Total Synthesis

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Enantioselective Synthesis of (−)-Exiguolide by Iterative Stereoselective Dioxinone-Directed Prins Cyclizations**

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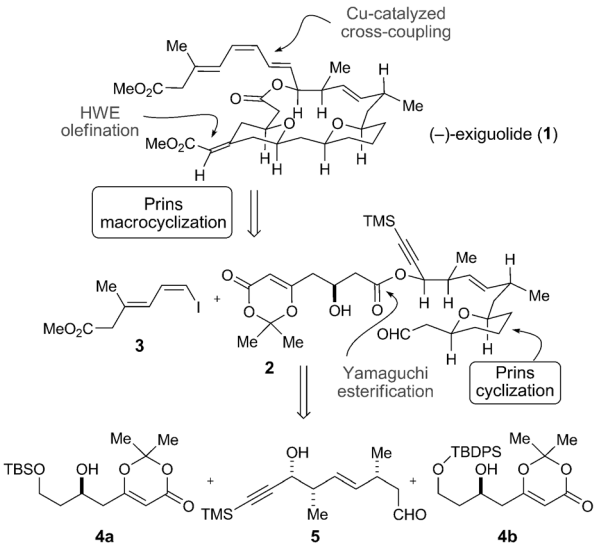
Exiguolide (**1**, Scheme 1) is an unusual natural product isolated in 2006 by Ohta, Ikegami, and co-workers from the marine sponge *Geodia exigua* Thiele.[1] This molecule inhibits the fertilization of sea urchin gametes (*H. pulcherrimus*) at a concentration of 20 μM but does not affect the development of the already fertilized eggs at higher concentrations (100 μM), thus indicating that it might possess relevant anticancer activity.[2] The similarity of compound **1** to the bryostatin family of natural products, which are known antitumor compounds, was proposed by Cossy[3] and also intrigued us. In particular, the bispyran architecture and the exocyclic enoate appended onto a tetrahydropyran ring are motifs common to both exiguolide and the bryostatins.[4]

The first synthesis of exiguolide was reported by Lee and co-workers, who established the absolute configuration of the natural product.[5a] The current synthetic approaches to this 16-membered macrolide tend to rely on linear macrolactonization strategies by esterification to establish the primary ring system.[5] While these polyketide/macrolide strategies are effective, we sought a complimentary approach by focusing on maximum convergency and flexibility for biological studies. Indeed, this target seemed ideal to deploy a unified strategy to construct the tetrahydropyran (THP) rings and the macrocycle in an efficient manner.[6] Given the inherent challenges involving macrocyclizations in many total synthesis campaigns with only slight modifications of related substrates,[7] this target also offered the opportunity to expand our Prins-type cyclization strategy[8] to larger ring sizes beyond those previously examined by us.[6c] Herein, we report the enantioselective synthesis of (−)-exiguolide by employing iterative and stereoselective dioxinone-based Prins reactions.

Our synthetic plan, detailed in Scheme 1, involved 1) a late-stage Cu^{I}-mediated cross-coupling to construct the triene side chain, 2) an olefination with an enantiomerically enriched Horner–Wadsworth–Emmons (HWE) reagent to install the exocyclic unsaturated ester, and 3) an intramolecular dioxinone Prins cyclization to simultaneously build the 16-membered macrocycle and generate one of the two THP rings. The linear precursor (**2**) would be assembled by an intermolecular Prins cyclization of a dioxinone (**4b**) and an aldehyde (**5**) to create the 2,6-*cis*-tetrahydropyran ring. An esterification to append a second dioxinone fragment (a carboxylic acid derived from **4a**) would install the entire carbon framework without the triene side chain and the exocyclic enoate. Notably, a key β-hydroxy dioxinone fragment would be employed twice to construct aldehyde **2**, thereby streamlining the synthesis and improving the overall efficiency.



Scheme 1. Retrosynthetic strategy.

Our synthesis commenced with a catalytic, asymmetric acyl halide/aldehyde cyclocondensation developed by Nelson et al.[9] of alkyne **6** and propionyl bromide **7** in the presence of Al^{III} catalyst **I** to provide the *cis*-substituted β lactone **8** (Scheme 2). The lactone was converted to the Weinreb amide **9** (72% yield over two steps), which facilitated the assessment of the diastereoselectivity (d.r. > 20:1) and enantioselectivity (90% *ee*) of the cyclocondensation process. The resulting

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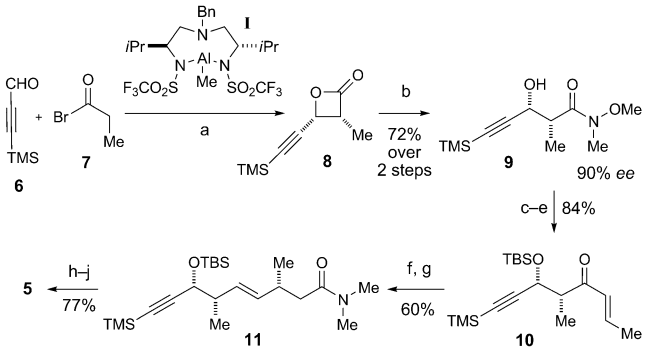
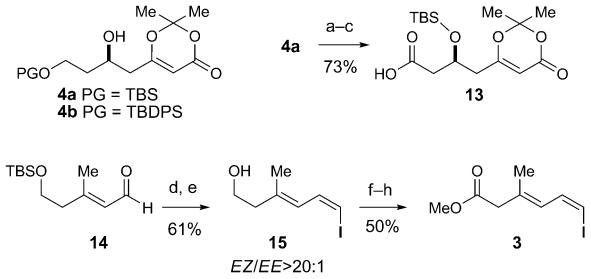
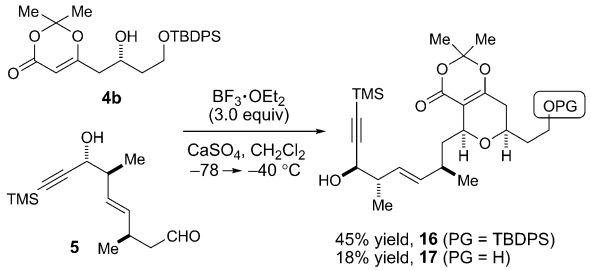


Scheme 2. Aldehyde fragment synthesis. a) iPr_2NEt, 10 mol% **I**, CH_2Cl_2, −50°C; b) MeONHMe·HCl, iPr_2NEt, CH_2Cl_2, 72% over 2 steps; c) TBSCl, imidazole, CH_2Cl_2, 89% yield; d) allylMgBr, diethyl ether, 0°C; e) iPr_2NEt, 94% over 2 steps; f) (*S*)-CBS catalyst (**12**), BH_3·OMe_2, THF, −15°C, 70% yield; g) $MeC(OMe)_2NMe_2$, xylenes, 140°C, 85% yield; h) $LiNH_2BH_3$, THF, 0°C, 93% yield; i) DMP, $NaHCO_3$, CH_2Cl_2, 99% yield; j) HCl (aq), THF, 84% yield. Bn = benzyl, DMP = Dess–Martin periodinane, (*S*)-CBS = (*S*)-(−)-2-methyl-CBS-oxazaborolidine, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.



Scheme 3. Dioxinone and vinyl iodide syntheses. a) TBSCl, imidazole, DMF, 91% yield; b) PPTS, EtOH, 83% yield; c) PDC, DMF, 97% yield; d) $PPh_3CH_2I_2$, NaHMDS, HMPA, DMF, −78°C; e) PPTS, MeOH, 61% yield over two steps; f) DMP, CH_2Cl_2; g) $NaClO_2$, NaH_2PO_4, 2-Me-2-butene, *t*BuOH, H_2O; h) $TMSCHN_2$, MeOH, benzene, 50% yield over 3 steps. DMF = *N*,*N*-dimethylformamide, HMDS = hexamethyldisilazide, HMPA = hexamethylphosphoramide, PDC = pyridinium dichromate, PG = protecting group, PPTS = pyridinium *p*-toluenesulfonate, TBDPS = *tert*-butyldiphenylsilyl.



Scheme 4. Fragment-assembly Prins cyclization.

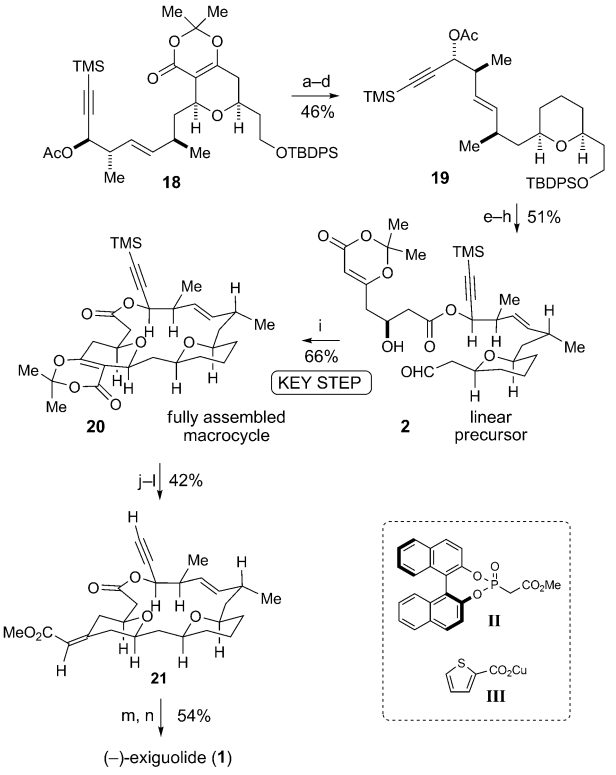
alcohol **9** was protected as the TBS ether, and an allyl Grignard addition followed by an olefin isomerization, which was catalyzed by Hünig's base, afforded α,β-unsaturated ketone **10**. A subsequent asymmetric reduction to the allylic alcohol was performed using Corey–Bakshi–Shibata conditions[10] and followed by heating with *N*,*N*-dimethylacetamide dimethyl acetal in order to promote an Eschenmoser–Claisen rearrangement[11] to deliver amide **11** in 85% yield. This sequence efficiently and selectively installed the *E* olefin with the necessary geometry and established the stereocenter that bears the methyl group. The transformation to aldehyde **5** occurred by reduction of amide **11** with $LiNH_2BH_3$ to the primary alcohol,[12] subsequent oxidation with Dess–Martin periodinane to the aldehyde,[13] and removal of the TBS protecting group under acidic conditions (77% yield over three steps).

The related dioxinone fragments **4a** and **4b** were accessed using a catalytic enantioselective vinylogous aldol reaction reported by Scettri and co-workers (Scheme 3).[6c,14] Protecting-group manipulations and oxidation of dioxinone **4a** afforded acid **13** in 73% yield over three steps. The requisite vinyl iodide fragment **3** was constructed by a Wittig olefination of aldehyde **14**[15] by using the Stork–Zhao protocol.[16] To obtain the desired *E*/*Z* selectivity of the diene, it was essential to use DMF as solvent with HMPA, and to maintain the reaction temperature at −78°C.[17] The removal of the TBS group from the vinyl iodide product afforded alcohol **15**, which underwent sequential Dess–Martin and Pinnick[18] oxidations and treatment with diazomethane to afford coupling partner **3** (50% over three steps).

With the appropriate fragments constructed, we explored the first Prins cyclization for the union of aldehyde **5** and dioxinone **4b** (Scheme 4). Following an extensive survey of reaction conditions and protecting groups (not shown), we found that the desired cyclization proceeded only when we used more robust Lewis acids, such as BF_3·OEt_2; however, we observed variable loss of protecting groups under these conditions. The most reproducible and highest yielding reactions utilized BF_3·OEt_2 as the Lewis acid and calcium sulfate as the drying agent. Overall, this intermolecular dioxinone Prins coupling produced the desired pyranone ring in 55% yield on a gram scale (combined yields of **16** and **17**).

At this point, protecting-group manipulation of both **16** and **17** produced bicyclic dioxinone **18** (Scheme 5).[19] Subsequent decarboxylation of cyclization product **18** by heating in xylenes led to the cyclohexanone product. Removal of the carbonyl group from the THP ring was then achieved efficiently by reduction with sodium borohydride to form the pyranol, iodination, and radical-mediated dehalogenation to afford pyran **19**. The acetate protecting group of **19** was removed and the resulting secondary alcohol was esterified with dioxinone acid **13**.[20] A global deprotection and the selective oxidation of the primary alcohol to the aldehyde was achieved with a silica gel accelerated catalytic oxidation using TEMPO and $PhI(OAc)_2$.[21]

The key macrocyclization of linear precursor **2** proceeded smoothly, forming both the THP ring and the macrocycle concurrently. In contrast to the earlier intermolecular Prins reaction, catalytic conditions using scandium(III) (50 mol% of $Sc(OTf)_3$) effectively promoted the cyclization of the 16-membered macrocycle and the second pyran ring in 66% yield. The decarboxylation of bicyclic dioxinone **20**, a Horner–Wadsworth–Emmons olefination with a phosphonate derived from (*S*)-1,1′-bi-2-naphthol (**II**),[22] and deprotection of the TMS group afforded terminal alkyne **21** with an enoate



Scheme 5. Macrocyclization and completion of the synthesis. a) Xylenes, H_2O, 130 °C, 81 % yield; b) $NaBH_4$, MeOH, −10 °C, 76 % yield; c) NIS, PPh_3, imidazole, CH_2Cl_2, 82 % yield; d) Bu_3SnH, AIBN, toluene, 80 °C, 91 % yield; e) DIBAL-H, hexanes, −78 °C, 76 % yield; f) acid **13**, $C_6Cl_3H_2COCl$, NEt_3, DMAP, THF, 91 % yield; g) HF·pyridine, THF, 85 % yield; h) TEMPO, SiO_2, $C_6H_5I(OAc)_2$, CH_2Cl_2, 86 % yield; i) 50 mol % $Sc(OTf)_3$, $CaSO_4$, MeCN, 0 °C, 66 % yield; j) DMSO, H_2O, 130 °C, 85 % yield; k) phosphonate **II**, NaHMDS, THF, −78 °C → −40 °C, 62 % yield; l) nBu_4NF, THF, 0 °C, 80 % yield; m) 0.5 mol % $[Pd_2(dba)_3]$, 2 mol % Cy_3PHBF_4, 20 mol % iPr_2NEt, $HSnBu_3$, toluene, −78 °C, 72 % yield; n) vinyl iodide **3**, CuTC **III**, NMP, 0 °C, 75 % yield. AIBN = azobisisobutyronitrile, Cy = cyclohexyl, dba = *trans*,*trans*-dibenzylidenacetone, DIBAL-H = diisobutylaluminium hydride, DMAP = 4-dimethylaminopyridine, DMSO = dimethyl sulfoxide, NIS = *N*-iodosuccinimide, NMP = *N*-methylpyrrolidinone, TC = thiophene carboxylate, TEMPO = (tetramethylpiperidinyl)oxyl, Tf = trifluoromethanesulfonyl.

isomer ratio of $Z/E = 7{:}1$. The completion of the synthesis necessitated appending the polyene side chain with control of the sensitive *E*/*Z*/*E* triene. After significant development, a selective hydrostannylation proceeded smoothly to afford predominantly the *E*-vinyl stannane.[23] While a Pd^0-catalyzed Stille coupling afforded complex mixtures of products, a Liebeskind Cu^I-mediated coupling[24] afforded (−)-exiguolide, which gratifyingly possessed identical physical data to the natural material.[25]

Subsequently, we evaluated the ability of exiguolide to inhibit cancer cell growth. We suspected that exiguolide would possess antiproliferative activity because of its structural similarities to the bryostatin natural products, as well as its activity against sea urchin gamete formation. To test this hypothesis, a variety of late-stage intermediates, including exiguolide (**1**), 28-(*E*)-exiguolide (**22**), alkene **23**, and alkyne **21** were screened against nine cancer cell lines in an MTS

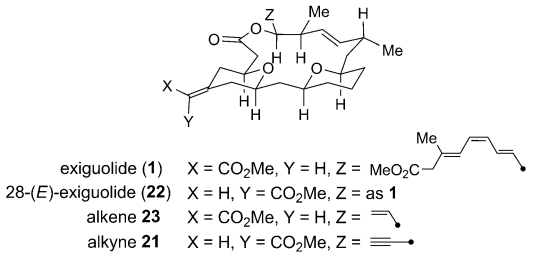


Figure 1. Exiguolide and analogues that were evaluated against tumor cell lines.

assay (Figure 1). From all of the cell lines examined,[26] exiguolide demonstrated significant antiproliferative activity against A549 lung cancer cells, inhibiting their growth by (52 ± 6) % at 10 μM and (26 ± 6) % at 1 μM. Additionally, the natural product also showed moderate growth inhibition against other cell lines, inhibiting growth of PC3 prostate cancer cells ((35 ± 7) %), MDA-MB-231 breast cancer cells ((30 ± 10) %), and BxPC3 pancreatic cancer cells ((33 ± 9) %) at 10 μM. The intriguing observation that exiguolide specifically inhibits A549 lung cancer cell growth with a higher potency than it exhibits against the other cell lines tested was first reported by Fuwa et al.[27] and subsequently confirmed by us. This fact underscores that this natural product or related congeners have potential as selective biological tools for oncology research and as chemotherapeutic agents. Interestingly, 28-(*E*)-exiguolide (**22**), macrocyclic alkene **23**, and macrocyclic alkyne **21** all demonstrated only minimal activity against all of the cell lines, thus indicating that the triene side chain and the *Z*-enoate geometry are both essential for the biological activity. The fact that only the *Z* enoate is active in our assays is particularly relevant, as this finding closely mirrors the results of structure–activity-relationship studies on the bryostatin family of natural products,[4b] and presents new structure–activity-relationship (SAR) data when compared to the recent report by Fuwa et al.[27] Further studies to enhance and understand this selective activity are underway.

In summary, we have completed a convergent synthesis of (−)-exiguolide in 26 steps (longest linear route) by employing a unified Prins cyclization approach. This strategy employs two highly diastereoselective dioxinone-directed Prins reactions, which are integral in constructing both tetrahydropyran rings of the molecule: the first to unify the highly functionalized substrates in the construction of the linear precursor of exiguolide, and the second in a 16-membered macrocyclization, which simultaneously installs the second THP ring. The route described herein is highly modular and combines two similar dioxinone fragments and one aldehyde component to generate the core structure of the target. Preliminary biological screening suggests that this natural product selectively inhibits the growth of a number of cancer cell lines, and that the triene side chain and *Z*-enoate geometry are required for the observed growth inhibition. This flexible strategy, which is driven by the Prins reaction, enables the coupling and cyclization of complex substrates and should be applicable to related targets to continue our chemical-biological investigations.

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[26] Tested cell lines: A549 (lung), HT-29 (colorectal), RT4 (urinary bladder), HT1080 (fibrosarcoma), FaDu (pharynyx), MDA-MB-231 (breast), OVCAR-3 (ovarian), BxPC-3 (pancreatic), and PC-3 (prostate). See the Supporting Information for details.
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