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Stereoselective Synthesis of Medium-Sized Cyclic Ethers by Sequential Ring-Closing Metathesis and Tsuji−Trost Allylation

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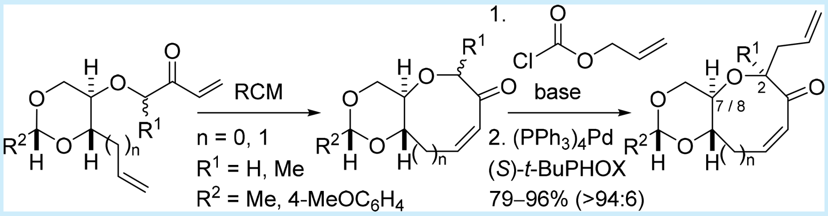
Supporting Information



ABSTRACT: Fully functionalized medium-sized cyclic ethers, of the type found in fused polyether natural products, have been prepared by sequential ring-closing diene metathesis, conversion of the resulting cyclic enone into an allylic enol carbonate, and Tsuji−Trost allylation using a chiral palladium complex. Very high levels of diastereocontrol, favoring the diastereomer in which there is a *cis* relationship between the allyl group at C-2 of the medium-ring ether and the substituent at C-7/C-8, are obtained in cases where catalyst control and substrate control are matched.

Medium-sized cyclic ethers occur frequently as subunits in marine natural products. Fused polycyclic ether natural products such as CTX-3C (**1**) (Figure 1) have structures that contain an abundance of both saturated and unsaturated medium-sized cyclic ethers ranging in size from seven to nine.[1] In addition, many smaller monocyclic marine natural products possessing seven-, eight- and nine-membered rings [e.g., laurenyne (**2**) and laurepinnacin (**3**)], have been isolated from marine sources.[2]

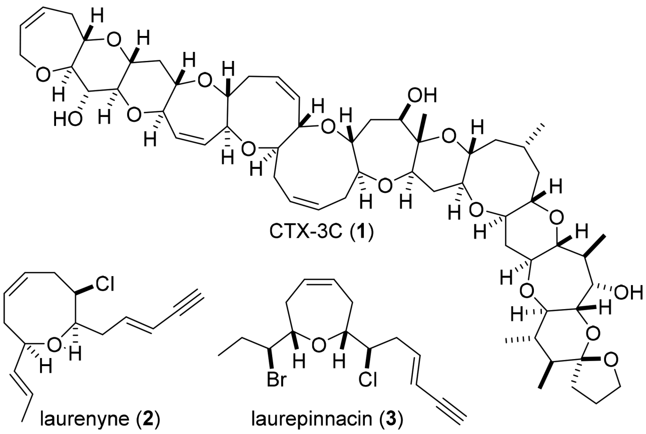
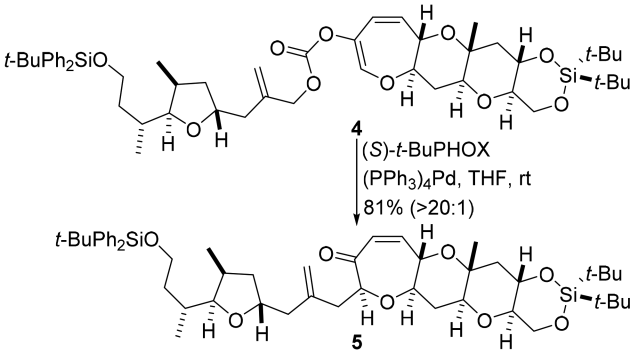

CTX-3C (**1**)
laurenyne (**2**)
laurepinnacin (**3**)

Figure 1. Examples of marine natural products that contain medium-sized cyclic ethers.

As part of our longstanding research program directed toward the synthesis of marine fused polyether natural products of the ciguatoxin and gambieric acid classes,[3] we are exploring novel methods for the rapid and stereoselective synthesis of highly functionalized medium-sized cyclic ethers and applying them to the efficient preparation of fused polycyclic ether frameworks by iterative ring construction.[4] In previous work, we employed an asymmetric variant of the Tsuji−Trost allylation reaction to couple highly functionalized fragments and thereby assemble the tetracyclic A−D fragment of the gambieric acids (Scheme 1).[5] In this case, treatment of carbonate **4** with a palladium complex of the (*S*)-*t*-BuPHOX ligand afforded the rearranged product **5** in good yield with a high level of diastereocontrol.[6]

The success of the fragment coupling reaction prompted us to explore the Tsuji−Trost allylation reaction as a general method for the synthesis of fully functionalized seven- and

Scheme 1. Asymmetric Tsuji−Trost Allylation Reaction Applied to Polyether Fragment Coupling



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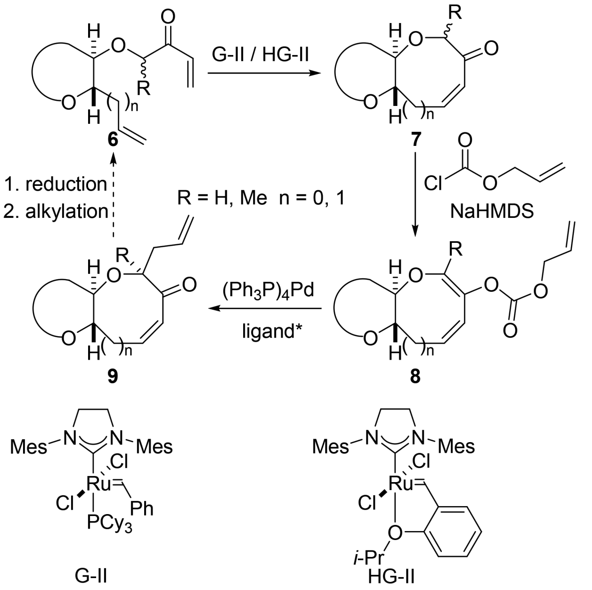
eight-membered cyclic ether building blocks and for the construction of fused polycyclic ether arrays by iterative construction of cyclic ethers (Scheme 2). We planned to perform ring-closing metathesis (RCM)[7] on enone **6** using either the Grubbs second-generation catalyst (G-II) or the Hoveyda–Grubbs second-generation catalyst (HG-II) and then convert the resulting cyclic enone **7** into the allylic enol carbonate **8** by treatment with base and allyl chloroformate. A stereoselective Tsuji–Trost allylation reaction would then be used to convert **8** into the *C*-allylated product **9**. Subsequent carbonyl reduction and functionalization would then allow the RCM and allylation sequence to be repeated.

Scheme 2. Stereoselective Iterative Synthesis of Fused Polyethers

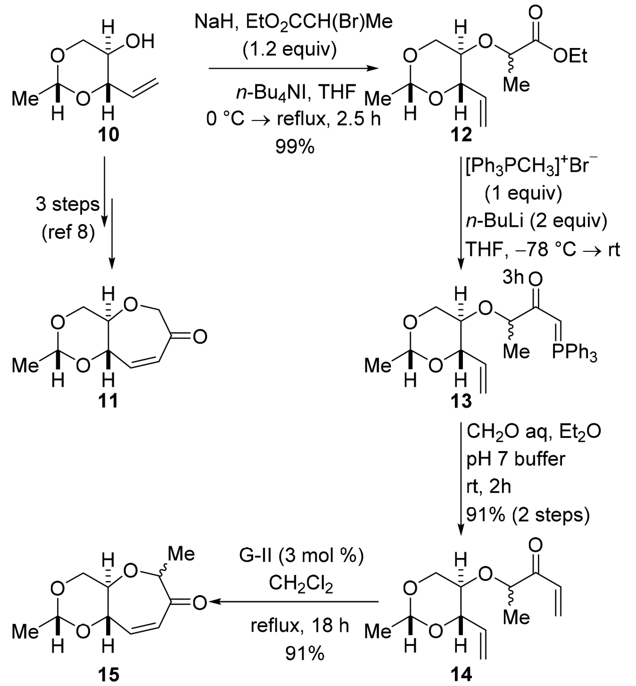


In previously published work,[4f] we have shown that hydrazones prepared from enones such as **7** (R = H) can be alkylated, but the levels of diastereocontrol are modest, and subsequent epimerization is required to deliver an acceptable level of diastereocontrol. An additional step is required to regenerate the ketone, and modest yields are obtained for the four-step sequence of hydrazone formation, alkylation, epimerization, and hydrazone cleavage, which detracts from the utility of the method.

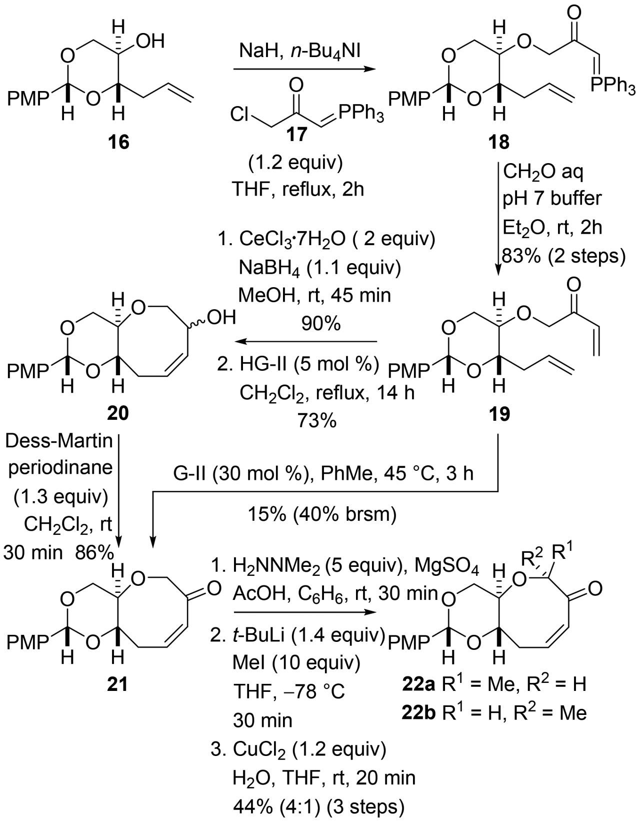
The seven-membered cyclic ether substrates required for the Tsuji–Trost allylation reaction were prepared as shown in Scheme 3. The first substrate, oxepenone **11**, was prepared from chiral-pool-derived alcohol **10** by the use of our published three-step route.[8] Preparation of enone **15**, the methyl-substituted analogue of oxepenone **11**, began with alkylation of alcohol **10** with ethyl 2-bromopropionate to give ether **12**. Reaction of the ethyl ester with methylenetriphenylphosphorane afforded stabilized ylide **13** directly, and subsequent reaction with formaldehyde delivered enone **14**.[9] Treatment of the enone with the G-II resulted in ring closure to produce enone **15** as a diastereomeric mixture.[10]

Eight-membered cyclic ether precursors for the Tsuji–Trost allylation reaction were prepared from the known alcohol **16**[4b] as shown in Scheme 4. Alkylation of **16** with chloroketophosphorane **17**[11] afforded phosphonium ylide **18**, and subsequent reaction with formaldehyde delivered enone **19** (Scheme 4).[12]

Scheme 3. Synthesis of Allylation Precursors 11 and 15



Scheme 4. Synthesis of Allylation Precursors 21 and 22



Direct RCM of **19** using G-II was problematic because a high catalyst loading (30 mol %) was required, and both the level of conversion and yield of the cyclized product **21** were low. To circumvent these problems, the enone was reduced to give a mixture of diastereomeric allylic alcohols, and RCM was performed thereafter to give a diastereomeric mixture of the

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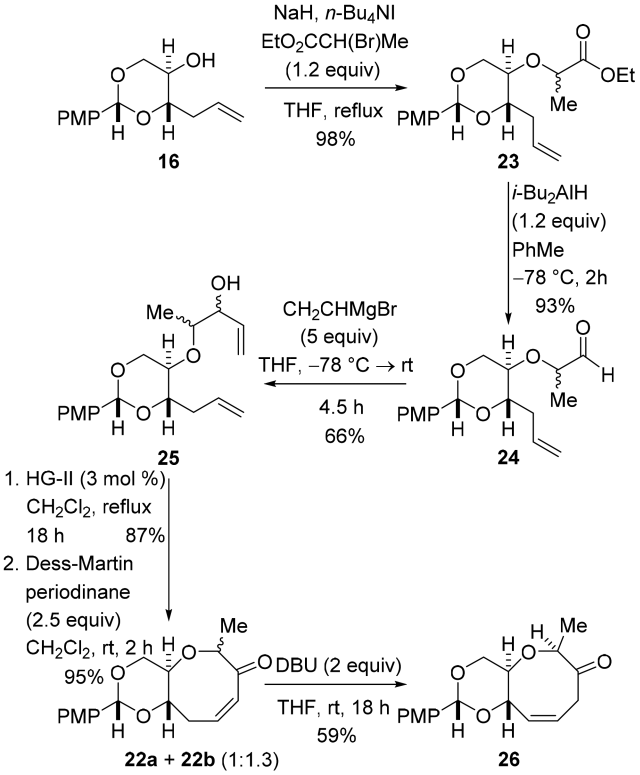
cyclized product **20** in good yield. Oxidation of alcohols **20** afforded the required oxocenone **21**, and this compound was methylated by sequential dimethylhydrazone formation, deprotonation, alkylation, and hydrazone cleavage to give a diastereomeric mixture (4:1) of enones **22a** and **22b** in 44% yield.[13] The mixture of diastereomers was used directly to generate the enol carbonate required for the Tsuji−Trost allylation reaction.

Scheme 5. Alternative Route for the Synthesis of Allylation Precursor 22



Enones **22a** and **22b** were also prepared by the more direct route shown in Scheme 5. Alcohol **16** was alkylated with ethyl 2-bromopropionate, and reduction of the resulting ester **23** using DiBAl-H produced a diastereomeric mixture of aldehydes **24**. Reaction of the aldehydes with vinylmagnesium bromide afforded a mixture of the four diastereomeric alcohols **25**, and subsequent RCM produced an isomeric mixture of the oxocenes in excellent yield. Oxidation of the alcohols then afforded enone **22** as a mixture of diastereomers (**a**:**b** = 1:1.3). Attempts to perform DBU-mediated epimerization of the diastereomeric mixture to give predominantly diastereomer **22a** resulted in deconjugation of the enone to produce ketone **26** as a single diastereomer, as judged by ^{1}H NMR analysis.[14]

Scheme 6. Stereoselective Allylation of Oxepenones 11 and 15

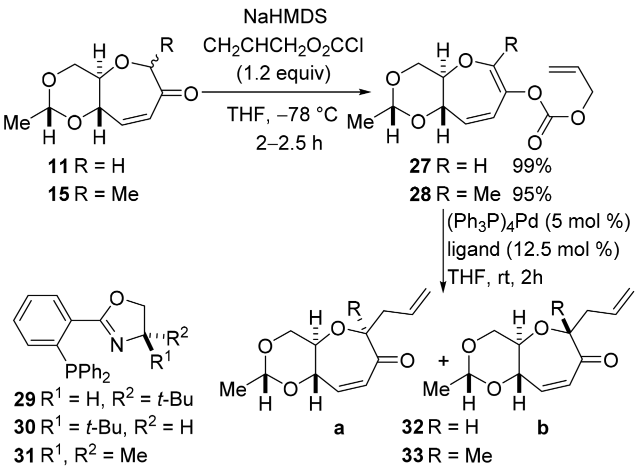


Table 1. Palladium-Mediated Rearrangement of Allylic Enol Carbonates 27 and 28

entry	substrate	ligand	product	a:b ratio[a]	yield (%)[b]
1	**27**	**29**	**32**	>97:3	96
2	**27**	**30**	**32**	13:87	75
3	**27**	**31**	**32**	69:31	92
4	**28**	**29**	**33**	>97:3	95
5	**28**	**30**	**33**	28:72	79
6	**28**	**31**	**33**	87:13	88

[a]Diastereomeric ratios measured by ^{1}H NMR spectroscopy. [b]Yields of products isolated after purification.

Preparation of the enone substrates **11**, **15**, **21**, and **22** allowed the Tsuji−Trost allylation reactions to be explored. Enones **11** and **15** were converted into enol carbonates **27** and **28** in excellent yield by deprotonation with sodium hexamethyldisilazide and *O*-acylation of the resulting enolates with allyl chloroformate (Scheme 6).[5] Highly stereoselective Tsuji−Trost allylation reactions were then accomplished by exposure of enol carbonates **27** and **28** to the palladium complex of (*S*)-*t*-BuPHOX (**29**) (Scheme 6 and Table 1). In the case of enol carbonate **27**, ketone **32** was obtained in 96% yield with a >97:3 preference for diastereomer **32a** (entry 1, Table 1).[15] When the reaction was repeated using the palladium complex of (*R*)-*t*-BuPHOX (**30**), a reversal in diastereoselectivity was observed, and a mixture of diastereomers (13:87) was obtained favoring diastereomer **32b** (entry 2, Table 1).[15] The Tsuji−Trost reaction performed using the palladium complex of the achiral PHOX ligand **31** delivered a 69:31 mixture of diastereomers favoring diastereomer **32a** (entry 3, Table 1). Thus, substrate control favors formation of diastereomer **32a**, and in the case of the reaction catalyzed by the palladium complex of (*S*)-*t*-BuPHOX (**29**), substrate and reagent control are matched. The same trend was observed in the case of methyl-substituted substrate **28**; reaction with the catalyst prepared from (*S*)-*t*-BuPHOX (**29**) delivered the product **33** in excellent yield with a >97:3 preference for diastereomer **33a** (entry 4, Table 1).[15] In the mismatched case, the palladium complex of (*R*)-*t*-BuPHOX (**30**) produced enone **33** as a 28:72 mixture of diastereomers favoring diastereomer **33b** (entry 5, Table 1), and when the reaction was performed using the palladium complex of the achiral ligand **31**, the product **33** was obtained as an 87:13 mixture of isomers with diastereomer **33a** predominating (entry 6, Table 1).[15] These results reveal that substrate control favors the formation of diastereomer **33a**. It is noteworthy that in the mismatched cases (entries 2 and 5, Table 1), the yields were significantly lower than those obtained from reactions in which the catalyst and substrate were matched (entries 1 and 4, Table 1).

The asymmetric Tsuji−Trost allylation reaction also proved to be highly effective for the preparation of fully functionalized oxocenes (Scheme 7 and Table 2). The enol carbonate precursors **34** and **35** were prepared from enones **21** and **22** by deprotonation and subsequent *O*-acylation with allyl chlor-

Scheme 7. Stereoselective Allylation of Oxocenones 21 and 22

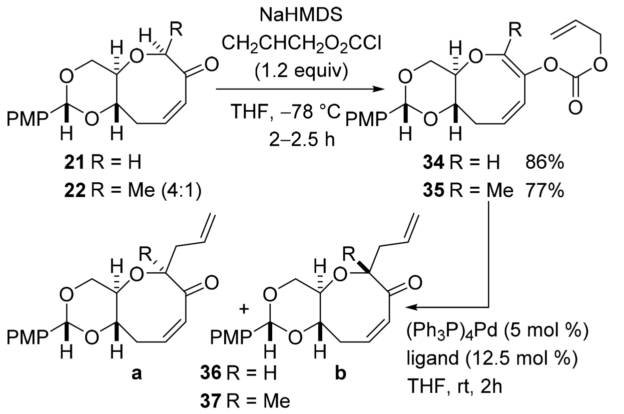


Table 2. Palladium-Mediated Rearrangement of Allylic Enol Carbonates 34 and 35

entry	substrate	ligand	product	a:b ratio[a]	yield (%)[b]
1	**34**	**29**	**36**	94:6	79
2	**34**	**30**	**36**	17:83	73
3	**34**	**31**	**36**	66:34	85
4	**35**	**29**	**37**	>97:3	81
5	**35**	**30**	**37**	55:45	81
6	**35**	**31**	**37**	91:9	86

[a] Diastereomeric ratios measured by ^{1}H NMR spectroscopy. [b] Yields of products isolated after purification.

oformate.[16] Treatment of enol carbonate **34** with the palladium complex prepared from the (*S*)-*t*-BuPHOX ligand (**29**) delivered the product **36** with a 94:6 preference for diastereomer **36a** (entry 1, Table 2).[15] In contrast, the mismatched pairing of substrate **34** with the palladium complex of the (*R*)-*t*-BuPHOX ligand (**30**) produced a 17:83 mixture of diastereomers favoring diastereomer **36b** (entry 2, Table 2).[15] Diastereomers **36a** and **36b** were produced in a ratio of 66:34 when an the palladium complex of achiral ligand **31** was employed as the catalyst (entry 3, Table 2). A similar trend was observed with the methyl-substituted substrate **35**. In this case, the matched pairing of substrate and catalyst produced diastereomer **37a** exclusively (entry 4, Table 2); the mismatched pairing of substrate and catalyst afforded a 55:45 mixture of isomers favoring diastereomer **37a**, and the achiral catalyst delivered a 91:9 isomer mixture with diastereomer **37a** as the major product.

The data in Tables 1 and 2 show that the methyl-substituted enol carbonates **28** and **35** exhibit greater intrinsic selectivity for the formation of diastereomers **33a** and **37a** than do the corresponding unsubstituted substrates **27** and **34** for diastereomers **32a** and **36a**. However, matched catalyst control is sufficient to ensure highly selective formation of all of the required products **32a**, **33a**, **36a**, and **37a**.

In summary, we have demonstrated that highly functionalized seven- and eight-membered cyclic ethers can be prepared efficiently by sequential diene RCM, enol carbonate formation, and Tsuji−Trost allylation using a chiral palladium complex. Exceptionally high levels of diastereocontrol can be achieved in cases where catalyst and substrate control are matched. The allylated products **32a**, **33a**, **36a**, and **37a** are fully functionalized building blocks that can be used for the preparation of polycyclic ether arrays, including those possessing ring-junction methyl substituents, which are found in marine polyether natural products such as the ciguatoxins and gambieric acids.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01082.

> Experimental procedures for the preparation of compounds **12**, **14**, **15**, **19−28**, and **32−37** along with compound characterization data and copies of ^{1}H and ^{13}C NMR spectra (PDF).

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Notes

The authors declare no competing financial interest.

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(13) The stereochemical assignments for **22a** and **22b** were made on the basis of NMR analysis. In the case of enone **22a**, a significant NOE was observed between the proton attached to the methyl-bearing carbon and the proton attached to the other carbon of the ether linkage in the eight-membered ring.

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(15) Stereochemical assignments for compounds **32a**/**b**, **33a**/**b**, **36a**/**b**, and **37a**/**b** were confirmed on the basis on NMR analyses (NOESY) performed in $CDCl_3$ and/or C_6D_6. NOEs were observed between protons across the medium-ring ether linkage in the case of **32a** and **36a** and between the proton and the methyl group across the medium-ring ether linkage in the case of **33a** and **37a**. NOEs were not observed for the corresponding diastereomeric compounds **32b**, **33b**, **36b** and **37b**.

(16) The diastereomeric ratio of enone **22** had a significant influence on the yield of enol carbonate **35**. Good yields were obtained when the enone enriched in isomer **22a** (4:1) was used. The yield of enol carbonate **35** was significantly lower when material containing a higher proportion of isomer **22b** was used. In this case, deprotonation of the enone at the γ-position and enolate trapping with allyl chloroformate delivered the regioisomeric enol carbonate. This observation suggests that the proton on the carbon adjacent to the carbonyl group in diastereomer **22b** (C-2) is less accessible to the base than that in diastereomer **22a**. This phenomenon was not observed in the case of enone **15**, where both diastereomers reacted to give enol carbonate **28** in good yield.

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