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Enantioselective Synthesis of the Unsaturated Fragment of Callyspongiolide

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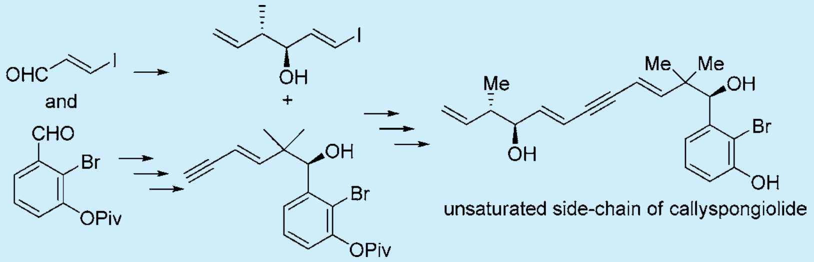
Supporting Information



ABSTRACT: A synthesis of the unsaturated side chain of callyspongiolide has been accomplished from two chiral building blocks prepared by catalytic asymmetric procedures applied on simple starting materials. The synthesis of the chiral benzylic alcohol was based on an enantioselective aldol reaction of a substituted benzaldehyde catalyzed by a chiral amine, whereas the chiral homoallyl alcohol was prepared by the enantioselective crotylboration of iodomethacryl aldehyde catalyzed by a chiral phosphoric acid. Both fragments were joined together by using standard Sonogashira coupling conditions.

Macrolides constitute a large family of compounds isolated from numerous natural sources that often possess biologically interesting properties.[1] A new member of this group, callyspongiolide, has recently been isolated[2] from a methanolic extract of the sponge *Callyspongia* sp. collected in Indonesia. It features an interesting conjugated diene-ynic side chain connecting a brominated benzene ring with a macrocylic ester having six stereocenters in its structure. The presence of the diene-ynic side chain is unprecedented among all marine macrolides reported so far, and even the brominated benzene ring occurs very rarely within this class of compounds. Aside from the above-mentioned structural features, callyspongiolide also possesses interesting biological activity. For example, it completely inhibited the growth of the murine lymphoma cell line L5178Y at a concentration of 10 μg/mL and had an IC_{50} value of 320 nM. In addition, it exhibited significant activities in other tests as well.[2,3] Thanks to the unprecedented structure and attractive biological properties, it constitutes an interesting and challenging synthetic target. Herein, we disclose our efforts toward the synthesis of the unsaturated unit of callyspongiolide (**1**), which could serve as an advanced intermediate for its total synthesis. Our strategy is based on organocatalytic enantioselective aldol and crotylation reactions.

During the preparation of this manuscript, two papers dealing with the total syntheses of callyspongiolide were reported by Xu and Ye et al.[3] and Ghosh and Kassekert,[4] and their results also clarified its absolute configuration. A separate synthesis of callyspongiolide's macrocyclic ring was reported as well.[5] Although the general strategy of the published routes and our route are in some aspects close, in our synthesis, the construction of chiral centers relies on the use of catalytic protocols whereas the previously published approaches were based on stoichiometric methods.

Our interest in callyspongiolide originated from the presence of the unique unsaturated moiety with its two asymmetric centers. Our retrosynthetic analysis of callyspongiolide is outlined in Scheme 1. Since callyspongiolide is a macrocyclic lactone, we envisioned that it could be assembled by employing a cross-metathesis of the upper fragment **1** with a suitably substituted alkenoic acid followed by macrolactonization and further functional group transformations. From a retrosynthetic perspective, the unsaturated fragment **1** could, in principle, be assembled from iodoallylic alcohol **2** and enyne **3** by Sonogashira coupling. The former could be prepared by enantioselective crotylation of the corresponding iodoacrylaldehyde **4** with a suitable crotyl nucleophile **5**. The synthesis of the latter, enyne **3**, could commence with an enantioselective aldol reaction between the protected 2-bromo-3-hydroxybenzaldehyde **7** with 2-methylpropanal, which would provide aldehyde **6**, which could be transformed into the enyne **3** by using a Takai–Utimoto haloolefination followed by a Sonogashira reaction with trimethylsilylethyne.

At the outset, the synthesis of chiral iododienol was undertaken. Out of several available methods for enantioselective crotylation of aldehydes,[6] we opted for crotylboration of 3-iodoacrylaldehyde **4** by a chiral Brønsted acid, which was shown by us to proceed with a rather high asymmetric induction in comparison with other methods.[7] Thus, a reaction of (E)-crotylboronic acid pinacol ester with **4** in the presence of

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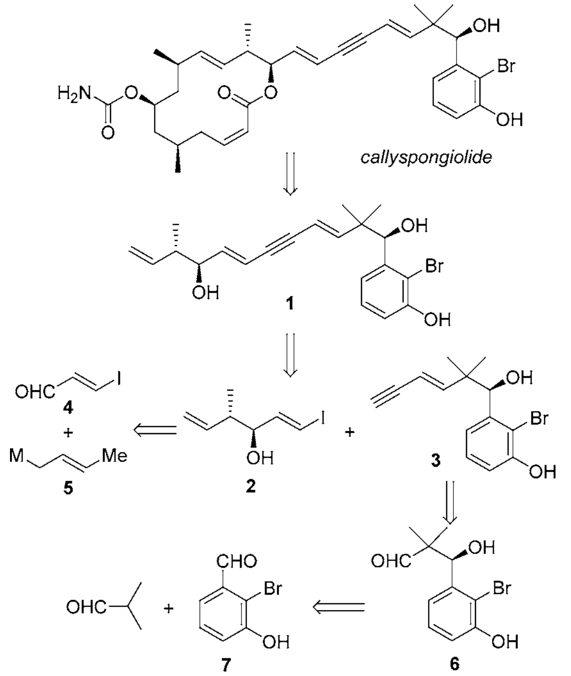
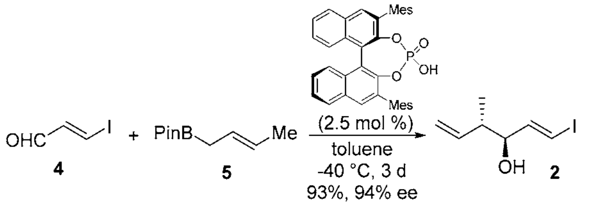
Scheme 1. Retrosynthetic Analysis of Callyspongiolide



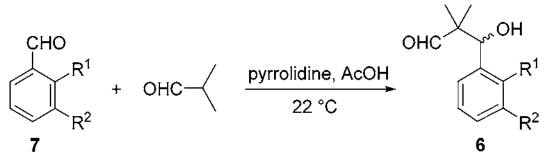
(*S*)-TRIP-PA (2.5 mol %) provided iododienol **2** in a yield of 93% and 94% ee (Scheme 2).

Scheme 2. Enantioselective Allylation of 3-Iodoacrylaldehyde 4



Despite the fact that the asymmetric aldol reaction of aldehydes has been a target of considerable endeavors, a number of challenges remain.[8] The preparation of aldol products possessing a quaternary carbon constitutes one challenge. It was thus envisioned that enantioselective aldol reaction of 2,3-disubstituted aldehyde **7b** with 2-methylpropanal to give chiral product **6** would be a difficult task. Although the aldol reaction of various aldehydes with substituted benzaldehydes was screened under both racemic (pyrrolidine catalysis)[9] and enantioselective[10] conditions, the scope of the reaction with respect to more complex substituted benzaldehydes has not been carried out. Moreover, when benzaldehyde with an electron-donating 4-MeO group was used, the yield was less than half of those obtained for compounds with electron-withdrawing substituents. Hence, we decided to test the aldol reaction of 2-methylpropanal with benzaldehydes **7a**–**g** (Table 1). Aldol reaction of a model benzaldehyde **7a** was carried out in both THF and DMSO (entries 1 and 2). A much better result was obtained in DMSO where **6a** was formed in an almost quantitative yield, and so DMSO was used for the rest of the substrates as a solvent of choice. Unfortunately, the reaction with **7b** having a free phenolic hydroxyl group proceeded with a very low efficiency, providing the desired product **6b** in only 6% yield (entry 3). A minor improvement was observed when the hydroxyl group was protected as acetate (**7c**, entry 4), the reason being a gradual cleavage of the acetyl group from the starting material during the course of the reaction. The aldol reaction of **7d** gave rise to **6d** in a high yield of 85% (entry 5), but the product then decomposed rapidly upon standing, even when kept in the freezer. The use of **7e** again failed to meet our expectations and reaction yield was just 15% (entry 6). Gratifyingly, the aldol reaction of **7f** proceeded well to give the desired product **6f** in a very good isolated yield of 87%. A pivaloyl group proved to be the most convenient protecting group, with benzaldehyde **7g** providing the product **6g** in 90% yield. Unlike the methoxy group, it could potentially be easily cleaved to give a free phenolic hydroxyl at a later stage in the synthesis.

Table 1. Racemic Aldol Condensation of 2-Methylpropanal with 7



7a R^1 = Br, R^2 = H
7b R^1 = Br, R^2 = OH
7c R^1 = Br, R^2 = OAc
7d R^1 = H, R^2 = OAc
7e R^1 = Br, R^2 = OBz
7f R^1 = Br, R^2 = OMe
7g R^1 = Br, R^2 = OPiv

entry	7	conditions	product	yield[a] (%)
1	**7a**	THF, 23 h	**6a**	48
2	**7a**	DMSO, 54 h	**6a**	92
3	**7b**	DMSO, 26 h	**6b**	6[b]
4	**7c**	DMSO, 94 h	**6c**	17
5	**7d**	DMSO, 23 h	**6d**	85
6	**7e**	DMSO, 70 h	**6e**	<15[c]
7	**7f**	DMSO, 24 h	**6f**	87
8	**7g**	DMSO, 26 h	**6g**	90

[a] Isolated yields. [b] Isolated as a mixture with the starting material. [c] Isolated as a mixture with a byproduct; possibly some migration of Bz group occurred.

Encouraged by these results, we decided to proceed with the enantioselective aldol reaction under the previously described conditions[10] by using (*S*)-(+)-1-(2-pyrrolidinylmethyl)-pyrrolidine as the catalyst (Table 2). At first, the reaction was carried out with **7a** in a set of solvents to assess their effect on asymmetric induction. A highly enantioenriched product **6a** was obtained in DMSO and DMF with 93 and 92% ee, respectively (entries 1 and 2), whereas in THF, dichloromethane, and MeCN the reaction proceeded with lower enantioselectivities (66–86% ee) (entries 3–5). The absolute configuration of **6a** was determined as *R* via Mosher ester analysis, which was consistent with the original procedure.[10] In view of the aforementioned results, compounds **6b**–**g** also possess the *R* configuration. Interestingly, the aldol reaction of **7c** proceeded better under these asymmetric conditions than with pyrrolidine/AcOH, providing **6c** in a reasonable isolated yield (41%) and a high enantioselectivity of 85% ee (entry 6). Almost no cleavage of the acetyl protecting group was observed. In the case of **7d**, a high yield of the aldol product was obtained, but we were not able to determine asymmetric induction due to decomposition of the product **6d** during enantioselective analysis (entry 7). The aldol reaction of **7f** gave **6f** in a good 79% isolated yield and a rather good enantioselectivity of 89%

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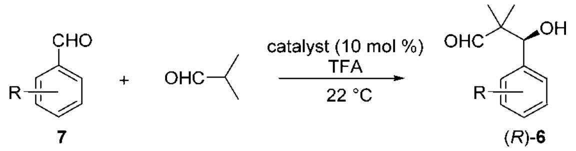
Table 2. Enantioselective Aldol Condensation of 2-Methylpropanal with 7



entry	7	conditions[a]	product	yield[b] (%)	ee[c] (%)
1	**7a**	DMSO, 23 h	**6a**	86	93
2	**7a**	DMF, 24 h	**6a**	83	92
3	**7a**	THF, 28 h	**6a**	19	73
4	**7a**	DCM, 50 h	**6a**	50	66
5	**7a**	MeCN, 28 h	**6a**	50	86
6	**7c**	DMSO, 23 h	**6c**	41	85
7	**7d**	DMSO, 98 h	**6d**	97	–[d]
8	**7f**	DMSO, 23 h	**6f**	79	89[e]
9	**7f**	DMSO, 23 h[f]	**6f**	46	93[e]
10	**7g**	DMSO, 26 h	**6g**	90	93

[a] (S)-(+)-1-(2-Pyrrolidinylmethyl)pyrrolidine (10 mol %). [b] Isolated yields. [c] Chiral HPLC (IA, hept/iPrOH 9/1). [d] Impossible to determine due to decomposition. [e] Chiral HPLC (IA, 208 nm, hept/iPrOH 95/5). [f] (S)-(+)-1-(2-Pyrrolidinylmethyl)pyrrolidine (5 mol %).

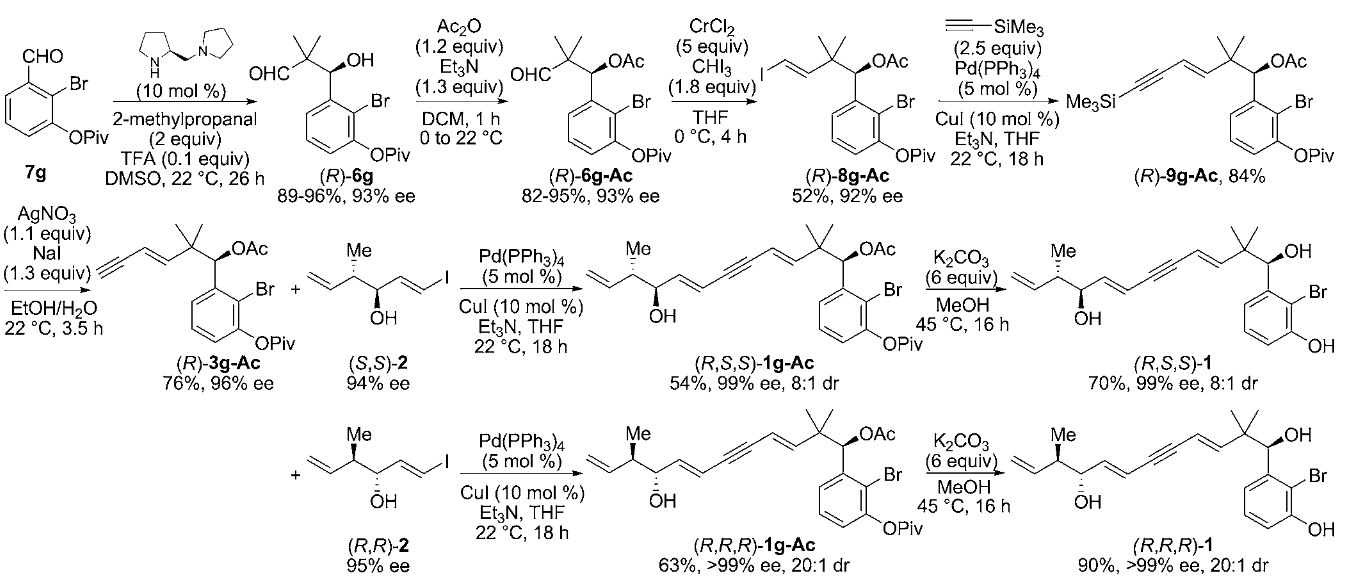
ee (entry 8). When the reaction was carried out with 5 mol % of the catalysts, the asymmetric induction remained high. However, the yield dropped to 46% (entry 9). Finally, an even better result was obtained with **7g**, which gave **6g** in a 90% yield and 93% ee (entry 10).

We now decided to explore feasibility of the proposed synthetic pathway toward synthesis of **1** by using racemic compounds with aldehydes **6f** and **6g** (these routes are described in detail in the Supporting Information). Having successfully proven that the chosen synthetic methodology was suitable and having both crucial enantioenriched intermediates **2** (90% ee) and (*R*)-**6g** (93% ee) in hand, we decided to execute an enantioselective synthesis of the fragment **1** (Scheme 3). Asymmetric synthesis of the same fragment with the methoxy group (starting from aldehyde (*R*)-**6f**) was also accomplished and is described in the SI. The benzylic alcohol of aldol product **6g** was first protected with an acetyl group (**6g-Ac**). We resorted to protection of the alcohol for we found that otherwise the aldol product tended to racemize and slowly decompose (by retro-aldolization) even when kept in the freezer.[11] Moreover, the acetate **6g-Ac** was stable and crystalline (vs sticky foam), so handling and purification were made much easier.

The acetate was then converted to vinyl iodide **8g-Ac** via Takai–Utimoto olefination.[12] With the racemic substrate, we tried the more economical version of this reaction using $CrCl_3 \cdot 6H_2O$ and zinc.[13] Except for one experiment when we obtained a nice yield of 59%, the results under these conditions were rather unpredictable with yields in the range of 10–30%. Therefore, we were forced to follow the original procedure using expensive $CrCl_2$, which proceeded uneventfully to give exclusively (*E*)-alkene **8g-Ac** in 52% yield and without loss of optical purity (92% ee). The reaction of **8g-Ac** with trimethylsilylethyne under the standard Sonogashira conditions[14] provided **9g-Ac** in 84% isolated yield. The alternative Wittig reaction of **6g-Ac** with the commercially available triphenyl(3-(trimethylsilyl)prop-2-yn-1-yl)phosphonium bromide was also attempted and provided product **9g-Ac** directly, but only as an unseparable mixture of *cis*/*trans* isomers in a roughly 1:4 ratio. We were unable to remove the *cis* isomer chromatographically even after removal of all the protecting groups. Interestingly, some of the starting material decomposed via retro-aldolization during the reaction, and the so-formed aldehyde **7g** underwent Wittig reaction to give byproduct **SI-1** as a mixture of *cis*/*trans* isomers (see the Supporting Information).

Desilylation using $AgNO_3$ and NaI yielded enyne **3g-Ac** in a 76% isolated yield with the other two protecting groups left in place. Finally, Sonogashira coupling of **3g-Ac** with enantioenriched iodohexadienol (*S*,*S*)-**2** under standard conditions ($Pd(PPh_3)_4$, CuI, Et_3N) gave rise to the desired fragment (*R*,*S*,*S*)-**1g-Ac** in a 54% isolated yield (a dimeric byproduct **SI-2g** was also formed (16%), but it was easily separated from the product).

Scheme 3. Enantioselective Synthesis of 1



To show the usefulness of our protocol, we prepared an enantiomeric iodohexadienol (*R*,*R*)-**2** using (*R*)-TRIP-PA as a catalyst and allowed it to react with the (*R*)-**3g-Ac** to obtain a diastereoisomeric fragment (*R*,*R*,*R*)-**1g-Ac** in 63% yield (14% of a dimeric byproduct **SI-2g** was formed; see the SI). Both products were then treated with K_2CO_3 in methanol to give the unprotected fragments (*R*,*S*,*S*)-**1** and (*R*,*R*,*R*)-**1** in 70 and 90% yield, respectively.

In conclusion, we developed a convergent synthetic approach to the unsaturated fragment of callyspongiolide based on the use of two chiral building blocks prepared by means of catalytic enantioselective reactions. The first was synthesized by asymmetric crotylboration of iodoacrylaldehyde catalyzed by a chiral Brønsted acid. The second was an enantioselective aldol reaction of a highly substituted benzaldehyde catalyzed by a chiral diamine. These catalytic methods enabled us to prepare the desired fragment of callyspongiolide **1**, as well as its diastereoisomer.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02897.

Experimental procedures and analytical data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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