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ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 7435–7438

Total synthesis of (−)-clavosolide A☆

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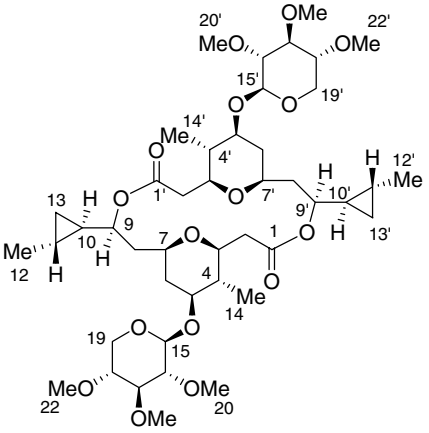
Received 5 July 2006; revised 11 August 2006; accepted 17 August 2006

Abstract—The total synthesis of (−)-clavosolide A is achieved employing a radical-mediated route to build the substituted tetrahydropyran unit, a Yamaguchi reaction to construct the diolide aglycon and the Schmidt method for the final glycosidation step.

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 xylose moieties, makes them synthetically challenging targets.[2–6] Syntheses of the originally assigned structure of clavosolide A by us,[2a] and earlier by Willis and co-workers,[2b] revealed that it was actually an isomer of the natural product and Willis and co-workers proposed a revised structure for clavosolide A based on NMR and molecular modelling.[2b] Subsequently, a total synthesis of the revised structure for clavosolide A was accomplished by Lee and co-workers.[3] Unfortunately, an error, which has been corrected recently by Lee and co-workers,[4] in the sign of the optical rotation led them mistakenly to conclude that the compound synthesized by them was the antipode of the natural product. This error has been revealed by Willis and co-workers,[5] as well as by Smith and Simov,[6] who have synthesized the revised structure and established that this is indeed the naturally occurring (−)-clavosolide A. The clavosolides represent yet another example of natural products whose structures were first wrongly assigned, but corrected later by chemical synthesis.[7] In this communication, we describe our synthesis of (−)-clavosolide A (**1**).

Our synthesis started with the tetrahydropyranyl chiral alcohol **2** (Scheme 1), which was synthesized earlier by us[2a] applying a methodology developed for the synthesis of highly substituted tetrahydropyrans by a Ti(III)-mediated opening of trisubstituted epoxy alcohols.[8]



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Oxidation of **2** was followed by the nucleophilic addition of the lithium propynilide, generated from propyne and LDA, to give propargylic alcohols **3** and **4** in an 85% overall yield with the former as the major product, in a 2:1 ratio.[2a] The isomers could be separated easily by standard silica gel column chromatography. Earlier we carried out the reduction of **3** with Red-Al to provide the corresponding *E*-allylic alcohol,[2a] which was subjected to a modified Simmons–Smith cyclopropanation reaction[9] giving the *syn* product selectively. However, the newly assigned structure of clavosolide A has an *anti*-relationship between the C9–O and the cyclopropane ring with (9*S*,10*R*,11*R*) and (9′*S*,10′*R*,11′*R*) configurations. This necessitated the use of the 9*R*-stereoisomer **4** to give the requisite (*R*,*R*)-cyclopropane

Keywords: Clavosolides; Clavosolide A; Epoxide opening; 2-Methyl-1,3-diol; Diolide.

☆ IICT Communication No. 060617.

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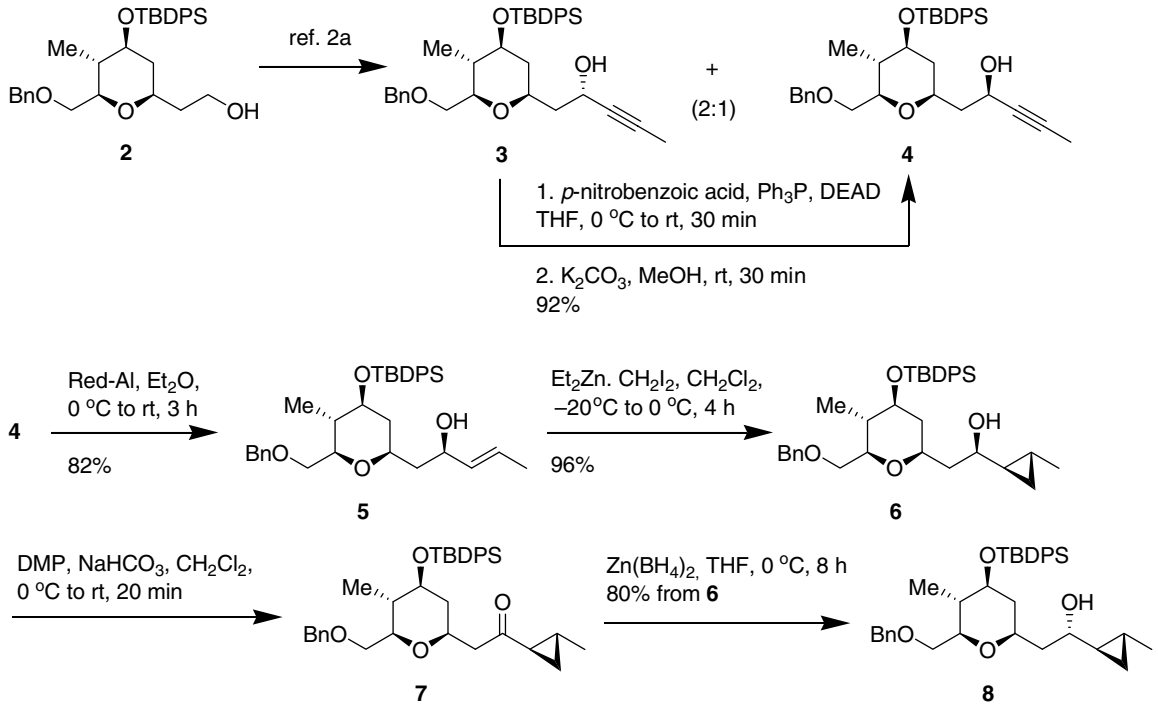
doi:10.1016/j.tetlet.2006.08.055



Scheme 1.

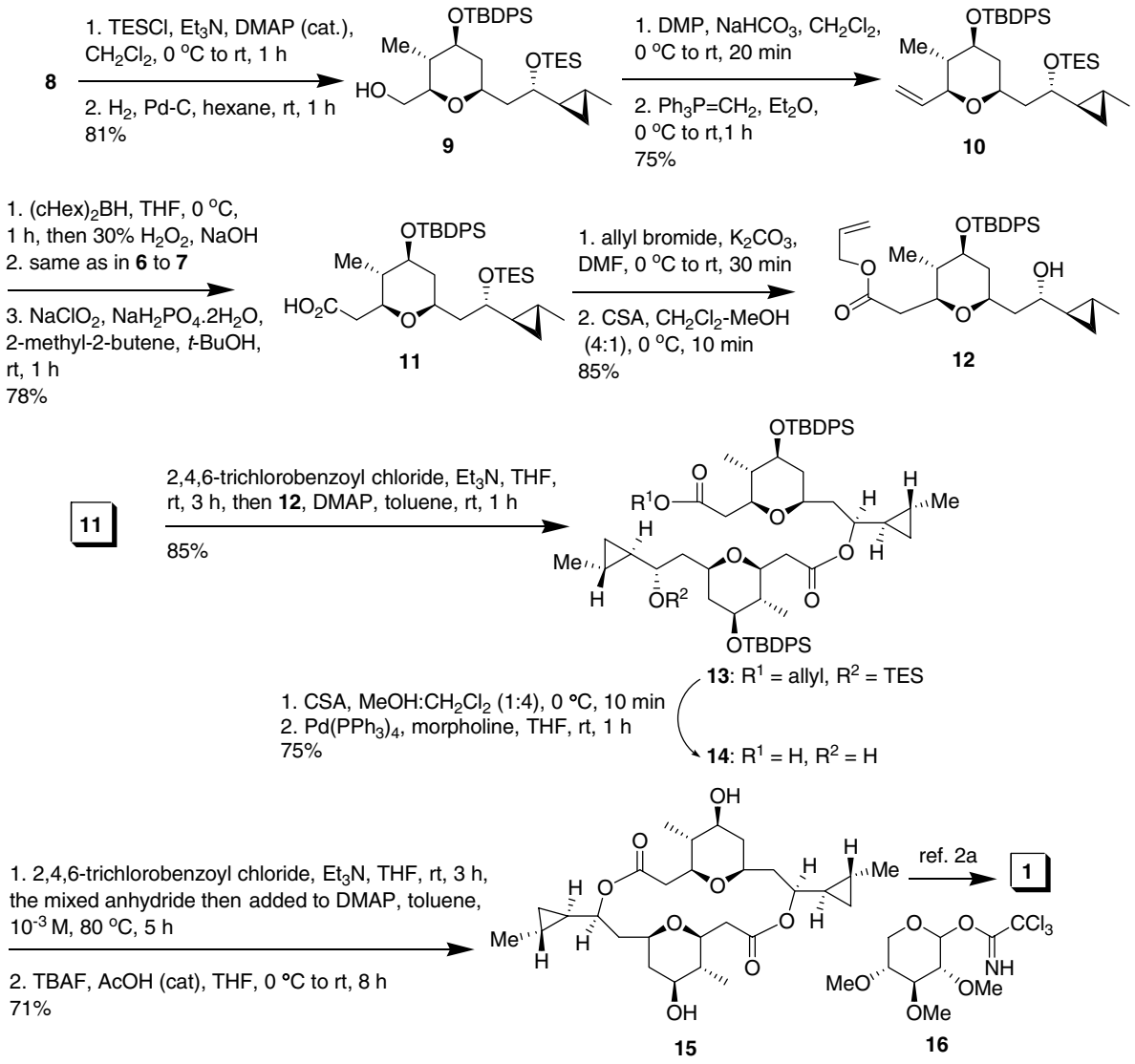
ring, since the cyclopropanation reaction is predominantly *syn*-selective.[10] It was envisaged that inversion of the C9–OH would re-establish the *S*-configuration in the product. In order to generate more of the requisite propargylic alcohol **4**, the major isomer **3** was subjected to Mitsunobu inversion[11] followed by benzoate deprotection under basic conditions to provide **4** in an 80% overall yield from **2**.

Red-Al reduction of **4** was followed by cyclopropanation of the resulting *E*-allylic alcohol **5** to give the expected *syn*-product **6** as the major isomer (de >96%) in a 79% yield from **4**. The stereochemistry of the major product was assigned based on earlier reports.[10] It now remained to invert the C9-stereocentre; however, Mitsunobu reaction failed to provide the inverted product. Therefore, an oxidation–reduction sequence was contemplated as there are many methods known for diastereoselective hydride reduction of cyclopropyl ketones.[12]

Oxidation of **6** with Dess–Martin periodinane (DMP)[13] provided the 9-keto intermediate **7**, which was subjected to hydride reduction using various reagents such as $Zn(BH_4)_2$, LAH, $LiBH_4$, $NaBH_4$, DIBAL-H, $NaBH_4$, $CeCl_3{\cdot}7H_2O$ and K-Selectride. The highest *anti*-selectivity was achieved with $Zn(BH_4)_2$ in THF at 0 °C, which gave the required 9*S*-isomer **8** as the major product in a 5:1 ratio and in an 80% overall yield. Surprisingly, K-Selectride, known to be an excellent *anti*-selective reducing reagent for such cyclopropyl ketones,[12] gave exclusively the *syn*-isomer here, which had misled us earlier to wrongly assign the structure of the resulting product while trying to predict the probable stereochemistry of the natural product.[2a]

The final steps of the synthesis are shown in Scheme 2. Silylation of the hydroxyl group of **8** furnished the TES-protected intermediate, which was subjected to benzyl ether deprotection to give the intermediate **9** in 81% yield. Next, a one-carbon extension by an oxidation–olefination sequence furnished **10** in 75% yield. Hydroboration of **10** gave, exclusively, a primary alcohol, which was oxidized to the corresponding acid **11** in two steps and 78% overall yield from **10**. Esterification of **11** with allyl bromide and K_2CO_3 followed by acid-catalyzed desilylation furnished the hydroxy component **12**, ready to be coupled with acid **11**, in 85% yield. Following the Yamaguchi procedure,[14] the mixed anhydride obtained by reacting **11** with 2,4,6-trichlorobenzoyl chloride was treated with alcohol **12** in the presence of DMAP to furnish the fully protected linear dimer **13** in 85% yield. Acid-catalyzed desilylation of **13** was followed by Pd-catalyzed deallylation to give hydroxy acid **14** in 75% yield.

The stage was now set to carry out the crucial macrolactonization reaction. Following a reverse-addition protocol, the mixed anhydride from **14** 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, which on desilylation using TBAF and a catalytic amount of acetic acid in THF gave the deprotected diolide aglycon **15** in 71% yield. A small amount of the cyclic tetramer (in ca. 10:1 ratio) was also formed during the macrolactonization step, which could easily be separated by standard silica gel column chromatography.[15] Schmidt glycosidation[16] of **15** with 2,3,4-tri-*O*-methyl-β-D-xylopyranosyl trichloroacetimidate **16**[17] following the



Scheme 2.

method reported earlier by us[2a] furnished the desired β,β-product **1** in a 21% isolated yield along with the unwanted α,α- (21%) and α,β- (43%) isomers. The ^{1}H and ^{13}C NMR spectra and optical rotation, $[\alpha]_D$ −42.4 (*c* 0.125, $CHCl_3$), of our synthetic product **1**[18] matched with those reported for the natural clavosolide A (literature $[\alpha]_D$ −48.5 (*c* 1, $CHCl_3$)).[1a]

Acknowledgement

V.R.R. and A.K.C. wish to thank CSIR, New Delhi, for research fellowships.

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15. (a) Under standard Yamaguchi reaction conditions (Ref. 14), in which DMAP was added to a solution of **14** 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 **11**, under normal Yamaguchi reaction conditions gave a mixture of intramolecularly cyclized monomer, the diolide dimer and also the triolide.
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18. Selected physical data of **1**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.42 (2H, dt, *J* 9, 1, 9-H, 9′-H), 4.26 (2H, d, *J* 7.5, 15-H and 15′-H), 3.95 (2H, dd, *J* 11.5, 5, 19-H and 19′-H), 3.61 (6H, s, 21-H_3 and 21′-H_3), 3.57 (6H, s, 20-H_3 and 20′-H_3), 3.48–3.43 (4H, m, 3-H and 3′-H, 7-H and 7′-H), 3.46 (6H, s, 22-H_3 and 22′-H_3), 3.27–3.21 (4H, m, 18-H and 18′-H, 5-H and 5′-H), 3.09 (2H, t, *J* 8, 17-H and 17′-H), 3.08 (2H, dd, *J* 11.5, 8, 19-H′ and 19′-H′), 2.95 (2H, t, *J* 8, 16-H and 16′-H), 2.54 (2H, dd, *J* 17, 3.5, 2-H and 2′-H), 2.41 (2H, dd, *J* 17, 6.5, 2-H′ and 2′-H′), 2.04 (2H, dd, *J* 11.5, 5, 6-H and 6′-H), 1.88 (2H, dt, *J* 15.7, 9, 8-H and 8′-H), 1.67 (2H, ddd, *J* 15.7, 2.4, 1, 8-H′ and 8′-H′), 1.37 (2H, q, *J* 11.5, 6-H′ and 6′-H′), 1.37 (2H, m, 4-H and 4′-H), 0.96 (12H, d, *J* 6.5, 12-H_3 and 12′-H_3, 14-H_3 and 14′-H_3), 0.83 (2H, m, 11-H and 11′-H), 0.72 (2H, tt, *J* 9, 5, 10-H and 10′-H), 0.33 (2H, tt, *J* 8, 5, 13-H and 13′-H), 0.22 (2H, tt, *J* 8, 5, 13-H′ and 13′-H′); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 171.07, 105.52, 85.52, 83.79, 83.18, 79.33, 77.16, 77.00, 74.81, 63.21, 60.84 (2C), 58.81, 42.49, 41.24, 40.66, 39.17, 24.70, 18.50, 12.60, 11.95, 10.88; HRMS (ESI) *m*/*z* 879.4687 $[M+Na]^+$, $C_{44}H_{72}O_{16}Na$ requires 879.4718.