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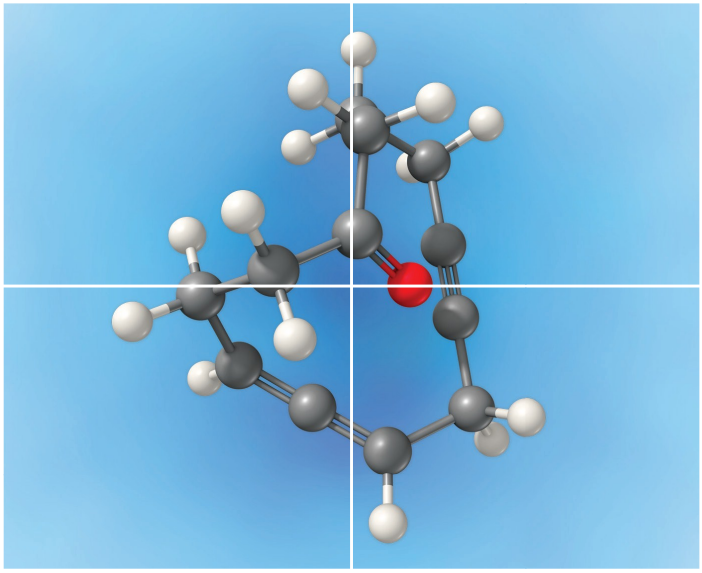

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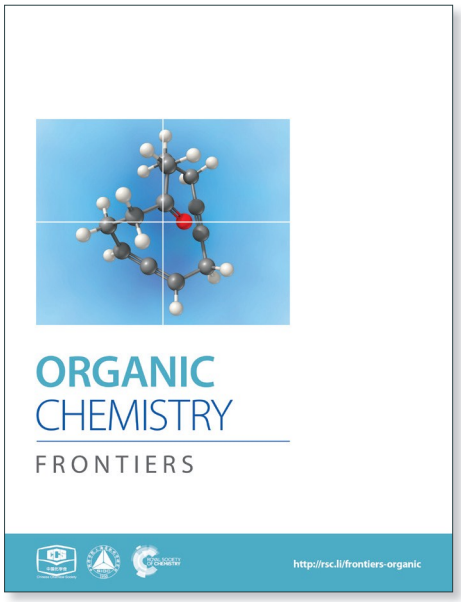

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COMMUNICATION

Concise Asymmetric Total Synthesis of Catunaregin

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The asymmetric total synthesis of catunaregin isolated from the Chinese mangrove is described. The synthesis involves an asymmetric *syn*-selective aldol reaction and the successive ketalization of a furan diol derivative under acidic conditions. This methodology is very concise and highly stereoselective. The asymmetric total synthesis of the optically pure catunaregin was accomplished in 7 steps from a known methyl ester.

Lignans, a class of natural products, are metabolites constructed from two phenylpropanoic acids by oxidative dimerization.[1,2] Catunaregin (**1**) and epicatunaregin (**2**) were isolated from the stem bark of *Catunaregam spinosa* Tirveng, a Chinese mangrove associate, by the Zhang group.[3] These natural products **1** and **2** possess an unprecedented norneolignan skeleton, involving an oxygen-bridged furopyran skeleton (Figure 1). They were initially found to exhibit inhibition against mammary cancer F10 cell lines. Later, it was reported that the novel norneolignan catunaregin (**1**) inhibited different VEGF-induced angiogenic phenotypes of HUVECs in vitro and vessel formation in transgenic zebrafish.[4] The optical rotation value of the natural catunaregin (**1**) is very low ($[\alpha]_D^{20}$ = +1.4 (c 0.8, MeOH)), leading Zhang

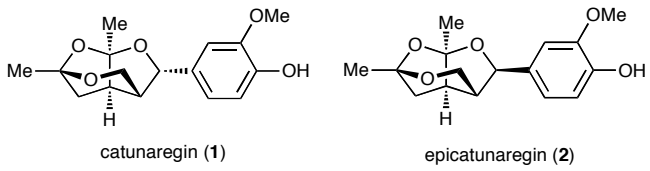
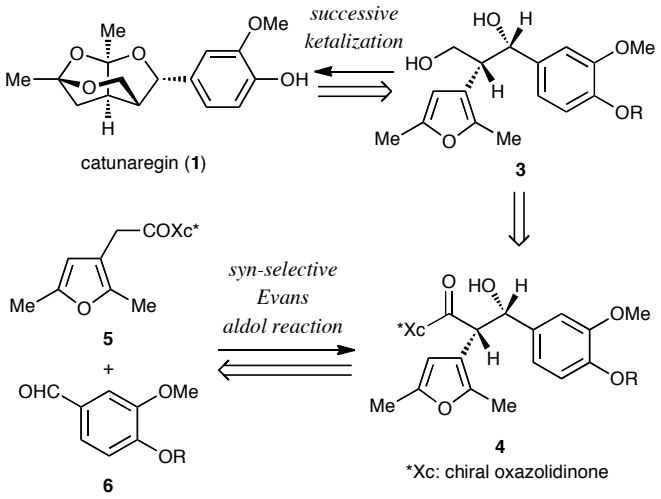


Figure 1. Structures of catunaregin (**1**) and epicatunaregin (**2**).



Scheme 1. Retrosynthetic analysis of catunaregin (**1**).

to surmise that the natural catunaregin is virtually racemic as a result of its biosynthetic pathway, which includes the production of benzofuran norneolignans with no enantioselective reduction. The structural features and biological properties of **1** attracted our attention, and we began a synthetic study of unique norneolignan **1** in the optically pure form. This report describes the asymmetric synthesis of catunaregin (**1**), which includes a *syn*-selective aldol reaction and construction of the oxygen-bridged furopyran skeleton by successive ketalization.

The retrosynthetic analysis of catunaregin (**1**) is outlined in Scheme 1. The target norneolignan could be obtained by the construction of the tricyclic skeleton by successive ketalization of furanyl diol derivative **3**, followed by cleavage of the protecting group of the phenolic hydroxyl group. The ketalization precursor **3** would be synthesized from furan derivative **5** and vanillin derivative **6** in two steps involving the asymmetric *syn*-selective aldol reaction of **5** with **6**, and reduction of the *syn*-aldol product **4**.

Our investigation started with the synthesis of the donor **11** with a chiral auxiliary for subsequent *syn*-selective Evans aldol

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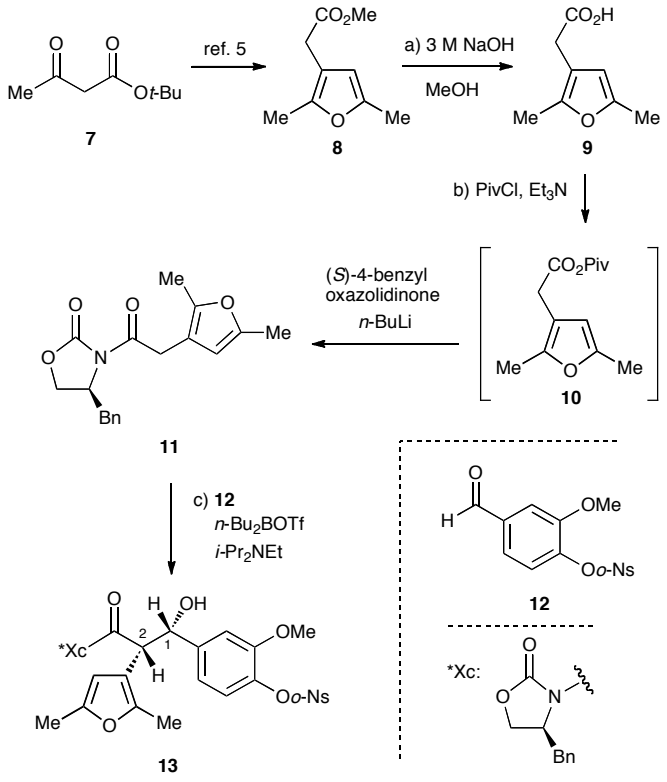
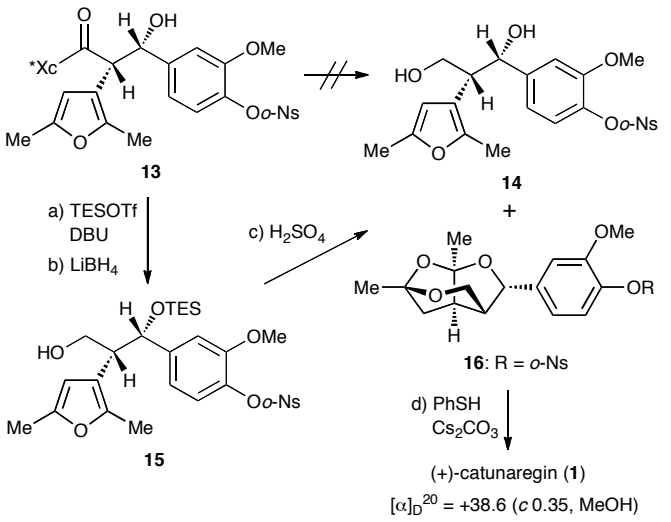


Scheme 2. Synthesis of key intermediate **13** via *syn*-selective Evans aldol reaction. Reagents and Conditions: a) 3 M NaOH aq., MeOH, rt, 2 h, quant.; b) PivCl, Et_3N, THF, –78 °C to 0 °C, 1 h, then (*S*)-4-Bn-oxazolidinone, *n*-BuLi, THF, –78 °C to 0 °C, 1 h, 93%; c) *n*-Bu_2BOTf, *i*-Pr_2NEt, **12**, CH_2Cl_2, –78 °C, 2.5 h, 98%, d.r. >95:5. Piv: pivaloyl; Bn: benzyl; *n*-Bu_2BOTf: di-*n*-butylboryl trifluoromethanesulfonate.

reaction. Saponification of methyl ester **8**, which was prepared from *tert*-butyl acetoacetate (**7**) in three steps according to the reported procedure,[5] with sodium hydroxide gave the carboxylic acid **9**[6] in 98% yield. Installation of the (*S*)-4-benzyloxazolidinone group as the chiral auxiliary was achieved by a 2-step operation: transformation of the carboxylic acid to the mixed anhydride, followed by addition of the lithiated oxazolidinone to the resulting mixed anhydride to afford **11** in 93% yield. The *syn*-selective Evans aldol reaction[7] of **11** and *O*-*o*-nitrobenzenesulfonyl (Ns)[8,9] vanillin derivative **12** with di-*n*-butylboryl trifluoromethanesulfonate and diisopropyl(ethyl)amine gave the desired Evans *syn* product **13** exclusively in 98% yield. The absolute stereochemistry at C1 of **13** was determined by the improved Mosher's method[10,11] as *S*.[12]

With the desired Evans *syn* product **13** in hand, we focused our efforts on the construction of the tricyclic fragment. As shown in Scheme 3, all attempts for removal of the chiral auxiliary of **13** by reduction with hydride reagents, $LiBH_4$, $LiAlH_4$, and DIBALH, failed with decomposition of **13**. Since we suspected that the naked hydroxyl group at the benzylic position caused a retro aldol reaction as a side reaction, the hydroxyl group was protected with a triethylsilyl group. Protection of the hydroxyl group with the TES group allowed



Scheme 3. Total synthesis of catunaregin (**1**). Reagents and Conditions: a) TESOTf, DBU, CH_2Cl_2, –50 °C, 20 h, 90%; b) $LiBH_4$, THF, 50 °C, 26 h, 77%; c) conc. H_2SO_4–THF (1:5), rt, 8 h, 62% for **16**, and 4% for **14**; d) PhSH, Cs_2CO_3, MeCN, rt, 1.5 h, quant. TESOTf: triethylsilyl trifluoromethanesulfonate; DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene.

cleavage of the oxazolidinone part. Thus, after treatment of **13** with TESOTf and DBU at –50 °C, hydride reduction of the resulting TES ether with $LiBH_4$ under mild conditions gave the primary alcohol **15**, the precursor to successive ketalization, in 69% yield over 2 steps. The key successive ketalization of **15** was then carried out. After many reaction conditions (acids, solvents, and temperature) were attempted, treatment of **15** with concentrated sulfuric acid in THF at room temperature for 8 h gave the best result to afford the tricyclic compound **16** in 62% yield along with a small amount of diol **14** (4%). Construction of tricyclic skeleton by this key reaction was achieved without generating benzyl cation due to electron withdrawing effect of *o*-Ns group.

Finally, cleavage of the *o*-Ns group of **16** with thiophenol and cesium carbonate[8,9] gave the target molecule in quantitative yield. The spectral data of the synthetic sample **1** was identical to those of the reported natural catunaregin (**1**). The optical rotation of the synthetic sample was $[\alpha]_D^{25}$ +38.6 (c 1.00, MeOH). This result confirms that the isolated natural catunaregin is in the racemic form as speculated by Zhang.

Conclusions

The first asymmetric total synthesis of catunaregin (**1**) was accomplished. The key steps of this synthesis involved *syn*-selective Evans aldol reaction and successive ketalization to construct the oxygen-bridged tricyclic furopyran framework. This result established that the naturally occurring catunaregin was isolated in racemic form. Studies of biological activity of the optically pure catunaregin are currently underway in our laboratory.

Acknowledgements

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