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Studies directed towards the total synthesis of clavosolides: synthesis of an isomer of clavosolide A☆

Tushar Kanti Chakraborty* and Vakiti Ramkrishna Reddy

Indian Institute of Chemical Technology, Hyderabad 500 007, India

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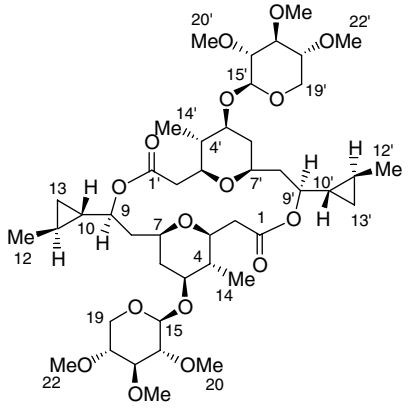
Abstract—The total synthesis of clavosolide A, employing a radical-mediated route to build its substituted tetrahydropyran unit, a Yamaguchi reaction to construct the diolide aglycon and the Schmidt method for the final glycosidation step, revealed that the reported structure is an isomer of the natural product.

The unusual, novel 16-membered diolides, clavosolides A–D were isolated from extracts of the marine sponge *Myriastra clavosa* collected in the Philippines.[1] The symmetric structure of the 16-membered core diolide ring in these molecules, with highly substituted tetrahydropyran units, disubstituted cyclopropyl rings and permethylated D-xylose moieties, makes them synthetically challenging targets. In this letter, we describe the total synthesis of the reported structure of clavosolide A (**1**). However, the spectral data of the synthetic product did not match those reported for the natural product. While we were attempting the synthesis of the correct diastereomer, Willis and co-workers reported their synthesis of the same isomer that we had prepared in our first attempt.[2] This prompted us to communicate our preliminary results at this stage.



1
(an isomer of clavosolide A)
[the reported structure (ref. 1)]

The salient feature of our synthesis is the application of a methodology that we developed recently for the synthesis of highly substituted tetrahydropyrans from a polyketide-based building block containing a 2-methyl-1,3-diol moiety,[3] which in turn was prepared by a Ti(III)-mediated opening of a trisubstituted epoxy alcohol.[4] The Yamaguchi method[5] was utilized to cyclodimerize the intermediate hydroxyl acid unit in a stepwise fashion to build the symmetric 16-membered dilactone framework and, for attaching the sugar units to the aglycon, the Schmidt glycosidation method[6] was employed.

Our synthesis started with the suitably protected intermediate **2** (Scheme 1), which was synthesized earlier by the Ti(III)-mediated opening of a trisubstituted 2,3-epoxy alcohol.[7] A three-step process—oxidation, olefination and reduction—transformed **2** into the allylic alcohol **3** in 82% overall yield. Sharpless epoxidation[8] of **3** with (−)-DIPT furnished an epoxy alcohol (de >96%) which was opened selectively using, Red-Al, at the 2-position to give the 1,3-diol **4** in 92% yield. Following the procedure reported by us earlier,[3] compound **4** was transformed into a tetrahydropyran in three steps—selective silylation of the primary hydroxyl, mesylation

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* Corresponding author. Tel.: +91 40 27193154; fax: +91 40 27193108/27160757; e-mail: chakraborty@iict.res.in

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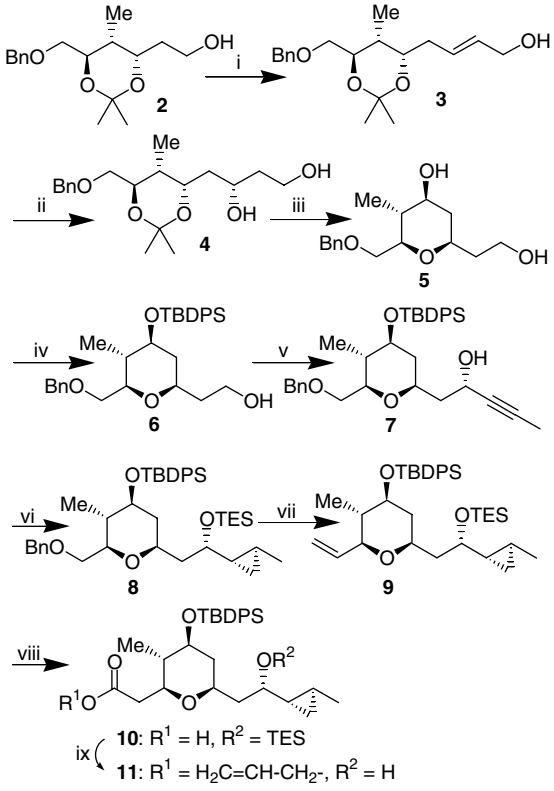
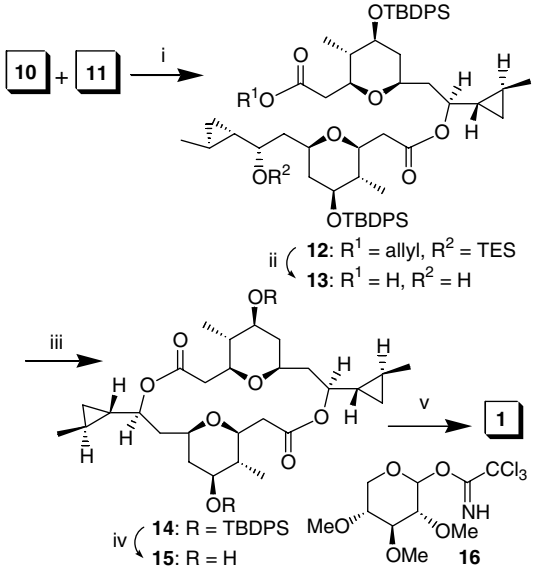


Scheme 1. Synthesis of the protected hydroxyl acids **10** and **11**. Reagents and conditions: (i) (a) $(COCl)_2$, DMSO, Et_3N, DCM, −78 to 0 °C, 1 h; (b) $Ph_3P{=}CH{-}CO_2Et$, DCM, rt, 4 h; (c) DIBAL-H, DCM, −78 °C, 20 min (82% from **2**); (ii) (a) D-(−)-DIPT, $Ti(O^iPr)_4$, TBHP, 4 Å MS, DCM, −20 °C, 3 h; (b) Red-Al, THF, −10 °C, 3 h (92% from **3**); (iii) (a) TBDPSCl, Et_3N, DMAP (cat), DMF, 0 °C to rt, 5 h; (b) MsCl, Et_3N, DMAP (cat), DCM, 0 °C to rt, 30 min; (c) CSA (cat), MeOH, rt, 48 h (75% from **4**); (iv) (a) TBDPSCl, imidazole, DMAP (cat), DMF, 0 °C to rt, 24 h; (b) TBAF, THF, 0 °C, 3 h; (v) (a) step (i)(a); (b) propyne, LDA, THF, −78 °C (44% from **5**); (vi) (a) Red-Al, Et_2O, 0 °C to rt, 2 h; (b) Et_2Zn, CH_2I_2, DCM, −20 to 0 °C, 4 h; (c) TESCl, Et_3N, DMAP, DCM, 0 °C to rt, 1 h (70% from **7**); (vii) (a) H_2, Pd–C, hexane, rt, 1 h; (b) SO_3–py, Et_3N, DCM, 0 °C to rt, 1 h; (c) $Ph_3P{=}CH_2$, Et_2O, 0 °C to rt, 1 h (62% from **8**); (viii) (a) BH_3–Me_2S, THF, 0 °C, 30 min, then H_2O_2, NaOH; (b) step (vii)(b); (c) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, 2-methyl-2-butene, *t*-BuOH, rt, 1 h (67% from **9**); (ix) (a) CH_2N_2, Et_2O, 0 °C, 10 min; (b) CSA, MeOH–DCM (1:4), 0 °C, 10 min; (c) allyl alcohol, K_2CO_3, rt, 1 h (70% from **10**).

of the secondary hydroxyl and acid-catalyzed deprotection of the acetonide with concomitant cycloetherification via a 6-*exo* S_N2 type ring closure—to furnish **5** in 75% overall yield. Disilylation of **5** followed by selective deprotection of the primary hydroxyl group furnished the intermediate **6**. Oxidation of **6** was followed by nucleophilic addition of the lithium propynilide, generated from propyne and LDA, to give the desired propargylic alcohol **7** with the 9*S*-stereochemistry as the major product in 44% overall yield in four steps from **5**.[9,10] Reduction of **7** with Red-Al provided the *E*-allylic alcohol which was subjected to a modified Simmons–Smith cyclopropanation reaction[11] to give, selectively, the *syn* product (de >96%). Finally silylation of the hydroxyl group furnished the protected intermediate **8** in 70% overall yield for the three steps. The stereochemistry of the major product was assigned based on earlier reports.[12] Deprotection of the benzyl ether of **8** was followed by a one-carbon extension by an oxidation–olefination sequence to furnish **9** in 62% yield. Hydroboration of **9** gave a primary alcohol which was oxidized to the acid **10** in two steps and 67% overall yield from **9**. Esterification of **10** with diazomethane and desilylation followed by conversion to an allyl ester furnished the hydroxy component **11**, to be coupled with the acid **10**, in 70% yield.

The final steps of the synthesis are shown in Scheme 2. Following the Yamaguchi procedure,[5] the mixed anhydride obtained by reacting **10** with 2,4,6-trichlorobenzoyl chloride was treated with the alcohol **11** in the presence of DMAP to furnish the fully protected linear dimer **12** in 80% yield. Acid-catalyzed desilylation of **12** was followed by Pd-catalyzed deallylation to give the hydroxyl acid **13** in 72% yield. The stage was now set to carry out the crucial macrolactonization reaction. Following a reverse-addition protocol, the mixed anhydride from **13** dissolved in toluene, after evaporation of THF under reduced pressure, was slowly added using a syringe pump over ca. 5 h to a solution of DMAP in toluene (final concentration 10^{-3} M) at 80 °C to furnish the desired dilactone **14** in 65% yield. A small amount of the cyclic tetramer (in ca. 10:1 ratio) was also formed which could easily be separated by standard silica gel column chromatography.[13] Desilylation of **14** using TBAF and a catalytic amount of acetic acid in THF gave the deprotected diolide aglycon **15** in 85% yield. Glycosidation of **15** using 2,3,4-tri-*O*-methyl-β-D-xylopyranosyl trichloroacetimidate **16**[14] furnished, as expected, a mixture of three products, which could be separated easily to give



Scheme 2. Synthesis of **1** (the reported structure of clavosolide A). Reagents and conditions: (i) **10**, 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, rt, 3 h, then **11**, DMAP, toluene, rt, 1 h (80%); (ii) (a) CSA, MeOH–DCM (1:4), 0 °C, 10 min; (b) $Pd(PPh_3)_4$, morpholine, THF, rt, 1 h (72% from **12**); (iii) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, rt, 3 h, the mixed anhydride then added to DMAP, toluene, 10^{-3} M, 80 °C, 5 h (65%); (iv) TBAF, AcOH (cat), THF, 0 °C to rt, 8 h (85%); (v) **16**, TMSOTf, DCM, 4 Å MS, 0 °C to rt, 2 h (21%).

the desired β,β-product **1** in 21% isolated yield along with the unwanted α,α (21%) and α,β (43%) isomers.

The ^{1}H and ^{13}C NMR spectra of synthetic **1**[15] did not match those reported for natural clavosolide A,[1] but were found to be identical with those reported for the recently synthesized diastereomer.[2] We believe that the stereochemistry of the C9 centre, or C10–C11 cyclopropyl segment, was probably wrongly assigned since the discrepancies in the spectra were mainly noticeable for the cyclopropyl ring protons. This assumption was further strengthened by ^{1}H NMR analysis of the model compounds, **17**–**20**.

Compound **17** was prepared in the same manner as **8**, except that the C9–OH was protected as an acetate. Swern oxidation of the intermediate with C9–OH was followed by diastereoselective reduction (K-selectride, THF, −78 °C)[16] to give exclusively the 9*R* isomer that on acylation furnished **18**. The minor 9*R* stereoisomer obtained during the synthesis of **7** was used to prepare **19** following the same procedure used for the synthesis of **17** and, once again, the same oxidation–reduction sequence described above was used to invert the C9-centre to furnish the *anti* product **20**. While the patterns of the chemical shifts of the cyclopropane ring protons of **17** were similar to those of the synthetic product **1** (Fig. 1), those of **18** were similar to those reported for the natural product,[1] albeit with different chemical shifts. The pattern of the chemical shifts of the cyclopropane ring protons of **19** did not match with those of either the natural product or **1**. The chemical shifts of the cyclopropane ring protons of **20** were similar to those of **19**. This tempts us to suggest that the natural product may have an *anti*-relationship between the C9–O and the cyclopropane ring, as shown in **18**, with (9*R*,10*S*,11*S*)- and (9′*R*,10′*S*,11′*S*)-configurations. Efforts are now in progress to synthesize the correct isomer of the natural product to assign its absolute stereochemistry unambiguously.

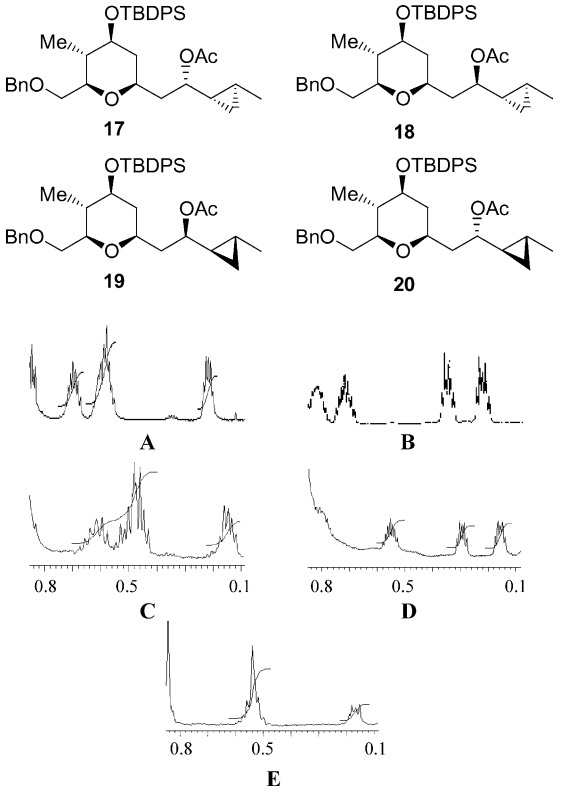


Figure 1. Sections of the ^{1}H NMR spectra in $CDCl_3$ (0.85–0.08 ppm) showing the cyclopropane ring proton signals of **1** (A), natural clavosolide A (B, reprinted with permission from Ref. 1a, Copyright 2002, American Chemical Society), **17** (C), **18** (D) and **20** (E).

Acknowledgements

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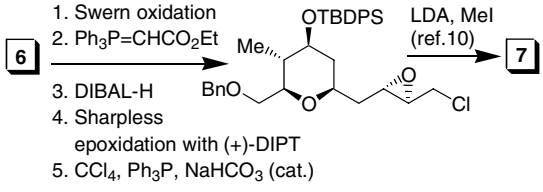
References and notes

1. (a) Rao, M. R.; Faulkner, D. J. *J. Nat. Prod.* **2002**, *65*, 386–388; (b) Erickson, K. L.; Gustafson, K. R.; Pannell, L. K.; Beutler, J. A.; Boyd, M. R. *J. Nat. Prod.* **2002**, *65*, 1303–1306.
2. Barry, C. S.; Bushby, N.; Charmant, J. P. H.; Elsworth, J. D.; Harding, J. R.; Willis, C. L. *Chem. Commun.* **2005**, 5097–5099.
3. Chakraborty, T. K.; Reddy, V. R.; Reddy, T. J. *Tetrahedron* **2003**, *59*, 8613–8622.
4. (a) Chakraborty, T. K.; Dutta, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1257–1259; (b) Chakraborty, T. K.; Das, S. *Tetrahedron Lett.* **2002**, *43*, 2313–2315.
5. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.
6. Schimdt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212–235.
7. Chakraborty, T. K.; Das, S. *J. Ind. Chem. Soc.* **1999**, *76*, 611–616.
8. (a) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1–299; (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.
9. The (9*S*)-stereochemistry of the major product **7** was confirmed by preparing the same product in the following manner.



10. Yadav, J. S.; Deshpande, P. K.; Sharma, G. V. M. *Tetrahedron* **1990**, *46*, 7033–7046.
11. (a) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1958**, *80*, 5323–5324; (b) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53–58.
12. (a) Charette, A. B.; Label, H. *J. Org. Chem.* **1995**, *60*, 2966–2967; (b) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977–1050.
13. (a) Under standard Yamaguchi reaction conditions (Ref. 5), in which DMAP was added to a solution of **13** and 2,4,6-trichlorobenzoyl chloride in toluene, the cyclic tetramer was formed as the major product; (b) The hydroxy acid, obtained by selective deprotection of the C9–OTES of **10**, under normal Yamaguchi reaction

conditions, gave a mixture of intramolecularly cyclized monomer, the diolide dimer **14** and also the triolide.

14. (a) Phelps, F. P.; Purves, C. B. *J. Chem. Soc.* **1929**, *51*, 2443–2449; (b) Chen, L.; Kong, F. *Carbohydr. Res.* **2002**, *337*, 2335–2341.
15. Selected physical data of **1**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.42 (2H, dt, *J* 9, 1, 9-H, 9′-H), 4.27 (2H, d, *J* 7.5, 15-H and 15′-H), 3.95 (2H, dd, *J* 11.7, 5.4, 19-H and 19′-H), 3.61 (6H, s, 21-H_3 and 21′-H_3), 3.58 (6H, s, 20-H_3 and 20′-H_3), 3.50–3.40 (4H, m, 3-H and 3′-H, 7-H and 7′-H), 3.46 (6H, s, 22-H_3 and 22′-H_3), 3.28–3.20 (4H, m, 18-H and 18′-H, 5-H and 5′-H), 3.10 (2H, t, *J* 8, 17-H and 17′-H), 3.09 (2H, dd, *J* 11.7, 8, 19-H′ and 19′-H′), 2.96 (2H, dd, *J* 9, 7.5, 16-H and 16′-H), 2.55 (2H, dd, *J* 17, 3.5, 2-H and 2′-H), 2.41 (2H, dd, *J* 17, 6.1, 2-H′ and 2′-H′), 2.05 (2H, dd, *J* 11.5, 5, 6-H and 6′-H), 1.92 (2H, dt, *J* 15.7, 9, 8-H and 8′-H), 1.69 (2H, ddd, *J* 15.7, 2.4, 1, 8-H′ and 8′-H′), 1.38 (2H, q, *J* 11.5, 6-H′ and 6′-H′), 1.37 (2H, m, 4-H and 4′-H), 1.00 (6H, d, *J* 6.1, 12-H_3 and 12′-H_3), 0.96 (6H, d, *J* 6.8, 14-H_3 and 14′-H_3), 0.70 (2H, tt, *J* 9, 4, 10-H and 10′-H), 0.63–0.53 (4H, m, 11-H and 11′-H, 13-H and 13′-H), 0.22 (2H, tt, *J* 8, 4, 13-H′ and 13′-H′); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.03, 105.47, 85.65, 83.92, 83.15, 79.50, 77.20, 77.00, 74.78, 63.27, 60.71, 60.70, 58.72, 42.62, 41.79, 40.80, 39.32, 24.95, 18.33, 12.63, 12.34, 10.97; HRMS (ESI) *m*/*z* 879.4761 $[M+Na]^+$, $C_{44}H_{72}O_{16}Na$ requires 879.4718.
16. Kazuta, Y.; Abe, H.; Yamamoto, T.; Matsuda, A.; Shuto, S. *J. Org. Chem.* **2003**, *68*, 3511–3521.