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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.

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 reidispongiolides and sphinxolides are of interest to natural products chemists and pharmacologists.[3] Studies on stereostructure of reidispongiolides 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 reidispongiolide 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 reidispongiolides, 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 reaction[12] 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 methylphosphonate[14] 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 triacetoxyborohydride[11] 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 ^{13}C chemical shifts of acetonide methyls (d_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 triacetoxyborohydride 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 ^{13}C 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 reduction[18] of **17b** followed by silylation provided benzoate **19** in good yield. However, removal of the benzoyl group in **19** under various conditions (DIBAL, $LiAlH_4$, MeLi, NaOH, etc.) failed. Thus, we stopped trying to differentiate between the two hydroxyl groups. Removal of the TBS

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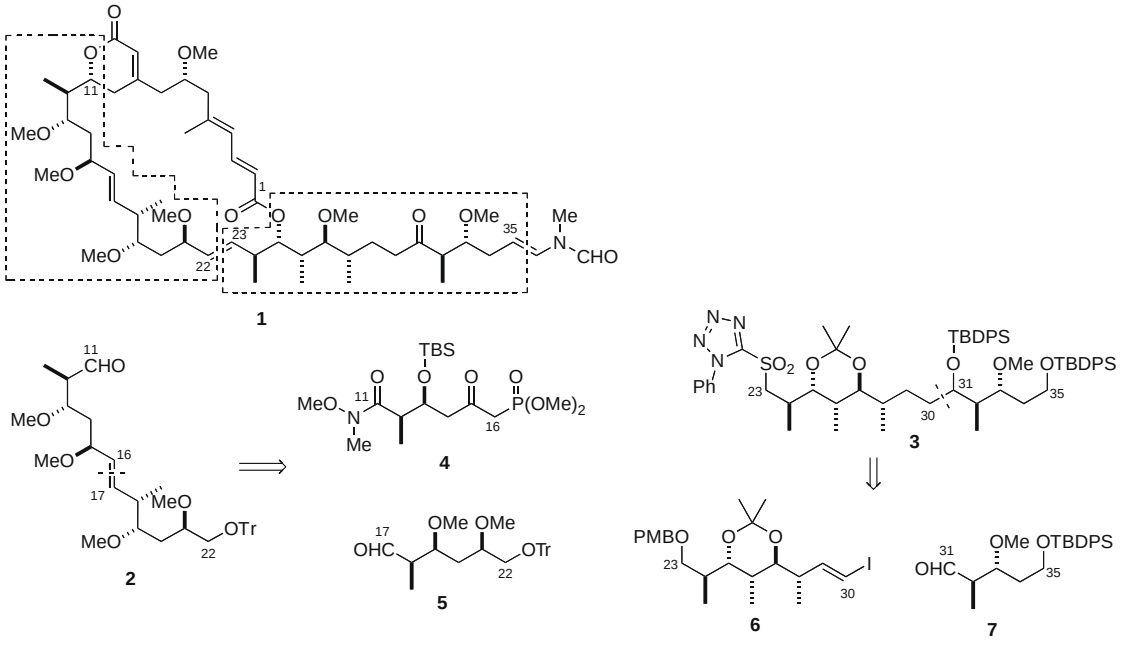
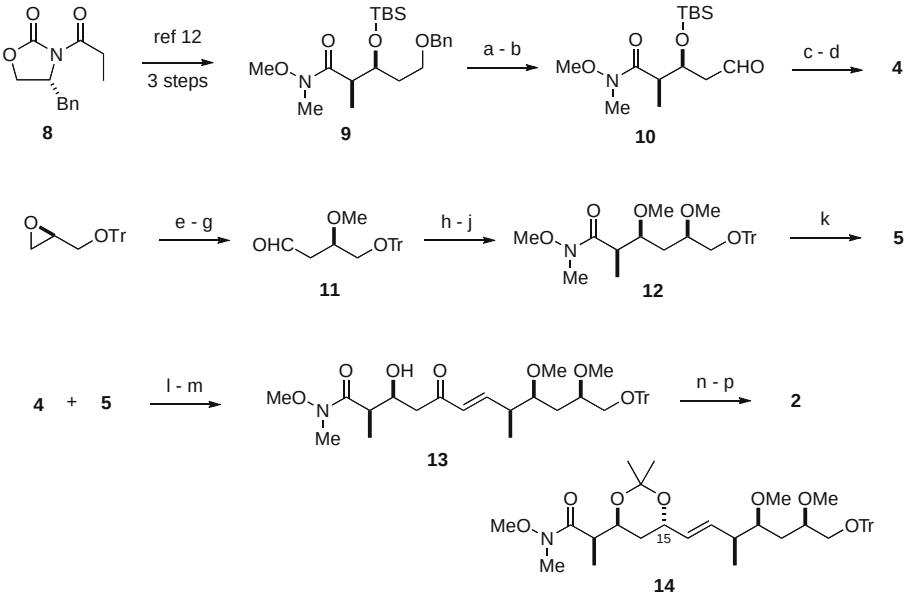


Figure 1. Structure of reidispongiolide A and retrosynthesis of the C11–C22 and C22–C35 segments.

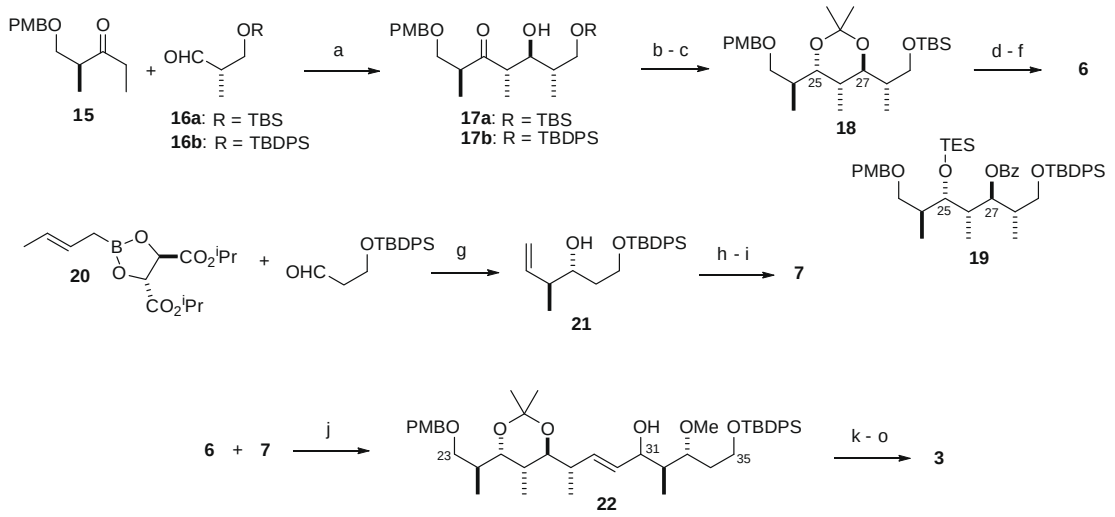
protecting group of **18** followed by oxidation of the resultant alcohol with TEMPO and $PhI(OAc)_2$[19] afforded aldehyde, which was transformed into C23–C30 vinyl iodide **6** using the Takai procedure.[20]

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 reidispongiolide A (**1**), an actin-depolymerizing marine macrolide, and further investigations toward the total synthesis of reidispongiolide 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, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C→0 °C, 86%; (c) ^{t}BuLi, $MeP(O)(OMe)_2$, THF, −78 °C, 84%; (d) Dess–Martin periodinane, CH_2Cl_2, rt, 87%; (e) $(CH_2{=}CH)MgBr$, CuCN, THF, −78 °C→−20 °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 °C→0 °C, quant.; (i) $MeNH(OMe)\cdot HCl$, Me_3Al, THF–toluene, 0 °C; (j) MeI, NaH, THF, rt, 87% in two steps; (k) DIBAL, THF–hexane, −78 °C, 95%; (l) $Ba(OH)_2$, THF–H_2O, rt, 95%, (m) HF·pyridine, pyridine, THF, 0 °C→rt, quant.; (n) $Me_4NBH(OAc)_3$, 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) $(cHex)_2BCl$, Et_3N, Et_2O, −78 °C→−20 °C; (b) $Me_4NBH(OAc)_3$, AcOH, MeCN, −25 °C; (c) $(MeO)_2CMe_2$, PPTS, acetone, rt 87% in three steps; (d) Bu_4NF, THF, rt, quant; (e) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, rt, 90%; (f) $CrCl_2$, CHI_3, THF, 0 °C, 82%; (g) MS 4 Å, toluene, −78 °C, 90%; (h) MeI, NaH, THF, rt, 88%; (i) OsO_4, NMO, acetone–H_2O rt, then $NaIO_4$ aq, rt, 93%; (j) $CrCl_2$, $NiCl_2$, DMSO, rt, 79%; (k) H_2, 10%Pd-C, EtOH, rt, 96%; (l) TBDPSCl, imidazole, DMAP, DMF, 60 °C; (m) DDQ, CH_2Cl_2–phosphate buffer (pH 7), rt, 71% in two steps; (n) 5-mercapto-1-phenyltetrazole, Bu_3P, DEAD, THF, rt, 86%; (o) H_2O_2, $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, EtOH, rt, 53%.

Acknowledgments

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14. When *n*-BuLi was used as a base, the yield was ca. 60% and was not reproducible.
15. *Compound* **2**: a colorless oil; $[\alpha]_D^{20}$ −3.8 (*c* 0.01, $CHCl_3$);IR ($CHCl_3$) 2818, 1724, 1448, 1090 (br), 974 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR ($CDCl_3$, 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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22. *Compound* **3** (a 2:1 diastereomeric mixture at C31): a colorless oil; IR ($CHCl_3$) 1463, 1343, 1224, 1108, 998, 761, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (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, 1 H), 2.37–2.24 (m, 1H), 1.92–1.75 (m, 2H), 1.75–1.40 (m, 7H), 1.18 [1.21] (s, 3 H), 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); ^{13}C NMR (100 MHz, $CDCl_3$) *d* 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 $(M+Na)^+$.