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Enantioselective Total Synthesis of (−)-Dactylolide

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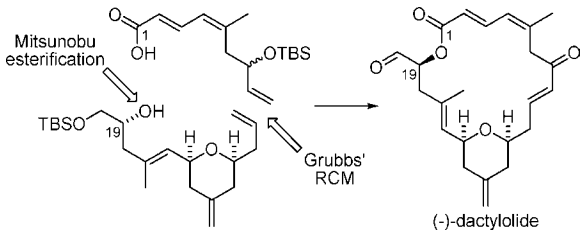
ABSTRACT



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 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]

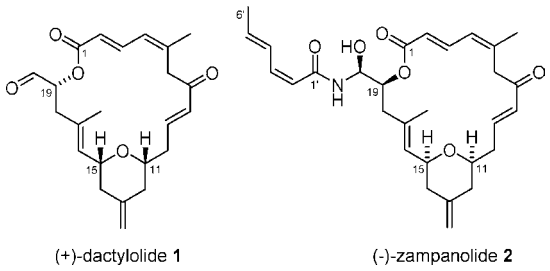


Figure 1. (+)-Dactylolide **1** and (−)-zampanolide **2**.

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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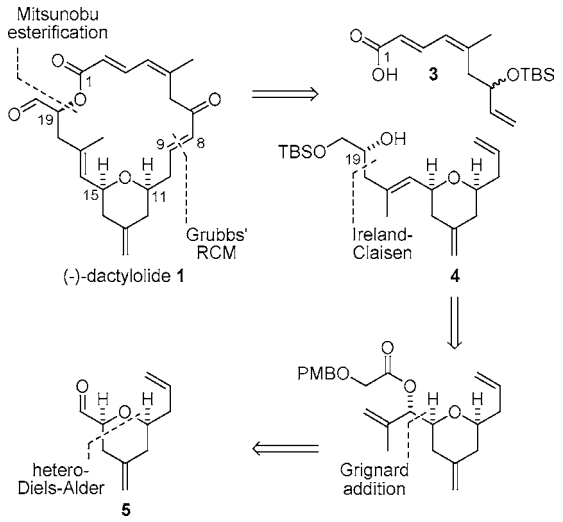
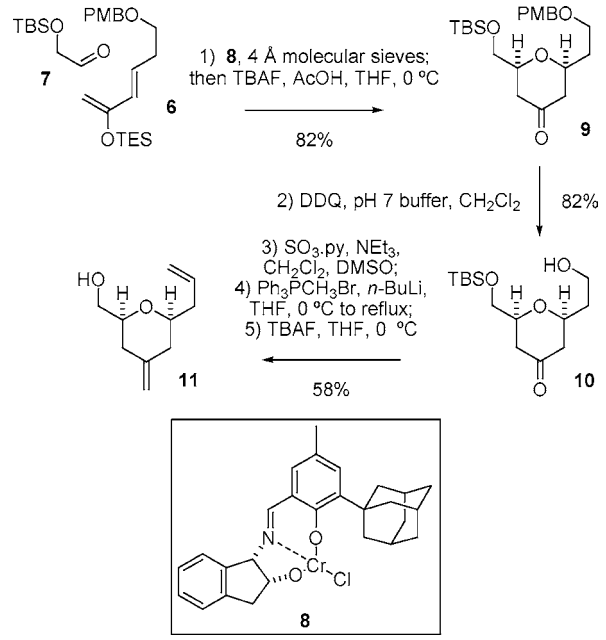
Scheme 1. Retrosynthetic Analysis



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**.

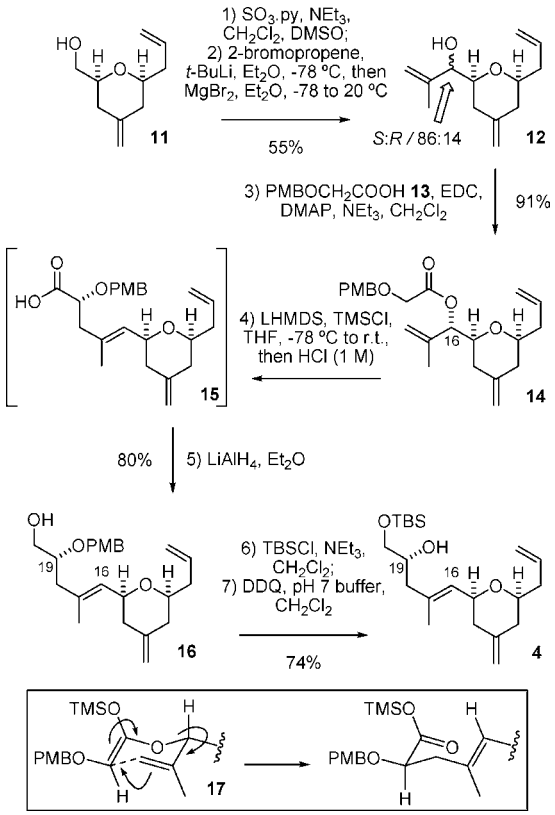
The synthesis of tetrahydropyran **4** began with the union of triethylsilyl enol ether **6** and aldehyde **7** in the presence of Jacobsen's chiral tridentate chromium(III) catalyst **8** (Scheme 2).[6,7] Careful workup of the resulting silyl enol ether

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

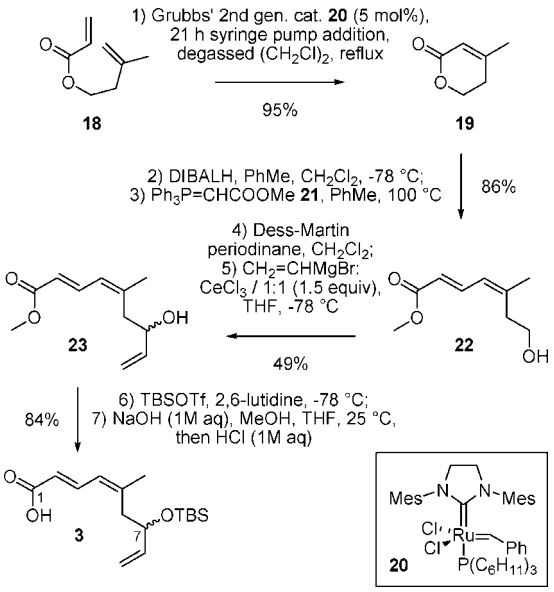
(6) Paterson, I.; Tudge, M. *Tetrahedron* **2003**, *59*, 6833.
(7) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398.
(8) The enantiomeric excess was determined using chiral HPLC (Chiralcel AD-H, 5% isopropyl alcohol/hexane) by comparison with both enantiomers 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.

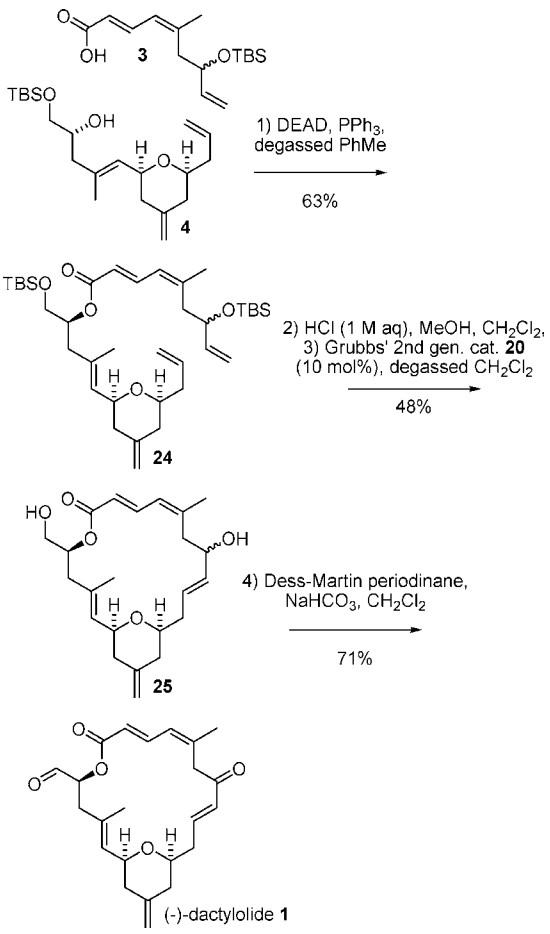
The Ireland−Claisen [3,3] sigmatropic rearrangement[13] of ester **14** afforded polar carboxylic acid **15**, which was not isolated but immediately reduced to give the primary alcohol **16** (80%) as a single diastereomer. Protection of primary alcohol **16** as the TBS ether and removal of the PMB 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 established *via* a six-membered lactone intermediate **19**. Treatment of the ester **18**[17] with Grubbs' second-generation catalyst **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

Scheme 4



Scheme 5



(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.