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Total Synthesis of (−)-Exiguolide

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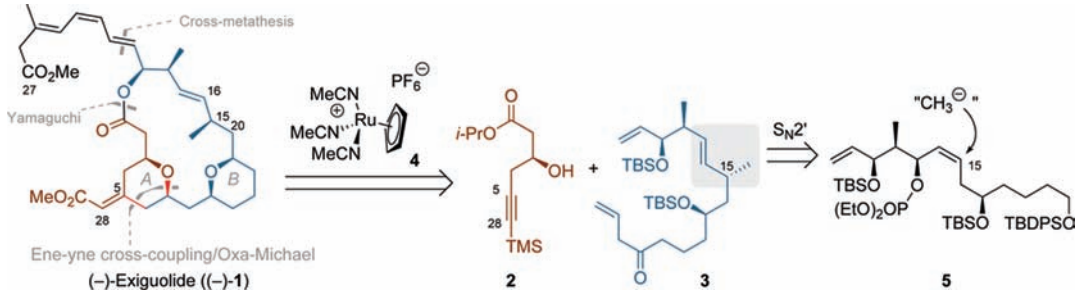
ABSTRACT



The first total synthesis of the naturally occurring enantiomer of exiguolide ((−)-1) has been completed. This very convergent synthesis features the following as main steps: (i) a Trost's ruthenium-catalyzed ene−yne cross-coupling reaction (this complex transformation allows the challenging control of the C5−C28 double bond geometry along with the stereoselective construction of the tetrahydropyran ring A) and (ii) a very efficient one-pot, two-step stereoselective conjugated allylic alcohol substitution that allowed the control of the C15 stereogenic center.

In 2006, the Ikegami group reported the isolation of (−)-exiguolide ((−)-**1**) from the marine sponge *Geodia exigua*.[1] From a structural point of view, **1** is a macrolide that displays a number of salient motifs rendering this challenging target quite attractive for synthetic chemists. (−)-Exiguolide ((−)-**1**) is a 16-membered macrolactone bearing five C−C double bonds, and seven stereogenic centers. The macrocycle is fused with two tetrahydropyran rings A and B, ring A bearing a methoxycarbonylmethylidene function at C5 with a *Z* configuration. This target does not only represent a synthetic challenge, since biological tests revealed interesting properties.[1] Thus, (−)-**1** inhibits the fertilization of sea urchin gametes, which indicates that this compound could inhibit the fusion of viruses with cell membranes.[2]

In 2008, Lee et al. reported the synthesis of *ent*-exiguolide ((+)-**1**), the enantiomer of the naturally occurring compound, thus establishing the right absolute configuration for this product.[3] They designed an approach featuring the macrocyclization by ring closing metathesis creating then the C16−C17 double bond. The installation of the methoxycarbonylmethylidene function at C5 was made by a Horner−Wadsworth−Emmons reaction but required a stoichiometric amount of an asymmetric phosphonoacetate to finally only deliver a *Z*/*E* mixture (5.8/1).

This original structure attracted our attention and teased our imagination leading to the retrosynthetic plan presented in the abstract. We identified the control of the configuration of the methoxycarbonylmethylidene function at C5 as one of the main challenges of this synthesis. Focusing on this, it appeared from the literature that one of the most expeditious methodologies allowing full control of this double bond would be the ene−yne cross-coupling reaction described by Trost et al.,[4] which is catalyzed by the cationic Ru^{II} complex $[CpRu(MeCN)_3]PF_6$ (**4**).[5] Furthermore, in the course of this reaction, the tetrahydropyran ring A would ideally be closed

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(2) Ikegami, S.; Kobayashi, H.; Myotoishi, Y.; Ohto, S.; Kato, K. H. *J. Biol. Chem.* **1994**, *269*, 23262–23267.
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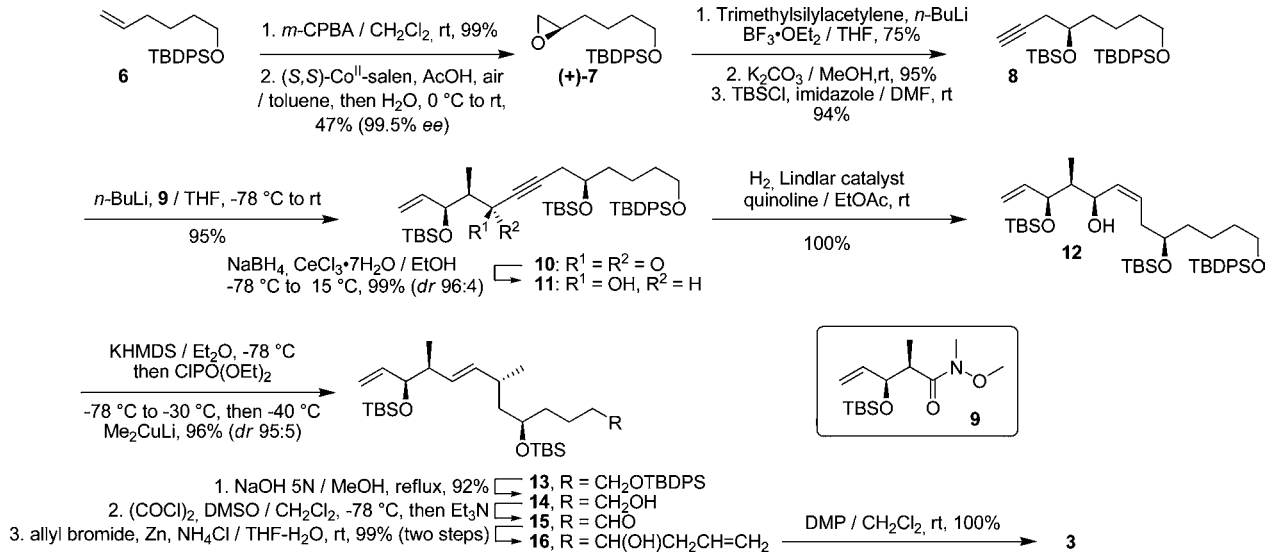
Scheme 1. Control of C15 Stereogenic Center by S_N2' and Synthesis of Fragment **3**



stereoselectively in the course of an intramolecular oxa-Michael addition. One must notice that a similar framework occurs in some other important natural product families of high biological interest such as in the bryostatins.[6] In 2008, as we were developing this study, Trost described the total synthesis of bryostatin 16 for which he made use of catalyst **4**.[7] For the construction of ring B we would use the classical reduction of the corresponding hemiketal. Securing the C15 stereochemistry was identified as another challenge, and here we thought it possible to perform a stereoselective S_N2' reaction on an asymmetric *Z*-allylic alcohol activated as a phosphate **5**. The macrolactonic ring would be closed by a classical Yamaguchi macrolactonization and we imagined bringing the C21−C27 side chain in the late steps of the synthesis by using a cross-metathesis reaction.

We commenced with the synthesis of the C6−C21 fragment **3** (Scheme 1). First, we accessed the enantio-enriched epoxide (+)-**7** using the Jacobsen hydrolytic kinetic resolution (HKR)[8] on the corresponding racemic epoxide *rac*-**7** obtained by *m*-CPBA epoxidation of alkene **6**. Alkyne **8** was furnished by reaction of epoxide (+)-**7** with lithium trimethylsilylacetylide, followed by removal of the TMS alkyne protective group and protection of the alcohol function. The lithium acetylide of **8** was condensed with the known Weinreb amide **9**.[9] This efficient cross-coupling step afforded propargylic ketone **10** in 95% yield. The ketone function of **10** was reduced into alcohol **11** with a good diastereoselectivity by using Luche conditions.[10] The semireduction of the alkyne function of **11**, using the Lindlar catalyst, led to *Z* allylic alcohol **12**. Our S_N2' strategy for the control of the allylic C15 stereogenic center is based on the assumption that the constrained geometry of Z allylic alcohols blocks the rotation of the allylic C−C bonds, which is not the case with the corresponding *E* isomers. As a consequence, S_N2' on activated *Z* allylic alcohols would furnish only one product by attack of the nucleophile *anti* to the leaving group allowing then a good transfer of chirality (*E* isomers usually give mixtures). A similar strategy has been reported in the literature that made use of perfluorobenzoate esters as leaving groups.[11] Unfortunately we met troubles in synthesizing the required perfluorobenzoate ester from alcohol **12** as this ester appeared unstable and was obtained in poor yields. After many experiments, screening various leaving groups and cuprates, we finally found simple and efficient one-pot, two-step conditions allowing a direct transformation of the *Z* allylic alcohol **12** into the desired alkene **13** in high yield (96%) and a very good transfer of chirality (dr around 95:5 by ^{1}H NMR spectroscopy).[12] In this protocol, alcohol **12** was first activated as phosphate **5** (KHMDS in Et_2O, and addition of $ClPO(OEt)_2$) and subsequently substituted by methyl cuprate (Me_2CuLi) formed in Et_2O. This protocol has been applied to various kinds of *Z* allylic alcohols with success.

Next, the TBDPS protective group was selectively removed under basic conditions[13] affording alcohol **14**, which was oxidized into aldehyde **15** under Swern conditions.[14] The latter was transformed with use of the Luche[15] procedure into homoallylic alcohol **16** (1/1 mixture of diastereoisomers)

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(11) Harrington-Frost, N.; Leuser, H.; Calaza, M. I.; Kneisel, F. F.; Knochel, P. *Org. Lett.* **2003**, *5*, 2111–2114.
(12) We have synthesized the unwanted diastereosomer of **13** in order to locate it in ^{1}H NMR spectra of **13** (see the Supporting Information for the full reference).
(13) Kabat, M. M.; Lange, M.; Wovkulich, P. M.; Uskoković, M. R. *Tetrahedron Lett.* **1992**, *33*, 7701–7704.
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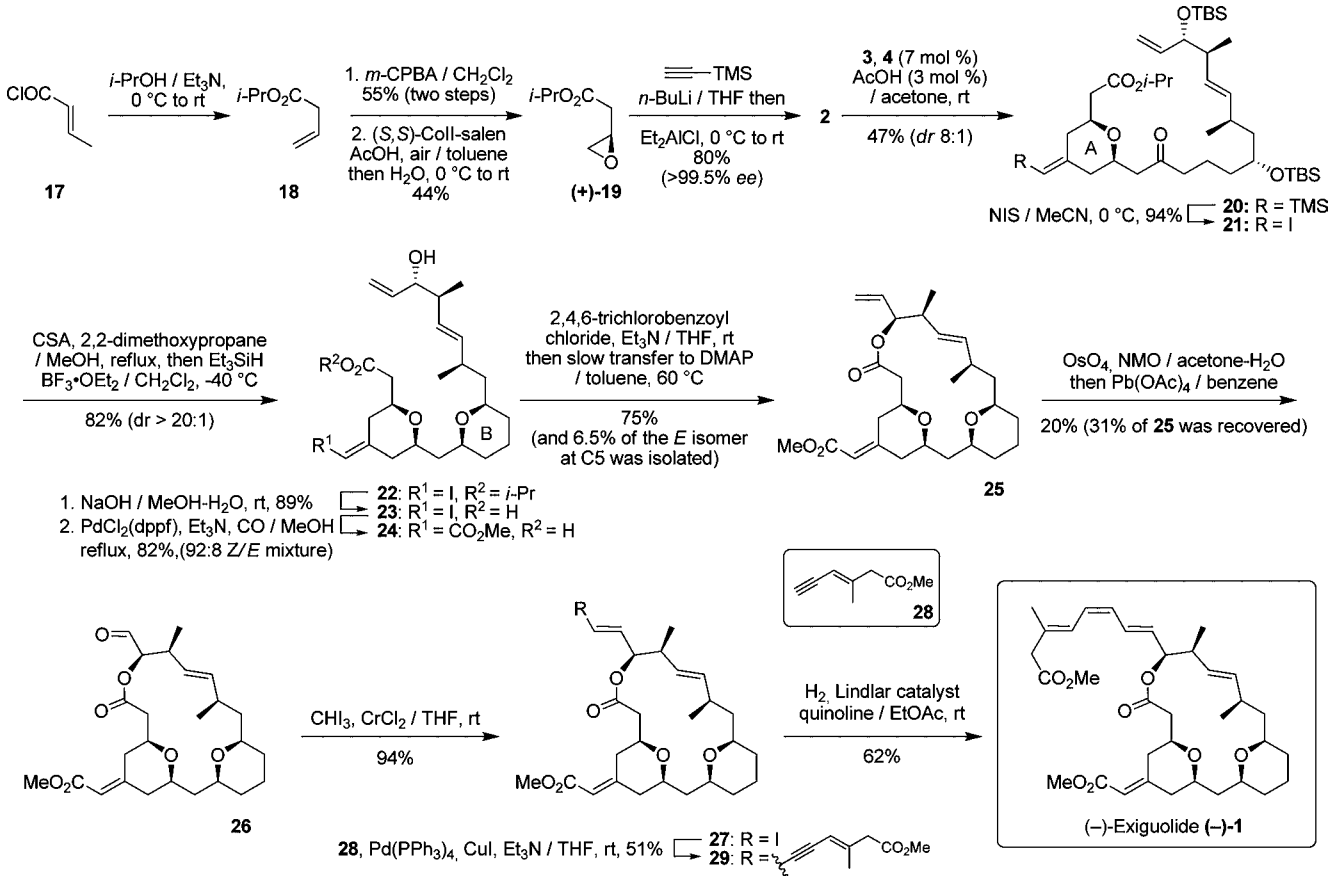
(15) Pétrier, C.; Luche, J.-L. *J. Org. Chem.* **1985**, *50*, 910–912.

Scheme 2. Ruthenium-Catalyzed Coupling of Fragments **2** and **3**, Macrolactonization, and Final Steps



and readily oxidized by Dess−Martin periodinane[16] into β,γ-unsaturated ketone **3**, the key "ene" coupling partner of the Ru^{II} catalyzed ene−yne coupling (53.4% over 11 steps from (+)-**7**).

On the other hand, the known "yne" partner **2**[17] was accessed from *trans*-crotonoyl chloride **17**, which was transformed into β,γ-unsaturated ester **18** (Scheme 2).[18] An epoxidation by *m*-CPBA furnished *rac*-**19**, which was enantio-enriched by using the Jacobsen HKR method furnishing (+)-**19**.[8] Finally, **2** was cleanly obtained after reaction with an aluminum acetylide nucleophile,[19] the more classical reaction of the corresponding lithium acetylide in the presence of BF_3 led to decomposition.

We have already used Ru^{II} catalyst **4** to build the tetrahydropyran ring of (+)-neopeltolide,[20] and discovered that a catalytic amount of acetic acid accelerated the reaction also allowing a remarkable enhancement of the diastereoselectivity. The same conditions of cross-coupling of alkyne **2** with alkene **3** led to tetrahydropyran **20** in a 47% yield as a 8:1 mixture of diastereomers easily separated by HPLC. Anyway, this result compares favorably with the 34% yield (dr not given) obtained by Trost for his bryostatin 16 synthesis, on comparable substrates. Furthermore one should notice that in our case, the reaction was regioselective as the C20−C21 terminal double bond was not engaged in the cross-coupling. The TMS group of **20** being particularly acid sensitive, we performed its iodolysis leading to **21**, prior to the acid-promoted removal of the two TBS protective groups and subsequent cyclization into the hemiketal precursor of cycle B. The crude mixture of hemiketals was subsequently reduced by Et_3SiH in the presence of $BF_3{\cdot}OEt_2$ at −40 °C affording compound **22** (dr >20:1) now featuring the two tetrahydropyran rings A and B. After saponification we obtained acid **23**. Then, the methoxycarbonyl function was cleanly installed at C28 by a Pd^0-catalyzed carbonylation[21] of iodinated derivative **23** in MeOH furnishing the desired (*Z*)-α,β-unsaturated ester **24** (92:8 *Z*/*E* mixture). We proceeded then to the macrolactonization step using the Yamaguchi conditions[22] and obtained macrolactone **25** in a good 74% yield (9.2% over 17 steps). The order of these steps (saponification−carbonylation−macrolactonization) is slightly

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unusual but it was the way we found to make the carbonylation reaction work in a reproducible manner.

For the last step of the synthesis it was first envisioned to introduce the C21−C27 side chain directly by a cross-metathesis reaction[23] on alkene **25**. Unfortunately, none of the catalysts (Grubbs II and Hoveyda−Grubbs II (Figure 1)),

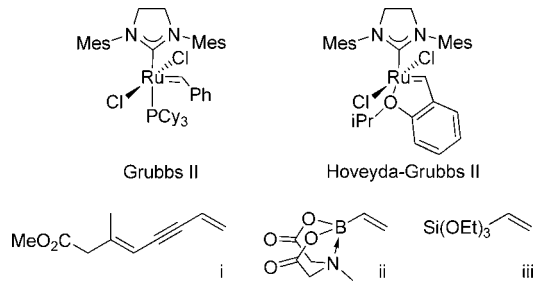

Figure 1. Catalysts and alkenes used for the cross-metathesis reaction at C20.

cross-coupling partners (i, ii,[24] and iii[25] and allylic alcohol (Figure 1)), and solvents (CH_2Cl_2, toluene, rt or reflux) we tried gave any product, in all cases the starting material **25** was totally recovered and not even dimers of **25** were formed. We then reconsidered our retrosynthetic analysis, and we thought it reasonable to expect selectivity from the OsO_4 promoted dihydroxylation reaction[26] toward the less hindered and not electron-deficient C20−C21 double bond of **25**. Surprisingly we observed a poor selectivity and identified various diols and tetraols, some resulting from the unexpected dihydroxylation of the α,β-unsaturated ester at C5−C28, the C16−C17 double bond remaining untouched. A mild reaction with $Pb(OAc)_4$[27] finally delivered aldehyde **26** from this mixture of diols with 20% yield over two steps and partial recovery of the starting material **25** (31%). The Takai−Utimoto[28] olefination reaction on aldehyde **26** furnished vinylic iodide derivative (−)-**27** in high yield, the enantiomer of which was described by Lee.[3] In the two final steps of this synthesis we followed the Lee strategy. Thus we introduced the C22−C27 side chain by Sonogashira cross-coupling of **27** with alkyne **28**,[3,29] which furnished dienyne **29**. The final step of semihydrogenation led to the targeted (−)-exiguolide (**1**), the characterization data of which are identical with those reported for the naturally occurring compound ($[\alpha]^{20}_D$ −95.0 (*c* 0.28, $CHCl_3$), lit.[1] $[\alpha]^{20}_D$ −92.5 (*c* 0.069, $CHCl_3$)).

In summary the first total synthesis of the naturally occurring enantiomer of exiguolide ((−)-**1**) has been completed. This very convergent synthesis furnished the target in 21 steps as the longest linear path (from (+)-**7**) in a 0.52% yield. This total synthesis features as main steps a Trost's ruthenium-catalyzed ene−yne cross-coupling reaction, allowing for control of the challenging C5−C28 double bond geometry, and a very efficient one-pot, two-step stereoselective conjugated allylic alcohol substitution used to control the C15 stereogenic center.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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