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Towards the total synthesis of clavosolide A

Pedduri Yakambram,* Vedavati G. Puranik and Mukund K. Gurjar*

National Chemical Laboratory, Pune 411 008, India

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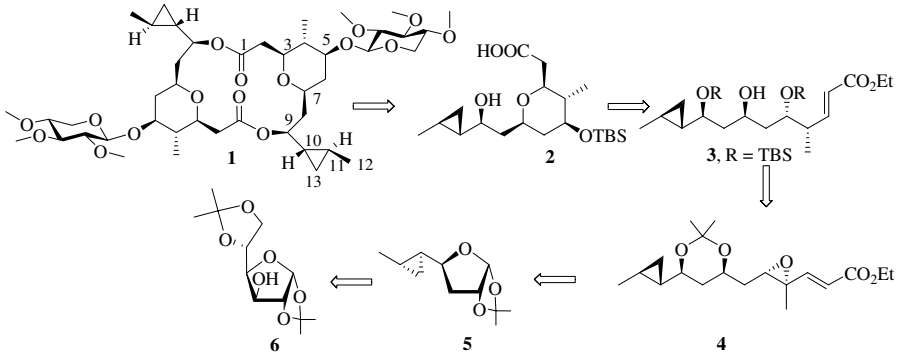
Abstract—The synthesis of the monomeric unit of clavosolide A from 1,2:5,6-di-*O*-isopropylidene-α-D-glucose is presented.

Clavosolides A–D were isolated from the marine sponge *Myriastra Clavosa* collected from Phillipines. Faulkner et al. and Gustafson et al. independently investigated the structures of these natural products and reported an unusual structural framework associated with them.[1] For instance, clavosolide A **1** is a symmetrical dimeric 16-membered cyclic macrolide and its monomeric unit consists of a densely functionalized tetrahydropyran ring glycosylated with permethylated D-xylose and substituted with a branched cyclopropyl residue. Due to the structural novelty and limited availability, the clavosolide class of compounds have become a source of inspiration for chemists to devise a synthetic strategy leading to a total synthesis. While we were at an advanced stage of our synthetic route towards clavosolide A, the stereochemistry of the natural product came under scrutiny from the groups of Willis[2] and Lee.[3] It is pertinent to mention that the absolute stereochemical assignments of clavosolide A are 3*S*, 3′*S*, 4*R*, 4′*R*, 5*S*, 5′*S*, 7*S*, 7′*S*, 9*S*, 9′*S*, 10*R*, 10′*R*, 11*R*, 11′*R*. We describe herein the synthesis of the monomeric unit **2** of clavosolide A possessing the initially reported stereochemistry. Our retrosynthetic approach towards the seco acid **2** of clavosolide A **1** is outlined in Scheme 1.

1,2:5,6-Di-*O*-isopropylidene-α-D-glucose **6** was converted into the 3-deoxy derivative **7** by Barton–McCombie deoxygenation of the 3-hydroxyl group followed by selective acid hydrolysis of the 5,6-isopropylidene unit as reported.[4] Subsequent oxidative cleavage of the diol **7** followed by Wittig reaction with $Ph_3P{=}CHCH_3$ afforded predominantly the *cis*-alkene derivative **8a** as confirmed by the ^1H NMR spectrum (*cis*:*trans* 9:1). Alternatively, one-pot oxidative cleavage and Wittig–Horner reaction of the diol **7** in the presence of $NaIO_4$, triethyl phosphonoacetate and potassium carbonate in



Scheme 1. Retrosynthetic analysis.

Keywords: Clavosolide A; Diolide; Seco acid; Simmons–Smith cyclopropanation; Reductive oxirane opening.
* Corresponding authors. Tel.: +91 20 25902588; fax: +91 20 25893614 (M.K.G.); e-mail addresses: p.yakambram@ncl.res.in; mk.gurjar@ncl.res.in

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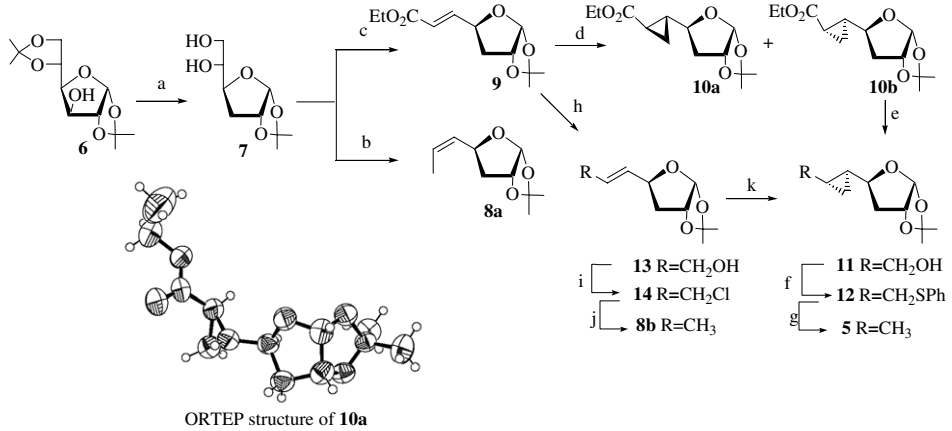
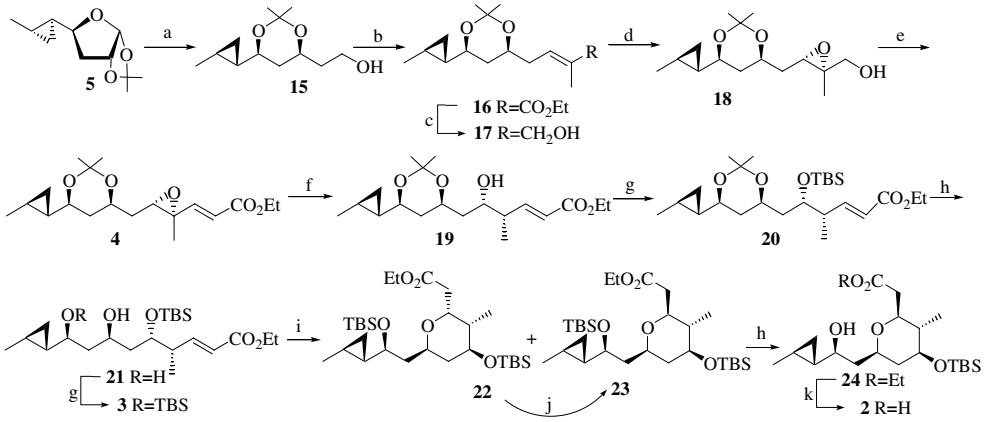
aqueous media gave exclusively the *trans* ester **9**.[5] The Corey–Chaykovsky cyclopropanation[6] of **9** in the presence of trimethylsulfoxonium methylide provided an easily separable diastereomeric mixture of **10a** and **10b** (1:1).[7] A single crystal X-ray crystallographic study of **10a**[8] established the stereochemistry of the cyclopropane ring and indirectly also supported the assigned structure of **10b** (Scheme 2).

Although we were successful in transforming **10b** into the desired product **5** by reduction of the ester followed by nucleophilic displacement with phenyl sulfide and desulfurization,[9] considering the poor selectivity in the Chaykovsky cyclopropanation, we instead chose to synthesise **8b** from **9** and then to cyclopropanate using the Simmons–Smith reaction. Reduction of the ester **9** using DIBAL-H at −78 °C, chlorination of the resulting allylic alcohol **13** and dehalogenation of the chloride **14** using $LiAlH_4$ afforded **8b** ($J_{olefinic} = 15.2$ Hz). Cyclopropanation of **8b** under Furukawa modified Simmons–Smith cyclopropanation conditions[10] using Et_2Zn–CH_2I_2 at −40 °C gave **5**[11] in good yield (Scheme 2).

Next, compound **5** underwent a sequence of simple and straightforward reactions including hydrolysis, one-carbon Wittig olefination, protection of the 1,3-diol and hydroboration–oxidation to furnish the intermediate **15**. Oxidation of **15** gave an aldehyde, which was immediately reacted with $PPh_3{=}CH(CH_3)CO_2Et$ to afford the corresponding (*E*)-α,β-unsaturated ester **16** whose reduction with DIBAL-H gave the allylic alcohol **17**. Sharpless asymmetric epoxidation of olefin **17** using (+)-DIPT as a chiral ligand at −20 °C gave the epoxy alcohol **18**[12] as a single diastereomer. Subsequent oxida-



Scheme 2. Reagents and conditions: (a) Ref. 4; (b) (i) $NaIO_4$ on silica, CH_2Cl_2, rt, 5 min, 86%; (ii) $CH_3CH_2PPh_3{}^+I^-$, *n*-BuLi, THF, 0 °C, 1 h, 62%; (c) $NaIO_4$, 5% aq $NaHCO_3$, triethyl phosphonoacetate, 6 M K_2CO_3, H_2O, 48 h, 98%; (d) trimethylsulfoxonium iodide, NaH, DMSO, 0 °C, 8 h, 39%; (e) 1 M DIBAL-H, toluene, −78 °C, 3 h, 93%; (f) PhSSPh, Bu_3P, THF, ↑↓, 5 h, 85%; (g) Raney Ni, ethanol, rt, 10 h, 87%; (h) 1 M DIBAL-H, toluene, −78 °C, 3 h, 90%; (i) PPh_3, CCl_4, ↑↓, 8 h, 78%; (j) $LiAlH_4$, THF, 0 °C, 1 h, 78%; (k) Et_2Zn (1.0 M in heptane), CH_2I_2, CH_2Cl_2, −40 °C, 48 h, 89%.



Scheme 3. Reagents and conditions: (a) (i) 0.4% aq H_2SO_4, 1,4-dioxane, 60 °C, 1 h; (ii) CH_3PPh_3I, *n*-BuLi, THF, 0 °C, 1 h; (iii) PTSA (cat.), 2,2-dimethoxypropane, CH_2Cl_2, rt, 0.5 h; (iv) $BH_3{\cdot}DMS$, THF, 0 °C, 3 N aq NaOH, 30% H_2O_2, 2 h, 56%; (b) (i) Dess–Martin periodinane, CH_2Cl_2, rt, 3 h; (ii) $Ph_3P{=}CH(CH_3)COOEt$, toluene, ↑↓, 0.5 h, 66%; (c) 1 M DIBAL-H, toluene, −78 °C, 4 h, 90%; (d) (+)-DIPT, $Ti(O^iPr)_4$, TBHP (3.3 M in toluene), CH_2Cl_2, −20 °C, 24 h, 88%; (e) (i) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, −78 °C, 1 h; (ii) $Ph_3P{=}CH_2COOEt$, CH_2Cl_2, rt, 1 h, 76%; (f) 5 mol % $Pd(PPh_3)_4$, $BH_3{:}Me_2NH$, AcOH, CH_2Cl_2, rt, 0.5 h, 66%; (g) TBSCl, imidazole, DMF, 0 °C, 1 h, **20**, 81%, **3**, 80% (based on recovered starting material); (h) PPTS, MeOH, rt, 1 h, **21**, 71%, **24**, 84% (based on recovered starting material); (i) LiOH, THF, 48 h, 60%; (j) *t*-BuOK, THF, 0 °C, 8 h; (k) LiOH, THF/MeOH/H_2O, 10:1:1, rt, 18 h, 60%.

tion and Wittig reaction with $Ph_3P{=}CH_2CO_2Et$ provided the key epoxy enoate **4**. The palladium(0) mediated regio- and stereoselective reduction[13] of the vinyl epoxide group in the presence of BH_3:Me_2NH–AcOH and catalytic $Pd(PPh_3)_4$ transformed **4** into the corresponding homoallylic alcohol **19**.[14] The corresponding TBS-ether derivative **20** was subjected to acetonide deprotection to give the diol **21** and the difference in reactivity of the two hydroxyl groups was exploited to protect selectively the cyclopropyl alcohol giving rise to the bis-TBS-ether derivative **3**. Intramolecular Michael addition was carried out in the presence of catalytic LiOH in THF to convert **3** into the tetrahydropyran derivatives **22** and **23** as a separable 5:2 diastereomeric mixture. The major isomer **22** was transformed into **23** by repeated treatment with *t*-BuOK (Scheme 3).

The structure of the requisite diastereomer **23** was established based on the NOE interactions of the tetrahydropyran ring protons. Treatment of **23** with catalytic PPTS in MeOH selectively removed one TBS group and provided **24**.[15] Finally, hydrolysis of the ester group of **24** with LiOH in THF–MeOH–H_2O gave the monomeric seco acid **2** of clavosolide A **1**. The spectroscopic data of **2** were in agreement with the assigned structure.[16]

In conclusion, the synthesis of the monomeric unit of clavosolide A, starting from D-glucose, was accomplished. We believe that the synthetic strategy described herein, is flexible to accommodate minor modifications, which could subsequently lead to the synthesis of the monomeric unit of **1** with revised stereochemistry.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.03.107.

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8. The crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as deposition No. CCDC-298070 for **10a**. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk].
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11. Spectral data of compound **5**: $[\alpha]_D^{25}$ +20.06 (*c* 2.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$); δ 0.28–0.35 (m, 1H), 0.55–0.60 (m, 2H), 0.68 (td, 1H, $J = 12.0, 5.5$ Hz), 1.05 (d, 3H, $J = 6.0$ Hz), 1.30, 1.45 (2s, 6H), 1.60 (ddd, 1H, $J = 13.3, 10.5, 4.5$ Hz), 2.12 (dd, 1H, $J = 13.3, 4.3$ Hz), 3.62 (ddd, 1H, $J = 10.5, 7.2, 4.3$ Hz), 4.70 (t, 1H, $J = 4.2$ Hz), 5.77 (d, 1H, $J = 3.8$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$); δ 9.93 (d), 11.63 (q), 18.39 (t), 22.25 (d), 25.99 (q), 26.56 (q), 38.77 (t), 80.45 (d), 81.67 (d), 105.10 (d), 110.53 (s); Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.65; H, 9.38.
12. Spectral data of compound **18**: $[\alpha]_D^{25}$ −4.23 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$); δ 0.28–0.38 (m, 1H), 0.40–0.65 (m, 3H), 1.04 (d, 3H, $J = 5.2$ Hz), 1.29, 1.39, 1.41 (3s, 9H), 1.50–1.90 (m, 4H), 3.08 (ddd, 1H, $J = 11.3, 7.5, 2.4$ Hz), 3.20 (dd, 1H, $J = 7.5, 4.2$ Hz), 3.50–3.75 (m, 2H), 3.92–4.10 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$); δ 9.61 (d), 11.62 (t), 14.28 (d), 18.41 (q), 19.59 (q), 24.71 (q), 30.02 (q), 35.32 (t), 37.10 (t), 57.12 (d), 60.08 (s), 65.37 (t), 66.99 (d), 73.39 (d), 98.46 (s); Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69. Found: C, 66.60; H, 9.80.
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14. The diastereomeric ratio (90:10) of compound **19** was determined by ^{1}H NMR spectroscopy.
15. Spectral data of compound **24**: $[\alpha]_D^{25}$ +12.19 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$); δ 0.05 (br s, 6H), 0.27 (dt, 1H, $J = 8.0, 4.0$ Hz), 0.50–0.60 (m, 3H), 0.90 (s, 9H), 0.92 (d, 3H, $J = 6.6$ Hz), 1.03 (d, 3H, $J = 5.5$ Hz), 1.25 (t, 3H, $J = 7.1$ Hz), 1.29–1.45 (m, 2H), 1.65 (dt, 1H, $J = 14.5, 2.5$ Hz), 1.75–1.83 (m, 2H), 2.39 (dd, 1H, $J = 14.5, 9.8$ Hz), 2.64 (dd, 1H, $J = 14.5, 2.5$ Hz), 3.12 (dt, 1H, $J = 8.0, 2.8$ Hz), 3.20 (br s, 1H), 3.35 (dt, 1H, $J = 10.0, 4.7$ Hz), 3.49 (dt, 1H, $J = 10.0, 2.0$ Hz), 3.58 (tt, 1H, $J = 10.6, 2.0$ Hz), 4.12–4.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$); δ −4.67, −3.92, 9.92, 11.51, 13.26, 14.18, 18.03, 18.51, 25.84, 26.31, 38.91, 42.10, 43.00, 43.63, 60.78, 73.59, 75.59, 76.25, 77.98, 171.61; Anal. Calcd for $C_{22}H_{42}O_5Si$: C, 63.72; H, 10.21. Found: C, 63.97; H, 10.56.
16. Spectral data of compound **2**: $[\alpha]_D^{25}$ +18.00 (*c* 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$); δ 0.05, 0.06 (2 s, 6H), 0.23–0.28 (m, 1H), 0.50–0.61 (m, 3H), 0.89 (s, 9H), 0.91 (d, 3H, $J = 6.6$ Hz), 1.01 (d, 3H, $J = 5.5$ Hz), 1.30–1.35 (m, 1H), 1.38–1.45 (m, 1H), 1.64–1.71 (m, 1H), 1.77–1.88 (m, 2H), 2.39 (dd, 1H, $J = 15.0, 10.0$ Hz), 2.66 (dd, 1H, $J = 15.0, 2.5$ Hz), 3.18 (br t, 1H, $J = 9.0$ Hz), 3.35 (dt, 1H, $J = 10.5, 5.0$ Hz), 3.49 (dt, 1H, $J = 10.0, 2.0$ Hz), 3.61 (br t, 1H, $J = 11.5$ Hz); Anal. Calcd for $C_{20}H_{38}O_5Si$: C, 62.14; H, 9.91. Found: C, 62.38; H, 10.01.