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Total synthesis of (−)-xanthatin

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Abstract

The first enantioselective total synthesis of xanthatin, a xanthanolide sesquiterpenoid exhibiting potent antibacterial activity against MRSA, has been accomplished from an optically pure bicyclic lactone, previously synthesized by our group.

Xanthanolides[1] are a class of sesquiterpenoids found in a plant of the Xanthium family. Because of their intriguing biological profiles, several members of this class have attracted considerable attention among synthetic organic chemists. Xanthatin (**1**) was first isolated from *Xanthium pennsylvanicum* by Little et al.[2] in their examination of the cocklebur for its antibacterial principle. Its structure was firmly established by Geissman et al.[3] who suggested that **1** would be derived from xanthinin during isolation, particularly on column chromatography.[4] Xanthatin (**1**) has also been isolated from *X. strumarium*,[1] *X. sibiricum*,[5] and *X. macrocarpum*,[6] and exhibits potent antibacterial activity against *Staphylococcus aureus* species, including MRSA.[5] The unique structural features of the xanthanolides have provided the motivation for the development of synthetic strategies toward these natural products.[7] In this Letter, we report the first total synthesis of (−)-xanthatin (**1**) (Fig. 1).

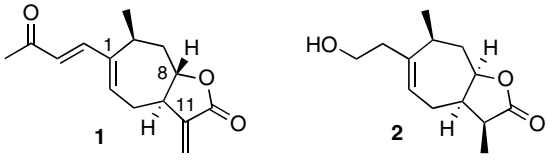
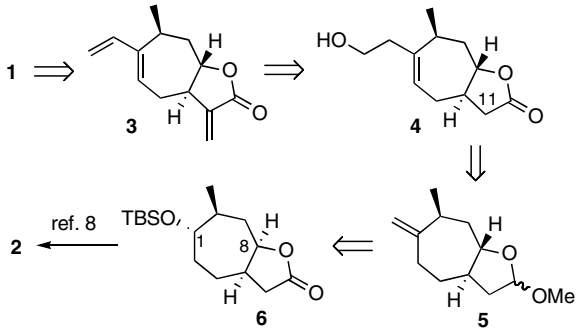


Fig. 1. Structures of (−)-xanthatin (**1**) and (+)-sundiversifolide (**2**).

We recently reported the total synthesis of sundiversifolide (**2**),[8] in which the bicyclic lactone **6** played an important role, and suggested that **6** could also be utilized as a common chiral building block in the total synthesis of **1**. The retrosynthetic analysis is shown in Scheme 1. Xanthatin (**1**) could be obtained by a cross metathesis[7a,b] between methyl vinyl ketone and **3**, which would be prepared from **4** by a methylenation at C11 (xanthatin numbering) and dehydration sequence. The ethanol side chain in **4** could be installed using the carbonyl ene reaction[9] of **5**, which in turn would be constructed from **6** via a key inversion at C8 and the introduction of the *exo*-methylene group at C1.

The treatment of **6**,[8] which has been prepared diastereoselectively from 4-pentenal via a 9-step sequence in 50% overall yield, with diethylamine and aluminum chloride[10]



Scheme 1. Retrosynthetic analysis of **1**.

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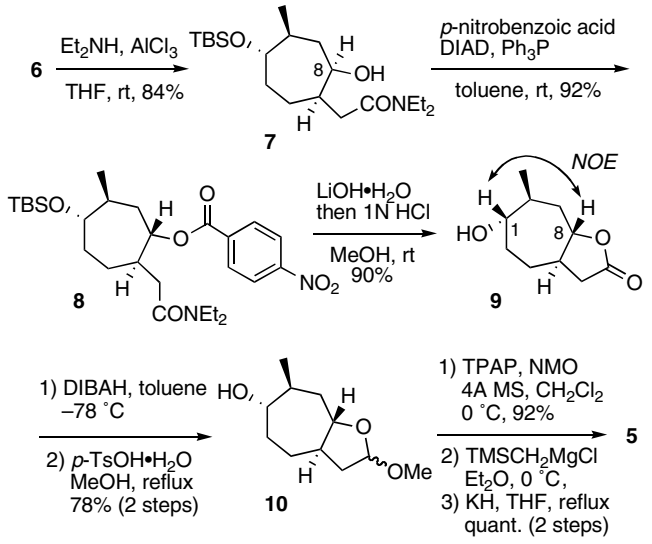
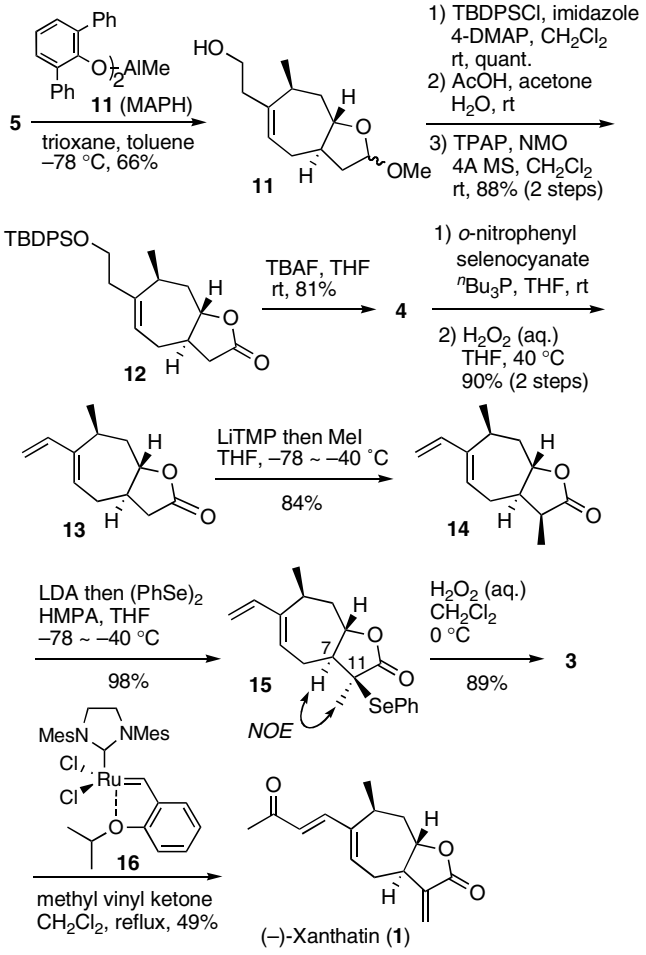


Scheme 2. Synthesis of **5**. DIAD = diisopropyl azodicarboxylate; DIBAH = diisobutylaluminum hydride; TPAP = tetrapropylammonium perruthenate; NMO = *N*-methylmorpholine *N*-oxide.

provided the amide alcohol **7**. The Mitsunobu reaction with DIAD, triphenylphosphine, and *p*-nitrobenzoic acid[11] cleanly produced the inverted benzoate **8**, which was then subjected to alkaline hydrolysis followed by acidic treatment to afford the trans-fused bicyclic lactone **9** in good overall yield. The desired stereochemistry at C8 was secured by the observation of a diagnostic NOE between C8-H and C1-H. After protection of the lactone carbonyl in **9** as the acetal, the secondary alcohol in **10** was oxidized with TPAP and NMO to provide the corresponding ketone. Attempted introduction of the *exo*-methylene moiety at C1 using conventional methods (e.g., Wittig and Horner–Wadsworth–Emmons protocols, and the Nozaki–Lombardo method[12]) gave only unsatisfactory results. However, Peterson olefination conditions[13] provided an excellent result. Thus, sequential treatment of the ketone with $TMSCH_2MgCl$ and KH in refluxing THF produced **5** quantitatively (Scheme 2).

Installation of the olefinic ethanol appendage at C1 was realized by the treatment of **5** with methylaluminum bis(2,6-diphenylphenoxide) (MAPH)[9] and trioxane to give **11**. Sequential protection of the primary hydroxyl group as the TBDPS ether, regeneration of the lactone moiety, and desilylation provided **4** in good overall yield. Exposure of **4** to *o*-nitrophenyl selenocyanate and $^nBu_3P$ gave the selenide, which was oxidized with hydrogen peroxide[14,15] to give diene **13**. Attempted introduction of the *exo*-methylene group at C11 under conditions employing the Eschenmoser salt[16] led to the formation of **3** in quite low yield. Therefore, compound **13** was treated with LiTMP and methyl iodide to give, as a single product, **14**, which was identical with the compound prepared by Morken, et al., during their total synthesis of (−)-11α,13-dihydroxanthatin.[7a] Introduction of a phenylselenyl group at C11 was carried out with LDA and diphenyl diselenide[17] to give



Scheme 3. Completion of total synthesis of **1**. LiTMP = lithium tetramethylpiperidide.

selenide **15** as a single diastereomer. The assignment of the stereochemistry at C11 was made based on the NOE between C7-H and C11-Me. Selenide **15** was then exposed to hydrogen peroxide to furnish the requisite triene **3** selectively. Final construction of the butenone side chain at C1 was successfully accomplished by a chemoselective cross metathesis[18] employing the Hoveyda catalyst **16**[19,7b] to provide (−)-xanthatin (**1**),[20] whose spectral data (^1H and ^{13}C NMRs) were identical with those of natural xanthatin (Scheme 3).

In summary, we have completed the first enantioselective total synthesis of the antibacterial xanthanolide, xanthatin (**1**), starting from the optically pure cis-fused bicyclic lactone **6** employing an efficient conversion to the trans-fused lactone **9** as the key step. The synthetic route developed here holds considerable promise for the synthesis of related natural products.

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