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Total Synthesis of the Marine Metabolite (–)-Clavosolide D

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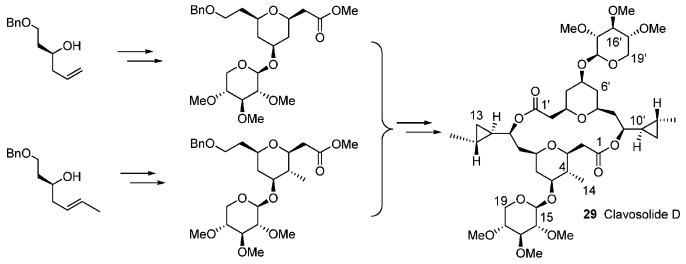
ABSTRACT



The first total synthesis of the marine natural product (–)-clavosolide D is described confirming the structure of the unsymmetrical 16-membered diolide glycosylated by permethylated D-xylose moieties. Following efficient assembly of the two tetrahydropyrans using stereoselective Prins cyclizations, the side chains were introduced via an allylation/isomerization/anti cyclopropanation sequence; the final macrolactonization step was achieved under Yamaguchi conditions.

The clavosolides are a family of unusual diolides isolated from extracts of the marine sponge *Myriastra clavosa* collected in the Philippines.[1] Following extensive spectroscopic and molecular modeling studies, the structure of clavosolide A was assigned as a symmetrical 16-membered ring dilactone assembled on a functionalized tetrahydropyran core with permethylated D-xylose moieties. The macrocycle is further adorned by two cyclopropyl containing side-chains which were originally assigned the configuration 10*S*,10′*S*,-11*S*,11′*S*. Following the total synthesis of this compound, we proposed a revised structure for the natural product in which the side-chains possess the 10*R*,10′*R*,11*R*,11′*R* configuration.[2] The unusual architecture of the clavosolides has attracted significant synthetic interest,[3] and this proposed revised structure has been confirmed by total synthesis.[4] Clavosolide B differs from clavosolide A in the extent of methylation of the D-xylose residues, and indeed, the structure has been confirmed recently by total synthesis.[5]

In 2002 Gustafson and co-workers isolated a small quantity (0.2 mg) of an additional natural product, clavosolide D, from extracts of *M. clavosa*.[1b] While the limited mass of this sample made complete spectral characterization difficult, it was proposed that unlike clavosolides A and B, the macrodiolide core of clavosolide D is unsymmetrical encompassing both tetra-and trisubstituted THPs, the latter lacking a methyl group at C4′. Herein we describe the first total synthesis of clavosolide D confirming its structure. By analogy to the revised structures of clavosolides A and B, on planning a synthetic strategy to this marine natural product we assumed that it possesses side-chains with the 10*R*,10′*R*,-11*R*,11′*R* configuration (Figure 1).

(1) (a) Rao, M. R.; Faulkner, D. J. *J. Nat. Prod.* **2002**, *65*, 386. (b) Erickson, K. L.; Gustafson, K. R.; Pannell, L. K.; Beutler, J. A.; Boyd, M. R. *J. Nat. Prod.* **2002**, *65*, 1303.

(2) Barry, C. S.; Bushby, N.; Charmant, J. P. H.; Elsworth, J. D.; Harding, J. R.; Willis, C. L. *Chem. Commun.* **2005**, 5097.

(3) Further synthetic investigations on the originally proposed structure of clavosolide A include: (a) Chakraborty, T. K.; Reddy, V. R. *Tetrahedron Lett.* **2006**, *47*, 2099. (b) Yakambram, P.; Puranik, V. G.; Gurjar, M. K. *Tetrahedron Lett.* **2006**, *47*, 3781.

(4) (a) Son, J. B.; Kim, S. N.; Kim, N. Y.; Lee, D. H. *Org. Lett.* **2006**, *8*, 661 and 3411. (b) Smith, A. B., III; Simov, V. *Org. Lett.* **2006**, *8*, 3315. (c) Barry, C. S.; Elsworth, J. D.; Seden, P. T.; Bushby, N.; Harding, J. R.; Alder, R. W.; Willis, C. L. *Org. Lett.* **2006**, *8*, 3319. (d) Chakraborty, T. K.; Reddy, V. R.; Chattopadhyay, A. K. *Tetrahedron Lett.* **2006**, *47*, 7435.

(5) Son, J. B.; Hwang, M-H.; Lee, W.; Lee, D-H. *Org. Lett.* **2007**, *9*, 3897.

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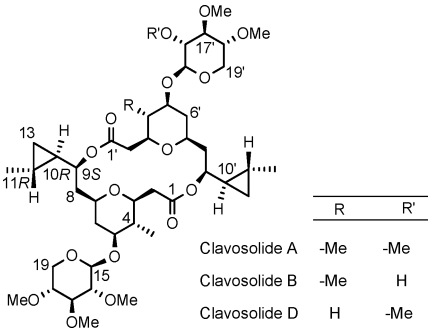
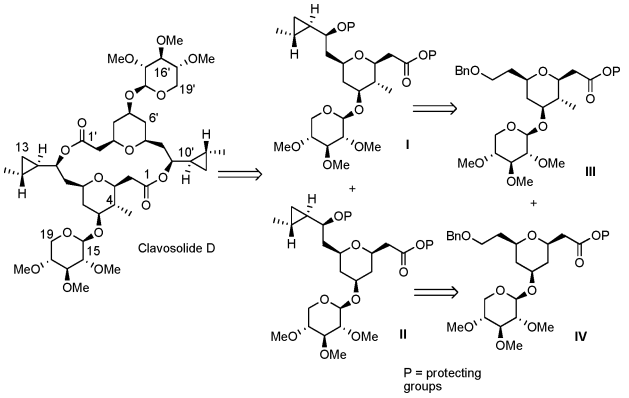


Figure 1. Clavosolides A, B, and D.

In the four reported total syntheses of clavosolide A,[4] the aglycone was assembled and the final step was glycosylation of the symmetrical parent diol, leading to a statistical mixture of [α,α]-, [*β*,*β*]-, and [α,*β*]-anomers resulting in yields in the range 12−21% of the required [*β*,*β*]-isomer. Thus, in designing the synthetic strategy to clavosolide D we aimed to introduce the permethylated D-xylose residues immediately following assembly of the two functionalized THPs which, in turn, were to be constructed using Prins cyclizations (Scheme 1). Further challenges to be addressed in the total

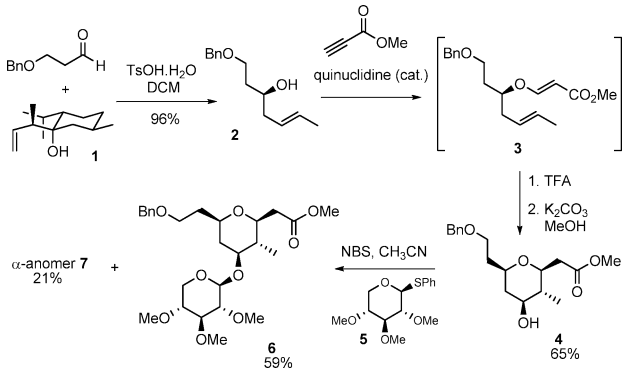
Scheme 1. Retrosynthesis of Clavosolide D



synthesis were the efficient stereocontrolled introduction of the required cyclopropyl side-chains and a stepwise macrolactonization using suitable orthogonal protection of intermediates **I** and **II**.

The synthesis began with construction of tetrasubstituted tetrahydropyran **4** using our previously described approach (Scheme 2).[4c] First (*S*)-homoallylic alcohol **2** was prepared in 94% yield by treatment of 3-benzyloxypropanal with Nokami's menthone derived crotyl transfer reagent **1**.[6] The pivotal Prins cyclization was achieved in a single-pot process by treatment of alcohol **2** first with methyl propiolate and catalytic quinuclidine to form enol ether **3** followed by addition of TFA giving, after hydrolysis of the trifluoroacetate, the required tetrahydropyran **4** in 65% overall yield from homoallylic alcohol **2** with the creation of three new

Scheme 2. Synthesis of Tetrahydropyran **6**



asymmetric centers. The next stage was glycosidation of alcohol **4** with a permethylated D-xylose derivative. Lee and co-workers used a Schmidt-type glycosidation in their synthesis of clavosolide B which gave a 1:1 mixture of anomers, and the required *β*-anomer was isolated in 47% yield.[5] We favored the use of a modification of the Nicolaou NBS glycosidation protocol[7] using a thioglycoside in the presence of acetonitrile to enhance *β*-selectivity.[8] It has been reported that benzylic methylene groups may be oxidized in the presence of NBS,[9] and indeed, initially this proved problematic. However, when the known[2] thioglycoside **5** was pretreated with 1 equiv of NBS at −40 °C in acetonitrile followed by addition of tetrahydropyran **4**, the required *β*-glycoside **6** was isolated in 59% yield, as well as the α-glycoside **7** (21% yield) with no observed benzylic oxidation.

With gram quantities of **6** in hand, we next turned our attention to the construction of the trisubstituted THP **IV** (Scheme 1) again using a Prins cyclization to construct the heterocycle. Brown allylation[10] of 3-benzyloxypropanal using (−)-DIPCl and allylmagnesium bromide gave (*S*)-homoallylic alcohol **8** in 93% yield and 85% ee (as determined via the Mosher's ester derivative). Interestingly, treatment of **8** with methyl propiolate and quinuclidine followed by addition of TFA gave, after mild hydrolysis, a 4:1 mixture of the required trisubstituted THP **10** and the epimer **11**. This reduced stereocontrol in the formation of the trisubstituted THP compared with the tetrasubstituted ring **4**, has precedent in the work of Hart and Bennett[11] who reported that a TFA

(6) (a) Nokami, J.; Nomiyama, K.; Shafi, S. M.; Kataoka, K. *Org. Lett.* **2004**, *6*, 1261. (b) Nokami, J.; Ohga, M.; Nakamoto, H.; Matsubara, T.; Hussain, I.; Kataoka, K. *J. Am. Chem. Soc.* **2001**, *123*, 9168.

(7) Nicolaou, K. C.; Seitz, S. P.; Papahatjis, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 2430.

(8) Ratcliffe, A. J.; Fraser-Reid, B. *J. Chem. Soc., Perkin Trans. 1* **1990**, 747.

(9) Dakir, M.; Auhmani, A.; Itto, M. Y. A.; Mazoir, N.; Akssira, M.; Pierrot, M.; Benharref, A. *Synth. Commun.* **2004**, *34*, 2001.

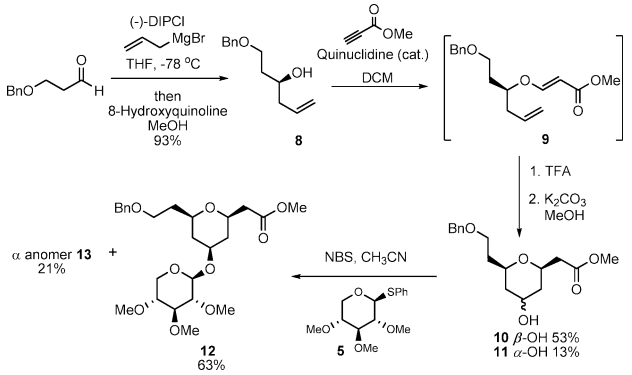
(10) (a) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092. (b) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401.

(11) (a) Hart, D. J.; Bennett, C. E. *Org. Lett.* **2003**, *5*, 1499. (b) Bennett, C. E.; Figueroa, R.; Hart, D. J.; Yang, D. *Heterocycles* **2006**, *70*, 119.

mediated cyclization of the analogous homoallylic enol ether with a benzyloxymethyl side-chain (rather than the benzyloxyethyl side-chain in **9**) resulted in a 1:1 mixture of epimeric alcohols accompanied by a bicyclic byproduct. These results implicate participation of the oxygen containing side-chain in formation of both the α-alcohol and the byproduct. NBS-mediated glycosidation of alcohol **10** with thioglycoside **5** under the optimized conditions described above gave the required pure trisubstituted tetrahydropyran **12** in 63% yield along with 21% of the α-anomer **13**.

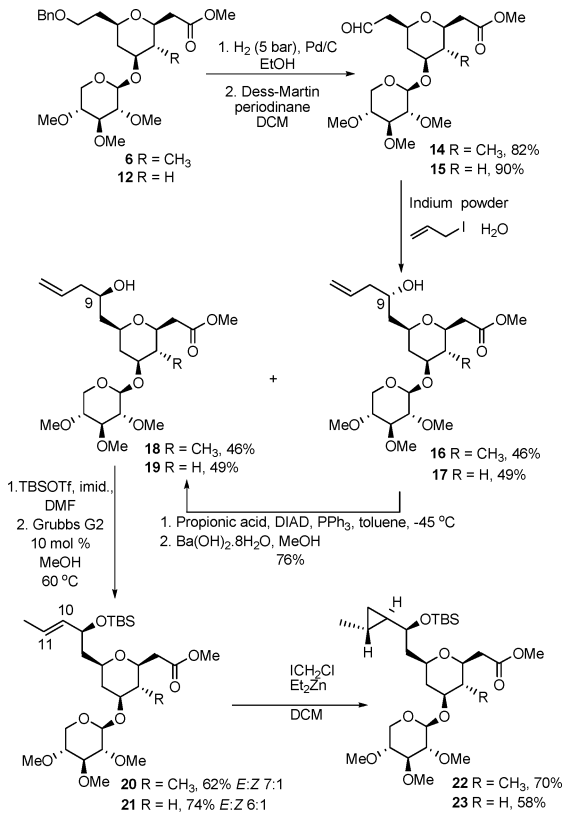
The next stage in the synthesis of clavosolide D was to elaborate the side-chains of the tetrahydropyrans to esters **I** and **II** possessing the anti cyclopropylcarbinyl moieties (Scheme 1). In our synthesis of clavosolide A[4c] the cyclopropyl side-chain of **I** was introduced via a nonselective Nozaki−Hiyama−Kishi propenylation[12] to give a 1:1 mixture of epimeric alcohols; recycling of the unwanted 9*R*-epimer to the required 9*S*-allylic alcohol proved problematic.[4c] Thus, ideally a more efficient method was required. Inspired by a recent report by Hannesian and co-workers[13] on the use of a thermally modified Grubbs second generation catalyst to effect the migration of terminal alkenes to an internal position, we investigated an allylation/isomerization/anti cyclopropanation strategy for the introduction of the required cyclopropyl side-chains (Scheme 4).

Scheme 3. Synthesis of Tetrahydropyran **12**



Facile conversion of tetrasubstituted tetrahydropyran **6** to aldehyde **14** was followed by a Brown allylation[10] of **14** which gave the required alcohol **18** as a single diastereomer but in only 18% yield. In contrast, an indium-mediated allylation[14] of **14** gave a 1:1 mixture of epimeric alcohols **16** and **18** in excellent yield which were readily separated by column chromatography. Neither homoallylic alcohol was crystalline, and so NMR analysis of the (*R*)-Mosher's ester derivatives[15] was employed to identify the correct diastereomer to carry forward in the synthesis of clavosolide D. A

Scheme 4. Elaboration of the Side Chains



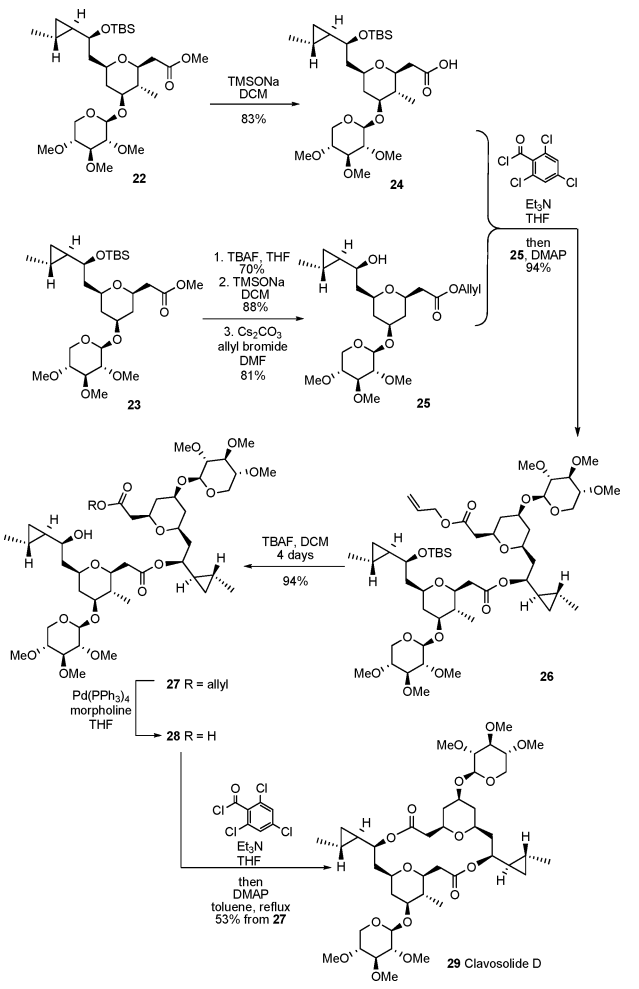
similar three-step protocol was used for conversion of trisubstituted tetrahydropyran **12** to homoallylic alcohol **19**. The unwanted epimeric alcohol **17** was inverted under Mitsunobu conditions[16] giving, after selective hydrolysis of the resultant ester, the required homoallylic alcohol **19** in 76% yield over the two steps.

Homoallylic alcohol **18** was further elaborated to the required fragment **22**, as shown in Scheme 4. First, the secondary alcohol **18** was protected as the TBS ether prior to isomerization of the alkene using Grubbs second generation catalyst in methanol[13] to give predominantly (*E*)-alkene **20** (δ_H 5.32, ddq, J = 15.5, 7.5, 1.4, 10H; δ_H 5.50, dq, J = 15.5, 6.4, 11H). Treatment of **20** with Et_2Zn and CH_2ICl[17] gave the required anti cyclopropyl derivative **22** as the major product. The second fragment **23**, assembled on a trisubstituted THP, was prepared in 43% overall yield from **19** using the same approach.

With the two key monomers **22** and **23** in hand, the final stages of the convergent synthesis of clavosolide D involved initial coupling of the two fragments followed by macrolactonization. We elected to couple acid **24** derived from the tetrasubstituted THP **22** with alcohol **25** from the trisubstituted THP **23**. We were concerned that in the penultimate step it may be problematic to selectively cleave the methyl ester to seco acid **28**. Interestingly, Paterson and co-workers had been faced with a similar hurdle in their

(12) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048. (b) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644.
(13) Hanessian, S.; Giroux, S.; Larsson, A. *Org. Lett.* **2006**, *8*, 5481.
(14) Chan, T. H.; Li, C. J.; Lee, M. C.; Wei, Z. Y. *Can. J. Chem.* **1994**, *72*, 1181.
(15) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
(16) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380.
(17) Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6974.

Scheme 5. Completing the Total Synthesis of (−)-Clavosolide D



elegant synthesis of swinholide A and, after exploring various conditions, had found that $Ba(OH)_2$ could be used to effect the required transformation in quantitative yield.[18] However, model studies on our system under a range of conditions, including with $Ba(OH)_2$, were not encouraging. Hence, we deemed it prudent to convert the methyl ester to an allyl ester which could be removed selectively under palladium mediated conditions.[5,19] Methyl ester **23** was hydrolyzed, and then the hydroxy acid converted to allyl ester **25** using Cs_2CO_3 and allyl bromide. Acid **24** was readily prepared by hydrolysis of methyl ester **22** using TMSONa. Acid **24** and alcohol **25** were cleanly coupled under modified Yamaguchi conditions,[20] and the required ester **26** isolated in 94% yield. Treatment of **26** with TBAF gave hydroxy ester **27**. Deprotection of the allyl ester of **27** then yielded hydroxy acid **28** which was immediately cyclized to give the required diolide **29** (*m*/*z* 865.4559 $[MNa]^+$) as a white crystalline solid. The X-ray structure confirms the overall connectivity and relative stereochemistry shown in Figure 2. Furthermore there was an excellent correlation of the ^1H and ^{13}C NMR data in both

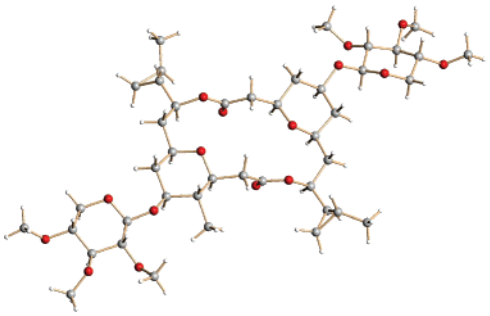


Figure 2. Molecular structure determined by X-ray diffraction. Water molecules and the secondary components of disordered atoms have been omitted for clarity.

$CDCl_3$ and C_6D_6 of synthetic clavosolide D with those of the natural product.

In conclusion, the first synthesis of (−)-clavosolide D has been achieved via stereoselective Prins cyclizations to create the two glycosidated tetrahydropyrans **6** and **12** in 37% and 31% overall yield, respectively, from 3-benzyloxypropanal. The cyclopropyl side-chains were introduced using an efficient allylation/isomerization/anti cyclopropanation sequence. Acid **24** and alcohol **25** were coupled then deprotection to seco acid **28** and cyclization furnished the target 16-membered ring diolide **29** in 43% yield over the four steps. These studies confirm the structure of clavosolide D as the unsymmetrical 16-membered diolide assembled on tetrasubstituted and trisubstituted THPs glycosylated by permethylated D-xylose moieties and further adorned with cyclopropyl side-chains with the (10*R*,10′*R*,11*R*,11′*R*) stereochemistry.

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Supporting Information Available: Preparation and characterization of new compounds described in the paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Paterson, I.; Yeung, K. S.; Ward, R. A.; Smith, J. D.; Cumming, J. G.; Lamboley, S. *Tetrahedron*, **1995**, *51*, 9467.

(19) Bavetsias, V.; Bisset, G. M. F.; Jarman, M. *Synth. Commun*. **1995**, *25*, 947.

(20) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.