the modified Mosher method: Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

(16) The (16*E*)-configuration of the alkene **16** was confirmed by the presence of a strong ^{1}H NMR NOESY cross-peak between the C16 alkene proton and the C18 allylic protons.

(17) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204.

(18) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(19) Hughes, G.; Kimura, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11253.

(20) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(21) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.

the key C1−C9 trienoic acid **3**. Notably, the stereochemistry at C7 becomes trivial as it is oxidized in the ultimate synthetic step to (−)-dactylolide **1**. Overall, the synthesis of the C1−C9 fragment **3** was achieved in seven steps and 33% yield from ester **18**.

The final stage of the synthesis involved the coupling of key subunits **3** and **4**, with inversion of configuration at C19, to form the macrocycle of (−)-dactylolide **1** (Scheme 5). Mitsunobu esterification[22] proceeded cleanly to provide the ester **24** as a 1:1 mixture of diastereomers about the C7 stereocenter in 63% yield.[23] Removal of the silyl ether protecting groups under mildly acidic conditions afforded the corresponding diol. This was subjected to ring-closing metathesis mediated by Grubbs' second-generation ruthenium catalyst **20**[18,24] in degassed dichloromethane to afford macrocyclic diols **25** with the (8*E*)-stereoisomer formed. The final step in the total synthesis of (−)-dactylolide involved the global oxidation of diols **25**. The oxidation was successfully accomplished using Dess−Martin periodinane[20] in the presence of solid sodium bicarbonate to provide (−)-dactylolide **1** in 71% yield. The spectroscopic data and optical rotation for synthetic (−)-dactylolide **1** ($[\alpha]^{20}_D$ = −169, *c* 0.42, MeOH) were in agreement with those previously reported in the literature.[2,5,25]

In conclusion, an efficient synthesis of (−)-dactylolide **1** has been achieved in 21 steps from commercially available but-3-en-1-ol. An expedient route to the C1−C9 trienoic acid subunit **3** has been developed. Notably, the absolute configuration of (−)-dactylolide **1** is ultimately derived from a single chiral catalyst by application of the Jacobsen catalytic asymmetric hetero-Diels−Alder reaction. The remote C19 stereocenter in fragment **4** is established by substrate control in an efficient sequence involving chelation controlled Grignard reaction and Ireland−Claisen rearrangement. Thus, application of the enantiomeric Jacobsen hetero-Diels−Alder catalyst *ent*-**8** also allows for the synthesis of (+)-dactylolide **1**. Using established methodology,[5a] (−)-dactylolide could be readily elaborated to prepare quantities of (−)-zampanolide **2**.

Acknowledgment. We thank the Australian Research Council (A00104181) for support.

Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra for **1**, **3**, **4**, **9**−**12**, **14**, **16**, **19**, and **22**−**25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) (a) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380. (b) Mitsunobu, O. *Synthesis* **1981**, 1.

(23) Inversion of the C19 configuration during the Mitsunobu esterification was confirmed by the synthesis of (−)-dactylolide **1**. By contrast, for a route targeting the synthesis of (+)-zampanolide **2** containing a related esterification at C19 that occurs with retention of configuration, see ref 2.

(24) This RCM reaction was inspired by the approach reported by Hoye for a structurally related substrate (ref 5a). In the final stages of this work a similar sequence of steps was applied to compound **24** by Jennings (ref 5b).

(25) The sign but not the magnitude of the optical rotation is consistent for all synthetically derived samples of dactylolide. For (−)-(11*S*,15*S*,19*S*)-dactylolide: $[\alpha]^{20}_D$ = −169 (*c* 0.42, MeOH), this work; $[\alpha]^{rt}_D$ = −128 (*c* 0.39, MeOH), ref 5a; $[\alpha]^{rt}_D$ = −136 (*c* 1.2, MeOH), ref 5b. For (+)-(11*R*,15*R*,19*R*)-dactylolide: $[\alpha]_D$ = +235 (*c* 0.52, MeOH), ref 2; $[\alpha]^{rt}_D$ = +163 (*c* 0.29, MeOH), ref 5c; $[\alpha]^{rt}_D$ = +134 (*c* 0.065, MeOH), ref 5d. The optical rotation of naturally occurring dactylolide is reported as $[\alpha]_D$ = +30 (*c* 0.29, MeOH), ref 1.