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

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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. 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.

As part of our longstanding research program directed toward the synthesis of marine fused polyether natural products of the ciguatoxin and gambieric acid classes, 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. 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).

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

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

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 as shown in Scheme 4. Alkylation of 16 with chloroketophosphorane afforded phosphonium ylide 18, and subsequent reaction with formaldehyde delivered enone 19 (Scheme 4).\(^{12}\)

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
 cyclized product \(20\) in good yield. Oxidation of alcohols \(20\) afforded the required oxocone \(21\), 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 en carbonate required for the Tsuji–Trost allylation reaction.

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 DiBAI-H produced a diastereomeric mixture of aldehydes \(24\). Reaction of the aldehydes with vinylmagnesium bromide afforded a mixture of the four diastereomeric aldehydes \(25\), 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 DUBU-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.\(^{14}\)

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).\(^{6}\) Highly stereoselective Tsuji–Trost allylation reactions were then accomplished by exposure of enol carbonates \(27\) and \(28\) to the palladium complex of \((R)-t\)-BuPHOX (30) (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) (Scheme 6), 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 chloro-
of enol carbonate 34 with the palladium complex prepared from the (S)-t-BuPHOX ligand (29) delivered the product 36a with a 94:6 preference for diastereomer 36a (entry 1, Table 2).15 In contrast, the mismatched pairing of substrate and catalyst produced a 40:60 mixture of diastereomers favoring diastereomer 36b (entry 2, Table 2).15 Diastereomers 36a and 36b were produced in a ratio of 66:34 when the palladium complex of achiral ligand 30 was employed as the catalyst (entry 3, Table 2). A similar trend was observed with the methyl-substituted substrate 35. In this case, the mismatched 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 diastereoccontrol 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.

**REFERENCES**


(10) For early examples of RCM reactions involving enones, see:


(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.


(15) Stereochemical assignments for compounds 32a/b, 33a/b, 36a/b, and 37a/b were confirmed on the basis of NMR analyses (NOESY) performed in CDCl3 and/or C6D6. 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 C2-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.