



Synthetic studies on reidispongiolide A, an actin-depolymerizing marine macrolide: synthesis of C11–C22 and C23–C35 segments

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ABSTRACT

The C11–C22 and C23–C35 segments **2** and **3** of reidispongiolide A (**1**), an actin-depolymerizing marine macrolide, were synthesized enantioselectively in 12 steps from (*R*)-glycidyl trityl ether and in 12 steps from chiral ketone **15**, respectively.

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Reidispongiolides and sphinxolides are cytotoxic 26-membered macrolides that interact with actin.¹ Reidispongiolide A (**1**) is a member of these macrolides that was isolated in 1994 by D'Auria et al. from the New Caledonian sponge *Reidispongia coerulea* (Fig. 1).² Actin-depolymerizing macrolides including reidispongolides and sphinxolides are of interest to natural products chemists and pharmacologists.³ Studies on stereostructure of reidispongolides and sphinxolides were based on detailed NMR analysis and degradation fragment synthesis,⁴ and the complete absolute stereostructure of reidispongiolide A was established by synchrotron X-ray analysis of actin-bound **1**.⁵ Synthetic studies on reidispongolide A have been carried out,⁴ and the first total synthesis of **1** was achieved by Paterson et al.⁶ Recently, synthesis of the tail analogs of reidispongiolide A and their effect on actin polymerization and depolymerization were reported.⁷ To investigate further structure-activity relationships and biological activities of reidispongolides, we began to study the synthesis of reidispongiolide A. We describe here the stereocontrolled synthesis of the C11–C22 and C23–C35 segments **2** and **3**.

The synthesis of C11–C22 segment **2** was carried out using a Horner–Wadsworth–Emmons reaction between C11–C16 phosphonate **4** and C17–C22 aldehyde **5** (Fig. 1). The synthesis of C23–C35 segment **3** was carried out by connecting C23–C30 vinyl iodide **6** and C31–C35 aldehyde **7** with Nozaki–Hiyama–Kishi reaction.⁸ The introduction of chiral centers to **4**, **5**, **6**, and **7** could be achieved by using the Evans aldol reaction,⁹ the Paterson aldol reaction,¹⁰ stereoselective reduction of β -hydroxy ketone,¹¹ and the Roush crotyl boration reaction¹² as the key steps.

The synthesis of C11–C22 segment **2** is shown in Scheme 1. The C11–C16 phosphonate **4** was synthesized from amide **9**¹³, which was prepared from imide **8**. Removal of the benzyl group of **9**

and Swern oxidation of the resultant hydroxyl group gave aldehyde **10**. Addition of lithiated dimethyl methylphosphonate¹⁴ followed by Dess–Martin oxidation provided C11–C16 phosphonate **4**. The synthesis of C17–C22 aldehyde **5** began with an alkylation reaction of vinyl magnesium bromide with an (*R*)-glycidyl trityl ether (Scheme 1). The hydroxyl group was methylated, and the olefin was cleaved to afford aldehyde **11**. The Evans aldol reaction between **8** and **11** (dr = 97:3), transamidation, and methylation of a hydroxyl group provided amide **12**, which was reduced with DIBAL to give C17–C22 aldehyde **5**. The Horner–Wadsworth–Emmons reaction between C11–C16 phosphonate **4** and C17–C22 aldehyde **5** afforded β -hydroxyketone **13** after desilylation. Stereoselective reduction of **13** with tetramethylammonium triacetoxymethylborohydride¹¹ provided an *anti*-1,3-diol (dr = 15:1), which was converted into C11–C22 segment **2**¹⁵ in 2 steps. The stereochemistry of the newly formed hydroxyl group at C15 was determined by the ¹³C chemical shifts of acetonide methyls (δ_{C} 25.3 and 26.4 ppm)¹⁶ of derived acetonide **14**.

The synthesis of C23–C35 segment **3** is shown in Scheme 2. The Paterson aldol reaction between ketone **15**¹⁷ and aldehyde **16a** afforded β -hydroxyketone **17a** stereoselectively (dr = 95:5). Stereoselective reduction of **17a** with tetramethylammonium triacetoxymethylborohydride gave an *anti*-1,3-diol (dr = 93:7)^{4c}, which was transformed into acetonide **18**. Its stereochemistry was determined as follows: based on the ¹³C chemical shifts of acetonide methyls (δ_{C} 23.4 and 25.3 ppm),¹⁶ the relative stereochemistry between C25 and C27 was determined to be *anti*. Proton–proton coupling constants ($J_{24,25}$ = 11.3 Hz and $J_{25,26}$ = 3.4 Hz) and NOE between H-25 and H-26 established the relative stereochemistry of C24, C25, and C26 to be *anti*-syn. We tried to differentiate between the two hydroxyl groups at C25 and C27. The samarium-catalyzed intramolecular Evans–Tishchenko reduction¹⁸ of **17b** followed by silylation provided benzoate **19** in good yield. However, removal of the benzoyl group in **19** under various conditions (DIBAL, LiAlH₄, MeLi, NaOH, etc.) failed. Thus, we stopped trying to differentiate between the two hydroxyl groups. Removal of the TBS

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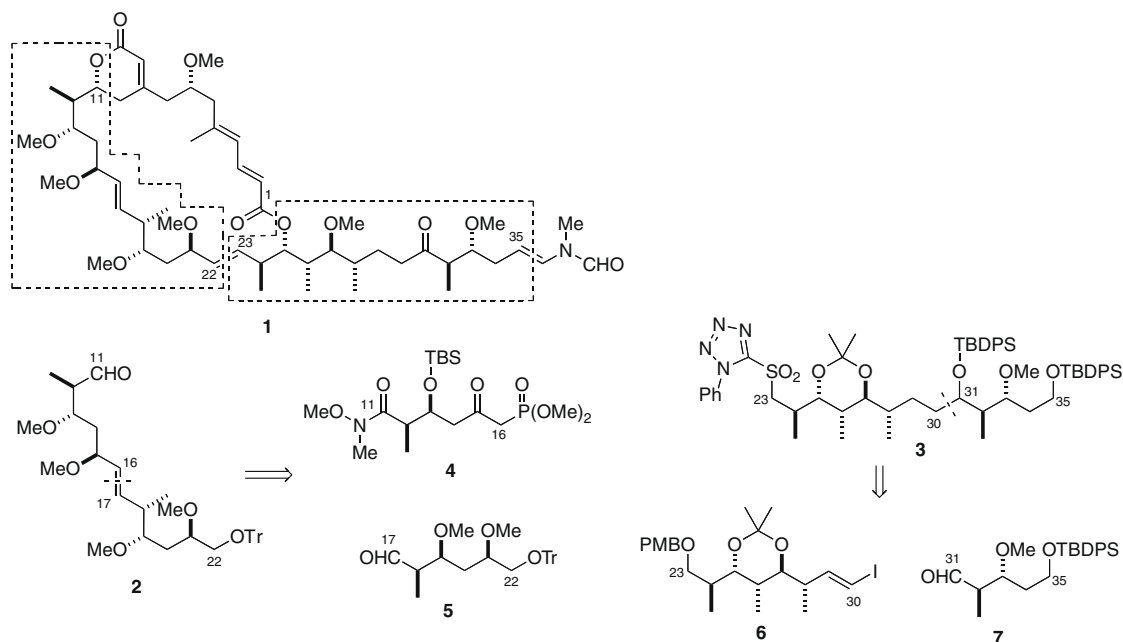


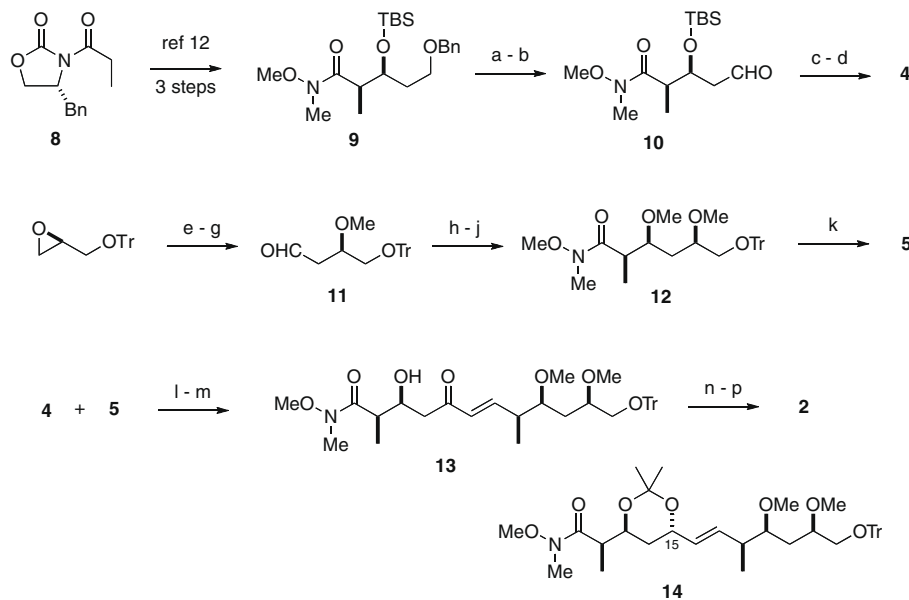
Figure 1. Structure of reidispongioliide A and retrosynthesis of the C11–C22 and C22–C35 segments.

protecting group of **18** followed by oxidation of the resultant alcohol with TEMPO and $\text{PhI}(\text{OAc})_2$ ¹⁹ afforded aldehyde, which was transformed into C23–C30 vinyl iodide **6** using the Takai procedure.²⁰

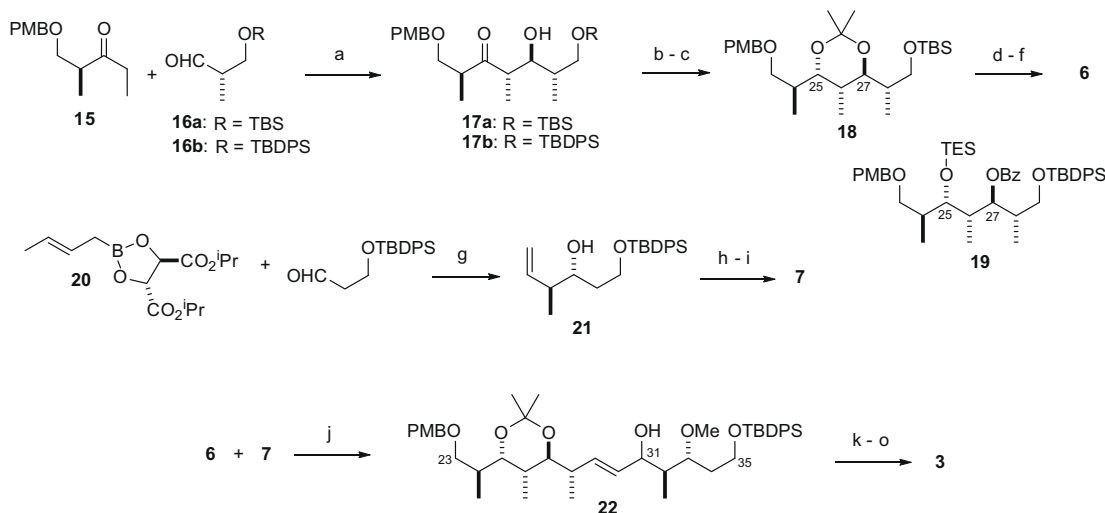
A Roush crotylboration reaction between boronate **20** and 3-*tert*-butyldiphenylsiloxypropanal afforded homoallylic alcohol **21**²¹ (dr 10:1) (Scheme 2). Methylation of a hydroxyl group of **21** followed by oxidative cleavage of the olefin provided C31–C35 aldehyde **7**. The Nozaki–Hiyama–Kishi reaction between **6** and **7** afforded a 2:1 diastereomeric mixture of allylic alcohols **22**. Since the hydroxyl group at C31 will be oxidized to ketone

in the later stage of the synthesis, alcohols **22** were used in the following reactions without the separation of diastereomers. Catalytic hydrogenation of a double bond in **22**, silylation of a hydroxyl group at C31, and removal of a PMB group gave a primary alcohol, the hydroxyl group of which was converted into a tetrazolyl sulfonyl group in two steps to afford C22–C35 segment **3**.²²

Thus, we have synthesized the C11–C22 and C23–C35 segments **2** and **3** of reidispongioliide A (**1**), an actin-depolymerizing marine macrolide, and further investigations toward the total synthesis of reidispongioliide A (**1**) are in progress.



Scheme 1. Synthesis of C11–C22 segment. Reagents and conditions: (a) H_2 , 10%Pd–C, EtOAc, rt, quant.; (b) DMSO, $(\text{COCl})_2$, Et_3N , CH_2Cl_2 , $-78^\circ\text{C} \rightarrow 0^\circ\text{C}$, 86%; (c) $^t\text{BuLi}$, $\text{MeP}(\text{O})(\text{OMe})_2$, THF, -78°C , 84%; (d) Dess–Martin periodinane, CH_2Cl_2 , rt, 87%; (e) $(\text{CH}_2=\text{CH})\text{MgBr}$, CuCN, THF, $-78^\circ\text{C} \rightarrow -20^\circ\text{C}$, 99%; (f) MeI, NaH, THF, rt, 89%; (g) OsO_4 , NMO, acetone– H_2O , rt; then NaIO_4 aq, rt, 90%; (h) **8**, Bu_2BOTf , Et_3N , CH_2Cl_2 , $-78^\circ\text{C} \rightarrow 0^\circ\text{C}$, quant.; (i) $\text{MeNH}(\text{OMe})\cdot\text{HCl}$, Me_3Al , THF–toluene, 0°C ; (j) MeI, NaH, THF, rt, 87% in two steps; (k) DIBAL, THF–hexane, -78°C , 95%; (l) $\text{Ba}(\text{OH})_2$, THF– H_2O , rt, 95%; (m) HF–pyridine, pyridine, THF, $0^\circ\text{C} \rightarrow \text{rt}$, quant.; (n) $\text{Me}_4\text{NBH}(\text{OAc})_3$, MeCN–AcOH, -20°C , 87%; (o) MeI, NaH, DMF, rt, quant.; (p) DIBAL, THF–hexane, -78°C , 95%.



Scheme 2. Synthesis of C23–C35 segment. Reagents and conditions: (a) (cHex)₂BCl, Et₃N, Et₂O, –78 °C → –20 °C; (b) Me₄NBH(OAc)₃, AcOH, MeCN, –25 °C; (c) (MeO)₂CMe₂, PPTS, acetone, rt 87% in three steps; (d) Bu₄NF, THF, rt, quant; (e) TEMPO, PhI(OAc)₂, CH₂Cl₂, rt, 90%; (f) CrCl₂, CHI₃, THF, 0 °C, 82%; (g) MS 4 Å, toluene, –78 °C, 90%; (h) MeI, NaH, THF, rt, 88%; (i) OsO₄, NMO, acetone–H₂O rt, then NaIO₄ aq, rt, 93%; (j) CrCl₂, NiCl₂, DMSO, rt, 79%; (k) H₂, 10%Pd–C, EtOH, rt, 96%; (l) TBDPSCl, imidazole, DMAP, DMF, 60 °C; (m) DDQ, CH₂Cl₂–phosphate buffer (pH 7), rt, 71% in two steps; (n) 5-mercapto-1-phenyltetrazole, Bu₃P, DEAD, THF, rt, 86%; (o) H₂O₂, (NH₄)₆Mo₇O₂₄·4H₂O, EtOH, rt, 53%.

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- When *n*-BuLi was used as a base, the yield was ca. 60% and was not reproducible.
- Compound 2**: a colorless oil; [α]_D²⁰ –3.8 (c 0.01, CHCl₃); IR (CHCl₃) 2818, 1724, 1448, 1090 (br), 974 cm^{–1}; ¹H NMR (400 MHz, CDCl₃) δ 9.79 (s, 1H), 7.50–7.45 (m, 6H), 7.32–7.20 (m, 9H), 5.66 (dd, *J* = 15.6, 6.8 Hz, 1H), 5.25 (dd, *J* = 15.6, 7.8 Hz, 1H), 3.85 (dt, *J* = 6.8, 3.4 Hz, 1H), 3.67 (m, 1H), 3.40 (s, 3H), 3.42 (m, 1H), 3.37 (s, 3H), 3.27 (dd, *J* = 10.2, 3.4 Hz, 1H), 3.23 (s, 3H), 3.12 (s, 3H), 3.03 (dd, *J* = 10.2, 4.4 Hz, 1H), 2.95 (m, 1H), 2.54 (m, 1H), 2.45 (m, 1H), 1.76–1.44 (m, 4H), 1.05 (d, *J* = 7.3 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 204.4, 144.1, 136.0, 130.0, 128.7, 127.7, 126.9, 86.4, 81.6, 78.9, 78.2, 77.4, 58.3, 57.6, 56.9, 55.9, 50.0, 39.0, 38.2, 32.8, 15.3, 8.0; MS (ESI) *m/z* 589 (M+H)⁺, 611 (M+Na)⁺.
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- Compound 3** (a 2:1 diastereomeric mixture at C31): a colorless oil; IR (CHCl₃) 1463, 1343, 1224, 1108, 998, 761, 703 cm^{–1}; ¹H NMR (400 MHz, CDCl₃) (signals due to minor diastereomer in brackets) δ 7.76–7.56 (m, 13H), 7.45–7.26 (m, 12H), 4.18–4.02 (m, 1H), 3.85–3.71 (m, 3H), 3.50–3.20 (m, 4H), 3.14 (s, 1H), 3.07 [3.01] (s, 3H), 2.81 [2.96] (m, 1H), 2.37–2.24 (m, 1H), 1.92–1.75 (m, 2H), 1.75–1.40 (m, 7H), 1.18 [1.21] (s, 3H), 1.16 [1.20] (s, 3H), 1.06–1.03 (m, 18H), 1.01 [1.05] (d, *J* = 6.8 Hz, 3H), 0.87 [0.85] (d, *J* = 6.4 Hz, 3H), 0.65 [0.75] (d, *J* = 6.4 Hz, 3H), 0.58 [0.74] (d, *J* = 7.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 154.3, 136.1, 136.0, 135.9, 135.8, 135.6, 135.5, 135.5, 133.9, 133.1, 131.4, 120.6, 120.5, 129.6, 129.5, 129.5, 129.4, 129.3, 129.3, 127.6, 127.6, 127.4, 127.3, 127.2, 125.4, 100.6, 100.6, 78.6, 78.2, 73.2, 71.6, 60.4, 60.1, 59.1, 56.6, 56.5, 39.8, 37.4, 36.7, 34.3, 34.2, 33.3, 32.2, 29.1, 29.0, 27.2, 27.1, 27.0, 26.9, 25.4, 25.3, 23.1, 21.0, 19.6, 19.5, 19.2, 19.1, 15.3, 15.3, 15.3, 15.0, 14.2, 12.3, 12.1, 10.6, 9.2; MS (ESI) *m/z* 1059 (M+H)⁺, 1081 (M+Na)⁺.