Natural Product Synthesis

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Total Synthesis of (+)-Exiguolide**

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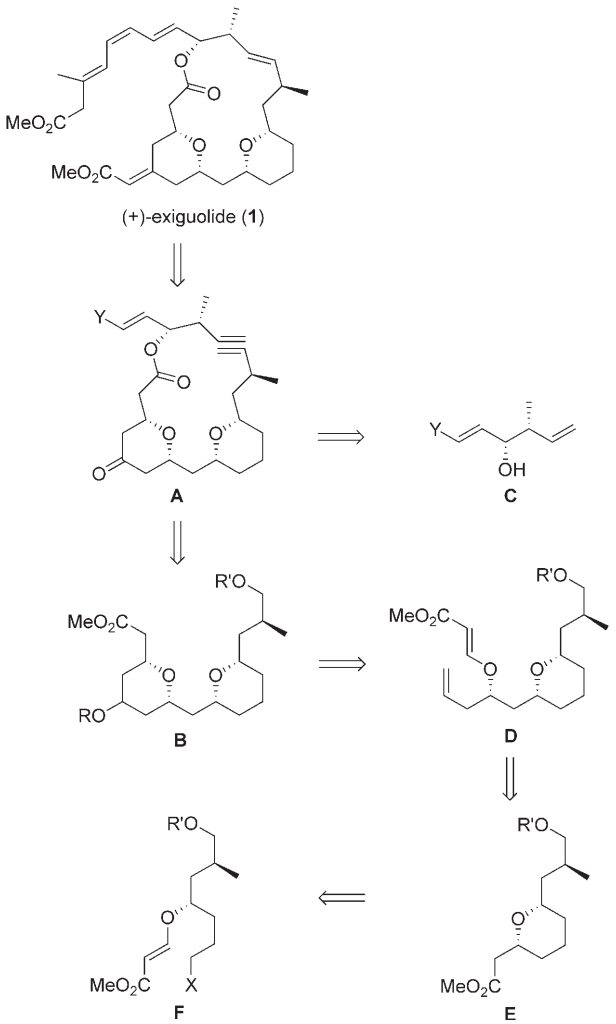
In memory of A. I. Scott

Exiguolide (**1**) is a unique 16-membered macrolide isolated from the marine sponge *Geodia exigua* Thiele (order Astrophorida, family Geodiidae).[1] It specifically inhibits fertilization of sea urchin (*Hemicentrotus pulcherrimus*) gametes but not embryogenesis of the fertilized egg. The macrolide structure incorporates two *cis*-2,6-disubstituted oxane rings, one of which carries an exocyclic enoate appendage reminiscent of bryostatins. The unique structural features and interesting biological activity of **1** has generated considerable interest in this compound, and herein we report our recent results for the total synthesis of **1**.

Scheme 1 shows the retrosynthetic analysis of **1**. Thus, the target would be synthesized through a ring-closing olefin metathesis reaction of the carboxylate ester **A** followed by construction of the triene side chain. Fragments **B** and **C** are the constituents of the ester **A**. Fragment **B** may be obtained from Prins cyclization[2] of the β-alkoxyacrylate **D**, which should be accessible from the oxane derivative **E**. Fragment **E** may in turn be obtained by radical cyclization[3] of the β-alkoxyacrylate **F**.

For synthesis of the **B** fragment, the secondary alcohol **3** was prepared from the known aldehyde **2**[4] through Brown allylation,[5] hydroboration–oxidation, and protection of the primary hydroxy group with TBS (Scheme 2). The reaction of **3** with methyl propiolate in the presence of *N*-methylmorpholine produced the corresponding β-alkoxyacrylate derivative, which was converted into the iodide **4** by cleavage of the TBS group and iodide substitution. Radical cyclization[3] of **4** in the presence of 1-ethylpiperidinium hypophosphite and triethylborane in ethanol[6] proceeded efficiently and selectively to yield, almost quantitatively, the oxane **5**. DIBAL reduction of **5** and a second Brown allylation led to a homoallylic secondary alcohol product, from which a second β-alkoxyacrylate derivative **6** was obtained by reaction with methyl propiolate. In the presence of trifluoroacetic acid, Prins cyclization[2] of **6** was successful and the products were hydrolyzed to a mixture (≈3:1) of alcohols, which was then converted into the ketone derivative **7** by Dess–Martin oxidation. There were signs of partial (≈7:1) racemization[7] in the Prins cyclization step. The keto ester **7** was converted into the keto acid **8** by dimethyl ketalization–hydrogenolysis, Dess–Martin oxidation, and rhodium-catalyzed methylenation[8] of the product aldehyde, followed by hydrolysis–deketalization and subsequent chromatographic separation.

The known aldehyde **9**[9] served as the starting material in the synthesis of the **C** fragment (Scheme 3). Brown crotylation[10] of **9** produced the allylic alcohol **10**, but a Sharpless kinetic resolution[11] step had to be included for improvement of the enantiomeric purity. For preparation of the final



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

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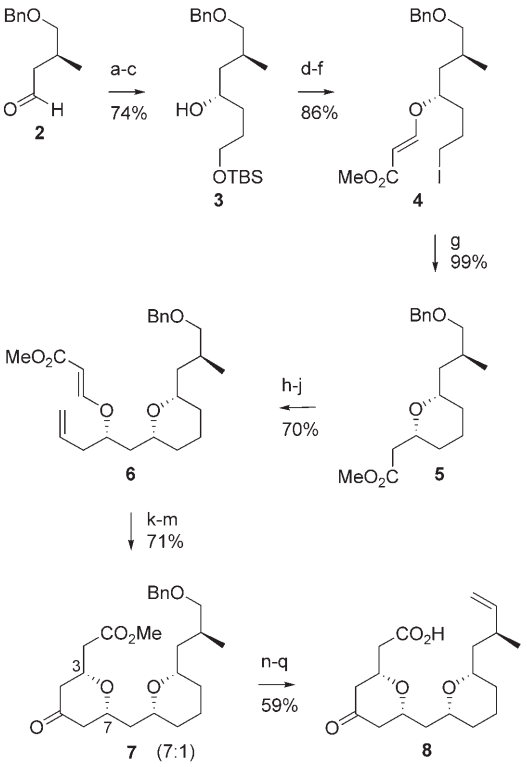
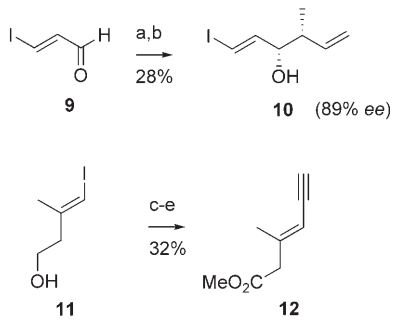
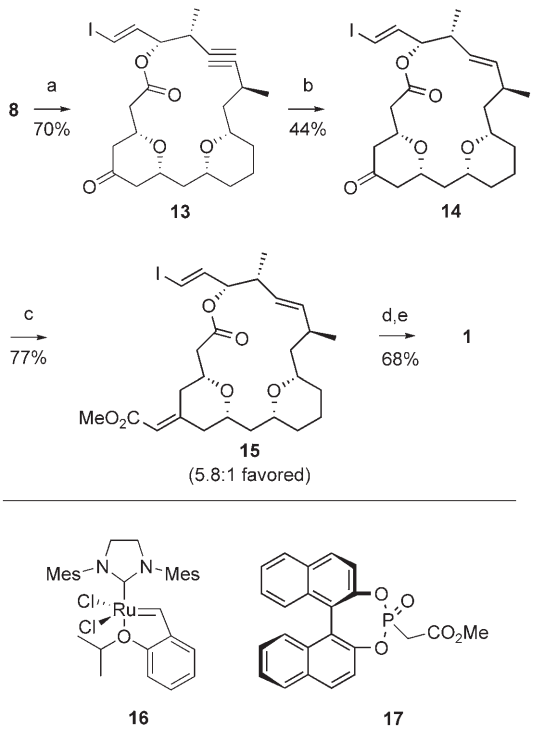


Scheme 2. Synthesis of the **B** fragment. Reagents and conditions: a) $CH_2CHCH_2B(^dIpc)_2$, THF, −80 °C; then H_2O_2, NaOH, 96%; b) $(sia)_2BH$, THF, 0 °C; then H_2O_2, NaOH, 85%; c) TBSCl, imidazole, DMAP, CH_2Cl_2, 91%; d) $CHCCO_2Me$, NMM, CH_2Cl_2, 94%; e) conc. HCl, MeOH, 100%; f) I_2, Ph_3P, imidazole, THF, 92%; g) H_3PO_2, 1-ethylpiperidine, Et_3B, EtOH, 99%; h) DIBAL, CH_2Cl_2, −78 °C, 88%; i) $CH_2CHCH_2B(^dIpc)_2$, Et_2O, −80 °C; then H_2O_2, NaOH, 85%; j) $CHCCO_2Me$, NMM, CH_2Cl_2, 94%; k) TFA, CH_2Cl_2, 0 °C→RT; l) K_2CO_3, MeOH, (81%, over 2 steps); m) DMP, CH_2Cl_2, 88%; n) cat. H_2SO_4, $HC(OMe)_3$/MeOH (4:1); then TEA; then H_2, Pd/C, 84%; o) DMP, CH_2Cl_2, 88%; p) $TMSCHN_2$, 2.5 mol% $[(Ph_3P)_3RhCl]$, Ph_3P, *i*PrOH, THF, 92%; q) LiOH, MeOH/H_2O (4:1); then 2.0 M HCl, 87%. Bn = benzyl, DIBAL = diisobutylaluminum hydride, DMAP = 4-dimethylaminopyridine, DMP = Dess–Martin periodinane, Ipc = isopinocampheyl (superscript *d* implies that it was prepared from (+)-α-pinene), NMM = *N*-methylmorpholine, sia = siamyl, TBS = *tert*-butyldimethylsilyl, TEA = triethylamine, TFA = trifluoroacetic acid, TMS = trimethylsilyl.



Scheme 3. Synthesis of the **C** fragment. Reagents and conditions: a) (*Z*)-$MeCHCHCH_2B(^dIpc)_2$ (2.0 equiv), THF, −78 °C; then H_2O_2, NaOH, 64%; b) $Ti(OiPr)_4$, D-(−)-DIPT, TBHP, 4-Å M.S., CH_2Cl_2, 44%; c) CHCMgCl, 5 mol% $[Pd(Ph_3P)_4]$, THF, 0 °C; then reflux, 69%; d) Jones reagent, acetone, 0 °C, 57%; e) CH_2N_2, Et_2O, 0 °C, 82%. DIPT = diisopropyl tartrate, Ipc = isopinocampheyl, M.S. = molecular sieves, TBHP = *tert*-butyl hydroperoxide.



Scheme 4. Synthesis of (+)-exiguolide (**1**). Reagents and conditions: a) **10**, DCC, DMAP, CH_2Cl_2 (0.1 M), 70%; b) **16** (30 mol%), benzene (5 mM), reflux, 44%; c) **17**, NaHMDS, THF, −78 °C; then **14**, −78→40 °C, 77%; d) **12**, $[Pd(Ph_3P)_4]$ (5 mol%), CuI, TEA, THF, 90%; e) H_2, Lindlar cat., quinoline, EtOAc, 75%. DCC = 1,3-dicyclohexylcarbodiimide, HMDS = hexamethyldisilazane.

fragment for the triene synthesis, the known vinyl iodide **11**[12] was treated with ethynyl magnesium chloride.[13] Subsequent oxidation and treatment with diazomethane gave the desired enyne **12**.

Esterification between keto acid **8** with alcohol **10** proceeded smoothly in the presence of dicyclohexylcarbodiimide and dimethylaminopyridine[14] to yield ester **13** (Scheme 4). The crucial intramolecular olefin metathesis reaction of **13** employed the second-generation Hoveyda–Grubbs catalyst **16**[15] and gave macrolide **14** in 44% yield. The correct exocyclic enoate isomer **15** was obtained as the major isomer (5.8:1) when **14** was treated with the sodium enolate of the chiral phosphonate **17**.[16,17] Sonogashira coupling[18] of **15** with enyne **12** proceeded smoothly, and partial hydrogenation of the product in the presence of Lindlar catalyst produced (+)-exiguolide (**1**), which proved to be the enantiomer of the natural macrolide[19].

In this synthesis, radical and Prins cyclization reactions of β-alkoxyacrylate substrates were judiciously employed for stereoselective construction of the oxane units in (+)-exiguolide (**1**). The absolute stereochemistry of the natural product was unambiguously determined through the total synthesis.

Experimental Section

Macrolide **14**: A solution of allylic alcohol **10** in CH_2Cl_2 (1.5 mL), DCC (44 mg, 0.213 mmol), and DMAP (5 mg, 0.041 mmol) were added successively to a solution of acid **8** (58 mg, 0.179 mmol) in CH_2Cl_2 (0.5 mL) at room temperature. After 30 min, the reaction mixture was diluted with hexanes (2 mL) and subsequent flash chromatography on silica gel (hexanes/EtOAc, 10:1) of the crude product gave ester **13** (69 mg, 70 %). $R_f = 0.38$ (hexanes/EtOAc, 4:1); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.48$ (dd, $J = 6.5$, 14.5 Hz, 1H), 6.41 (d, $J = 14.5$ Hz, 1H), 5.76–5.69 (m, 1H), 5.65–5.58 (m, 1H), 5.15 (t, $J = 6.5$ Hz, 1H), 5.12–5.07 (m, 2H), 4.98–4.93 (m, 2H), 4.09–4.04 (m, 1H), 3.90–3.84 (m, 1H), 3.37–3.32 (m, 1H), 3.27–3.23 (m, 1H), 2.66 and 2.54 (ABX, $J_{AB} = 15.3$ Hz, $J_{AX} = 7.8$ Hz, $J_{BX} = 4.8$ Hz, 2H), 2.50–2.23 (m, 4H), 2.01–1.95 (m, 1H), 1.82–1.79 (m, 1H), 1.62–1.42 (m, 6H), 1.28–1.13 (m, 4H), 1.04 (d, $J = 7.0$ Hz, 3H), 0.97 ppm (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 206.4$, 169.4, 144.4, 142.0, 138.4, 116.7, 113.6, 80.9, 79.0, 75.7, 74.3, 73.7, 73.4, 47.2, 47.1, 43.7, 42.7, 41.5, 41.2, 34.6, 32.1, 31.9, 23.8, 21.5, 15.4 ppm; IR (neat): $\tilde{\nu}_{max} =$ 2925, 1731, 1614, 1177 cm^{-1}; MS *m/z* (EI, relative intensity): 544($[M^+]$, 10), 417 (35), 323 (100), 307 (59), 255 (41), 237 (24), 195 (14), 157 (37), 135 (34), 93 (49), 79 (51), 55 (49); HRMS (EI): *m/z* calcd for $C_{25}H_{37}O_5I$ $[M^+]$: 544.1686; found: 544.1686; $[\alpha]_D^{25} = -14.2$ deg cm^3 g^{-1} dm^{-1} ($c = 0.004$ g cm^{-3}, $CHCl_3$).

The second-generation Hoveyda–Grubbs catalyst (24 mg, 0.038 mmol) was added to a solution of ester **13** (69 mg, 0.127 mmol) in benzene (25 mL), and the reaction mixture was heated under reflux. After 10 h, the reaction mixture was exposed to air for 2 h at room temperature. The solvent was then removed under reduced pressure and the crude product was purified by flash chromatography (hexanes/EtOAc, 15:1) to afford macrolide **14** (29 mg, 44 %). $R_f = 0.30$ (hexanes/EtOAc, 4:1); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.51$ (dd, $J = 6.5$, 14.5 Hz, 1H), 6.38 (d, $J = 14.5$ Hz, 1H), 5.45 (dd, $J = 9.5$, 5.0 Hz, 1H), 5.20 (dd, $J = 1.0$, 6.0 Hz, 1H), 5.11 (dd, $J = 9.5$, 15.0 Hz, 1H), 4.10–4.04 (m, 1H), 3.45 (t, $J = 10.8$ Hz, 1H), 3.31 (dd, $J = 10.3$, 8.8 Hz, 1H), 3.18 (t, $J = 11.3$ Hz, 1H), 2.63–2.55 (m, 2H), 2.54–2.47 (m, 1H), 2.45–2.31 (m, 5H), 1.85–1.77 (m, 2H), 1.63–1.39 (m, 5H), 1.29–1.08 (m, 3H), 1.06 (d, $J = 7.0$ Hz, 3H), 0.95 ppm (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 206.2$, 170.1, 142.8, 136.4, 131.8, 80.0, 79.8, 76.3, 75.2, 74.6, 73.3, 48.0, 46.8, 44.1, 43.3, 41.5, 41.3, 33.3, 32.6, 31.8, 24.1, 22.0, 14.5 ppm; IR (neat): $\tilde{\nu}_{max} = 2929$, 2865, 1739, 1612, 1372, 1213, 1175, 1090, 974, 862 cm^{-1}; MS *m/z* (CI, relative intensity): 561($[M^+ + 1]$, 13), 545 (5), 517 (100), 499 (12), 481 (4), 437 (7), 421 (6), 409 (11), 389 (83), 371 (14), 357 (6), 345 (8), 323 (4), 295 (4), 255 (28), 237 (8), 217 (6), 199 (4), 121 (11); HRMS (CI): calcd for $C_{23}H_{34}O_5I$ $[M^+ + 1]$: 517.1451; found: 517.1450; $[\alpha]_D^{25} = +15.5$ deg cm^3 g^{-1} dm^{-1} ($c = 0.008$ g cm^{-3}, $CHCl_3$).

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