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Synthetic studies towards potent cytostatic macrolide rhizopodin: stereoselective synthesis of the C16-C28 fragment†

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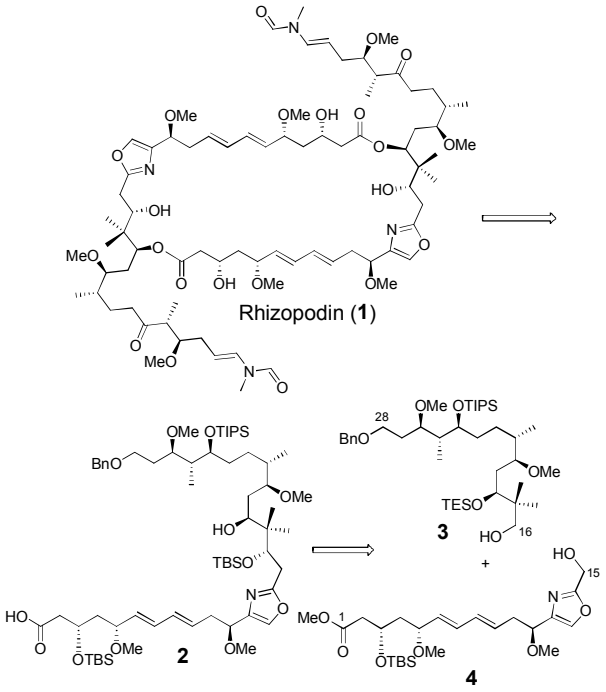
Abstract— A stereoselective synthesis of the C16-C28 fragment of cytostatic C_2-symmetric macrolide rhizopodin is described. Enantioselective addition of a chiral thiazolidinethione derived titanium enolate to acetal, Evans' aldol reaction, Hornerï Wadsworthï Emmons reaction and Mukaiyama aldol reaction were applied as key steps.

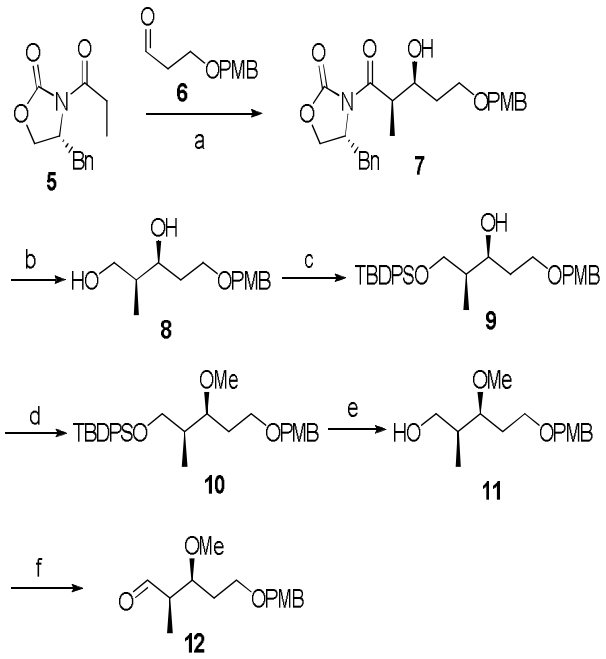
Keywords: Rhizopodin, cytostatic, actin polymerization, inhibitor, diolides, aldol reaction

Myxobacteria produce a wide variety of secondary metabolites with interesting biological activities and distinct structures.[1] Rhizopodin (**1**) is one such example, which was isolated from the culture broth of the myxobacterium, *Myxococcus stipitatus* in 1993 by Sasse *et al*.[2]



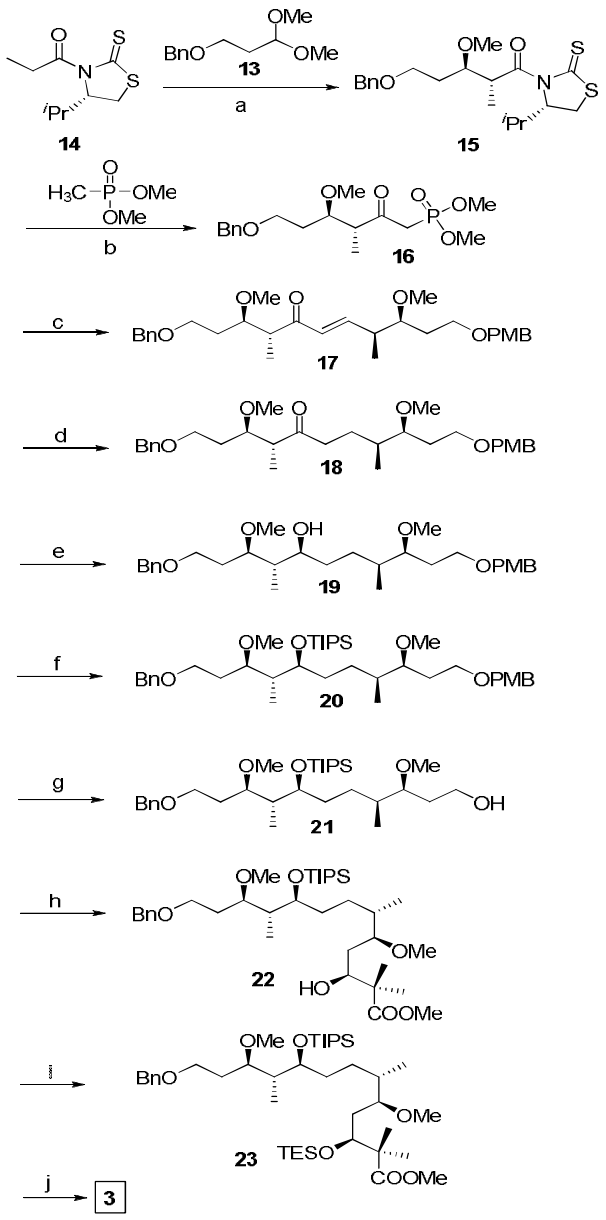
Scheme 1. Retrosynthetic analysis of Rhizopodin (**1**)

Initially it was proposed that rhizopodin was a 16-membered macrolide.[2] But later the structure was revised as a C_2-symmetric 38-membered dilactone bearing 18 stereogenic centers, two disubstituted oxazole rings, two conjugated diene systems and two enamide side chains by X-ray analysis of its complex with rabbit muscle G-actin and extensive NMR studies.[3-5]



Scheme 2. Synthesis of **12**: *Reagents and conditions:* a) $^{n}Bu_2BOTf$, DIPEA, CH_2Cl_2, 0 °C, 1 h, -78 °C, then **6**, 1.5 h at -78 °C, then 0 °C, 30 min, 90%; b) $NaBH_4$, THF:H_2O (5:1), 0 °C - rt, overnight, 76%; c) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, 0 °C - rt, overnight, 90%; d) NaHMDS, MeI, THF, 0 °C - rt, 4 h, 89%; e) TBAF, THF, 0 °C - rt, 7 h, 78%; f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to 0 °C, quant.

It showed potent cytostatic activity against a range of tumor cell lines in the low nanomolar range.[6] The cytostatic activity was attributed to the formation of a ternary complex with two G-actin molecules where the enamide side chains play a key role. It specifically binds to select sites of G-actin and disrupts the cytoskeleton there by inhibiting the actin polymerization.[5] Biological studies[7] further revealed that rhizopodin affects the dynamics of actin skeleton of macrophages there by showing significant changes in the phagocyte efficiency for yeast cells.



Scheme 3. Synthesis of **3**: *Reagents and conditions:* a) $TiCl_4$, CH_2Cl_2, 0 °C, 5 min, -78 °C, DIPEA, -40 °C, 2 h, $SnCl_4$, then **13**, 2 h, 82%; b) ^{n}BuLi, THF, -78 °C, 30 min then **15**, 30 min, 90%; c) $Ba(OH)_2.8H_2O$, THF, 30 min, then **12** (as a solution in 40:1 mixture of THF and H_2O), 30 min, rt, 77%; d) Pd-C/H_2, ^{n}BuNH$_2$, EtOAc, 15 min, quant.; e) (*R*)-B-Me-CBS, $BH_3{\cdot}SMe_2$, THF, -40 °C to 0 °C, 15h, 88%; f) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C - rt, 10 min, 85%; g) DDQ, $CHCl_3$:buffer (pH = 7, 20:1), rt, 20 min, 64%; h) i) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C - rt, 1 h, quant.; ii) Methyl trimethylsilyl dimethylketene acetal, $BF_3{\cdot}Et_2O$, CH_2Cl_2, -78 °C, 1 h, 64%; i) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C - rt, 10 min, 80%; j) DIBAL-H, CH_2Cl_2, -78 °C, 30 min, 79%.

Unique architecture coupled with interesting biological activities makes rhizopodin an attractive target for synthetic organic chemists.[8] In connection with our continuing interest in the development of C_2-symmetric peptidomimetics[9] and total synthesis of biologically active C_2-symmetric diolides,[10] we undertook the total synthesis of rhizopodin.

Scheme 1 discloses the retrosynthetic analysis of rhizopodin (**1**). Inspection of the structure of rhizopodin revealed that it could be synthesized by the macrolactonization/cyclodimerization of suitably protected compound **2** which in turn could be obtained from the two key intermediates **3** and **4**. Herein we report the synthesis of C16-C28 fragment (**3**) of the molecule.

Our synthesis commenced with the addition of boron enolate of (*R*)-4-benzyl-3-propionyloxazolidin-2-one (**5**) to the aldehyde **6,** which was prepared by the oxidation of mono-PMB protected 1,3-propanediol to furnish compound **7** in 90% yield (Scheme 2).[11] Reductive removal of the chiral auxiliary[12] using $NaBH_4$ gave a 1,3-dihydroxy compound **8** in 76% yield. Selective *O*-silylation of the primary hydroxyl group using TBDPSCl and Et_3N furnished the secondary alcohol **9,** which on etherification using NaHMDS and MeI afforded compound **10** in 81% yield over two steps. Desilylation with TBAF gave a primary alcohol, which on oxidation under Swern conditions[13] produced the aldehyde **12** in excellent yield.

Synthesis of the ketophosphonate **16** was started with the enantioselective addition[14a,b] of titanium enolate of (*S*)-1-(4-isopropyl-2-thioxothiazolidin-3-yl)propan-1-one (**14**) to the known[14c] dimethyl acetal **13** to furnish the compound **15** in 82% yield (Scheme 3). Displacement of thiazolidinethione auxiliary of compound **15** by the anion generated from dimethyl methylphosphonate[14d] using ^{n}BuLi resulted in the formation of *β*-keto phosphonate **16** in 90% yield. Keto phosphonate coupling between **16** and the aldehyde **12** using $Ba(OH)_2.8H_2O$ as a base[15] gave the *α,β*-unsaturated ketone **17** in 77% yield. Chemoselective hydrogenation[16] of the double bond provided compound **18** in quantitative yield. The keto functionality was then reduced under standard CBS conditions[17] to give **19** in 88% yield. Protection of the secondary hydroxyl group as its TIPS ether using TIPSOTf and 2,6-lutidine resulted in the formation of orthogonally protected compound **20** in 70% yield. Oxidative cleavage of PMB ether with DDQ[18] under buffered conditions gave the primary alcohol **21** in 64% yield. Oxidation of the primary alcohol using Dess-Martin periodinane[19] furnished a *β*-methoxy aldehyde in quantitative yield and was directly subjected to a 1,3-*anti* diastereofacial selective Mukaiyama aldol reaction[20] with methyl trimethylsilyl dimethylketene acetal to provide **22** as the major diasteromer in 64% yield (*dr* Ó8:1). The hydroxyl group was then protected as TES ether using TESOTf and 2,6-lutidine to get compound **23** in 80% yield. Reduction of the methyl ester using DIBAL-H delivered the C16-C28 fragment (**3**) of the rhizopodin[21] in an overall yield of 13.4% starting from **15** in a linear sequence of 10 steps.

In conclusion we have synthesized the C16-C28 fragment of rhizopodin by using enantioselective addition of a chiral thiazolidinethione derived titanium enolate to an acetal, Evansô aldol reaction, Hornerï Wadsworthï Emmons reaction and Mukaiyama aldol reaction as key steps. The efforts towards total synthesis of the molecule are underway in our laboratory and will be reported in due course.

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21. Analytical and spectral data of compound **3**: R_f = 0.3 (Silica gel, 10% ethyl acetate in petroleum ether); $[\alpha]_D^{24}$ = -17.7 (*c* 0.7, $CHCl_3$); IR (neat): ν_{max} 3473, 2950, 2870, 1461, 1379, 1090, 1009, 734, 674 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32-7.18 (m, 5H), 4.44 (ABq, 2H), 3.92 (m, 1H), 3.68 (dd, *J* = 7.55, 0.76 Hz, 1H), 3.56-3.41 (m, 3H), 3.29-3.12 (m, 9H), 1.96-1.72 (m, 3H), 1.64-1.05 (m, 7H), 0.99 (s, 21H), 0.96-0.85 (m, 12H), 0.84-0.71 (m, 9H), 0.65-0.52 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6, 128.3, 127.6, 127.5, 82.9, 79.6, 77.1, 73.5, 73.0, 70.4, 66.9, 57.6, 56.4, 42.4, 39.5, 34.1 33.3, 31.6, 31.0, 26.7, 22.6, 21.5, 18.3, 15.9, 12.9, 10.3, 7.1, 5.6; MS (ESI): m/z (%) 726 (80) $[M+H]^+$, 748 (25) $[M+Na]^+$; HRMS (ESI): calcd for $C_{41}H_{80}O_6NaSi_2$ $[M+Na]^+$ 747.5391, found 747.5394.