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Formal Total Synthesis of Actinoranone and Asymmetric Synthesis of Labda-7,13-(*E*)-dien-15-ol

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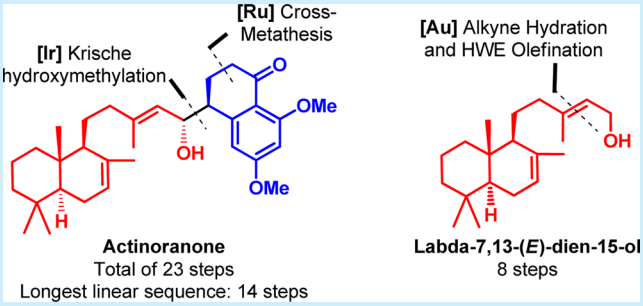
Supporting Information

ABSTRACT: The syntheses of the polyketide and terpenoid fragments of actinoranone are reported in a concise fashion, relying on catalytic methods. Minimization on the use of protecting groups and redox reactions allowed the synthesis of the carbon backbone of actinoranone in 20 steps (11 steps for LLS). The asymmetric synthesis of labda-7,13-(*E*)-dien-15-ol is also disclosed.



Natural products (NPs) and structures inspired by their molecular architectures have played a remarkable role in the drug discovery field, representing more than half of all small-molecule approved drugs between 1981 and 2014.[1] These structures usually display more stereogenic centers, sp^3-hybridized carbon atoms, and a higher number of oxygen atoms than synthetic compounds not related to NPs. In view of this unique structural diversity, natural products are still considered privileged scaffolds for drug discovery. However, the synthesis of complex NPs has always been a challenging task, and due to several factors, especially funding constraints, there is an urgent need to shorten the routes for obtaining these complex molecules. New strategies, such as catalytic methods and/or protecting group-free syntheses, or even better, the identification of key fragments responsible for the desired biological effect could simplify the synthetic endeavor.[2]

In view of our interest in the application of NPs as lead compounds for the development of new antitumor agents,[3] we turned our attention to the natural meroterpenoid actinoranone, which was isolated in 2013 by Fenical and co-workers from marine actinomycetes (strain CNQ-027). This unusual compound, with diterpene and polyketide scaffolds, showed substantial in vitro cytotoxicity (LD_{50} = 2.0 μg/mL) against the human colon carcinoma cell line (HCT-116).[4]

Fenical's work detailed the structure elucidation of actinoranone leading to the establishment of relative configuration of the octalin terpenoid motif. The use of advanced Mosher's method[5] and NOESY analysis allowed the definition of the (*R*) configuration at C15 and the (*R*) configuration at C8′, respectively (Figure 1).

Very recently, Xu, Ye, and co-workers reported the first synthesis of actinoranone and three other diastereoisomers, thereby assigning the correct structure of this NP. Their synthesis was accomplished in 29 steps (19 steps for the longest linear sequence)[6] and allowed comparison with the isolation

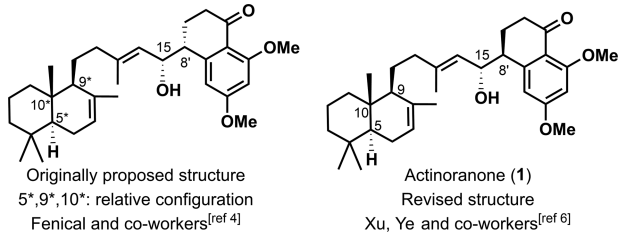


Figure 1. Originally proposed (left) and revised (right) structures for actinoranone (**1**).

data. Thus, the absolute configuration of the terpenoid fragment was established as (5*S*,9*S*,10*S*), the stereogenic center at C15 was confirmed as (*R*), and C8′ was revised as possessing the (*S*) configuration (Figure 1). Once again, this work highlights the difficulty to correctly elucidate the structure of complex natural products, despite the considerable developments in spectroscopic methods over the last decades.[7]

With the aim of understanding more about this natural product, we intended to develop a concise approach to actinoranone (**1**), which would be suitable for the easier preparation of analogues and also establish short routes for its key moieties (terpenoid and polyketide), enabling the assessment of their importance for the bioactivity of this class of compounds.

In terms of our retrosynthetic approach, we chose the option to use the same final disconnection employed by Xu and Ye, relying on the connection of the key intermediates vinyl iodide **2** and the alcohol **5**. We envisioned that iodide **2** could be prepared via a decarboxylative iodination using ester **3**, and its exocyclic *E*-alkene would arise from a Horner−Wadsworth−Emmons (HWE) olefination (Scheme 1). As for the tetralin

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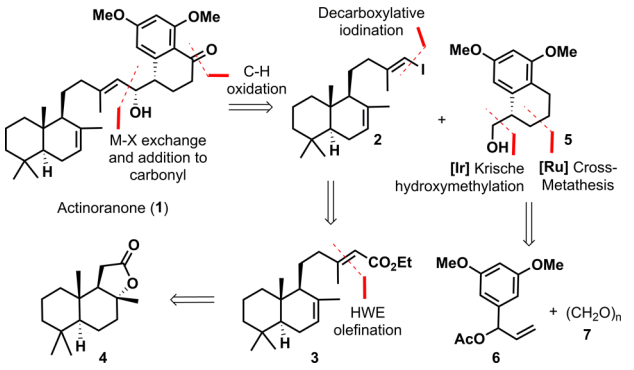
moiety, the alcohol **5** could be prepared using ruthenium and iridium catalysts, starting from the allylic acetate **6** and paraformaldehyde (**7**) (Scheme 1).

Scheme 1. Retrosynthetic Analysis to Actinoranone



The first challenge addressed was the formation of the endocyclic trisubstituted alkene. Initially, we employed a sequence previously reported by de la Torre,[8] consisting of the conversion of (+)-sclareolide (**4**) to the Weinreb amide **8** and elimination of the tertiary alcohol with $SOCl_2$ in pyridine (Scheme 2). This elimination protocol furnished the *exo*-olefin as the major product (70% yield), whereas the desired product was obtained in only 21% yield. Moreover, exhaustive separations of the isomers using column chromatography were necessary to obtain pure **9**. Isomerization of the *exo*-olefin to the *endo*-olefin promoted by *p*TSA as reported by de la Torre furnished poor results in our hands, which led us to seek an alternative strategy.

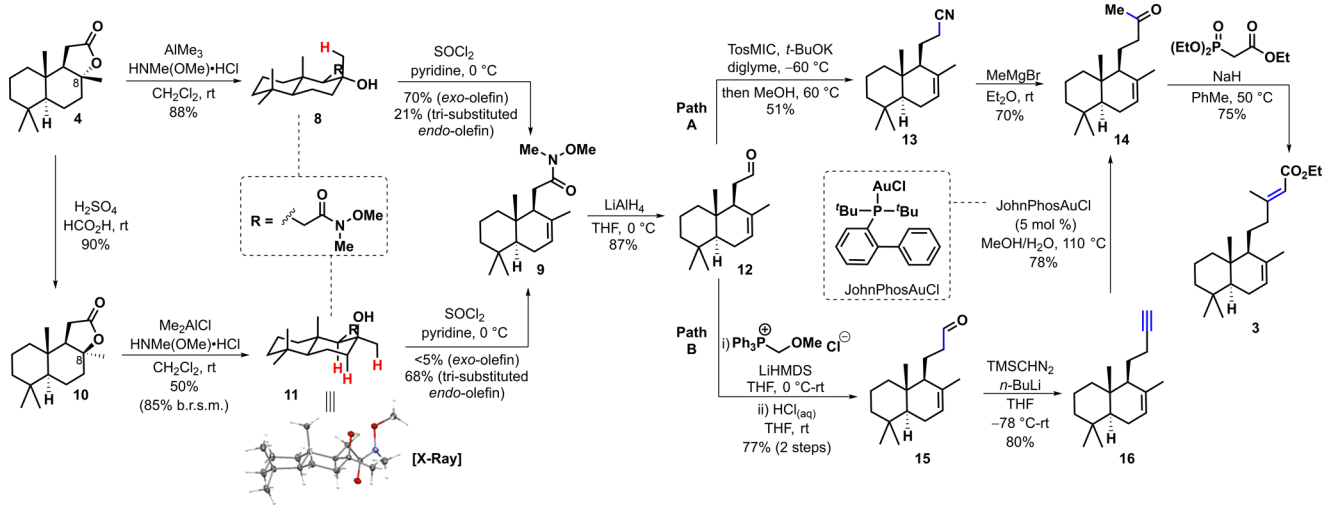
Since compound **8** has the hydroxyl group in an equatorial position, elimination to furnish the *endo*-olefin **9** would occur only by E1 elimination, while the *exo*-olefin could be generated either by E1 or E2 (red hydrogen) mechanisms. To allow the E2 mechanism toward the desired *endo*-olefin **9**, the hydroxyl group should therefore be in the axial position. Thus, this strategy was initiated by epimerization of (+)-sclareolide at C8, using sulfuric acid in formic acid.[9] Next, Weinreb amide **11** was produced using Me_2AlCl[10] in 50% yield (85% based on recovered starting material). Evaluation of longer reaction times or higher temperatures did not improve the yield of amide **11**. As we anticipated, X-ray diffraction analysis confirmed the stereochemistry of compound **11** having the hydroxyl group in the axial position. To our delight, when the same elimination conditions were applied with **11**, the desired trisubstituted *endo*-olefin **9** was obtained in 68% yield with a small amount of the *exo*-olefin (<5%).

Thereafter, we undertook the elaboration of the side chain, reducing Weinreb amide **9** with $LiAlH_4$ to aldehyde **12**. The latter was subjected to homologation to the corresponding nitrile **13** via a van Leusen reaction[11] followed by a Grignard addition to deliver methyl ketone **14**. An alternative approach employed a one-carbon homologation of aldehyde **12** via a Wittig reaction using the ylide generated from methoxymethyltriphenylphosphonium chloride, followed by hydrolysis of the respective enol ether. The resulting aldehyde (**15**) was converted to the corresponding terminal alkyne **16** by treatment with $TMSCHN_2$ and *n*-BuLi. Next, alkyne **16** was converted to methyl ketone **14** using a gold(I)-catalyzed alkyne hydration.[12] Finally, a HWE olefination afforded *α,β*-unsaturated ester (**3**).

Vinyl iodide **2** was synthesized from ester **3** in two steps by means of basic hydrolysis followed by a decarboxylative iodination[13] of acid **17** (Scheme 3). It is worth mentioning that in our approach this key intermediate was obtained in nine steps from **4**, which represents a considerable improvement when compared to the 15 steps described in the work of Xu and Ye. Our shorter synthesis of compound **2** was possible mainly by avoiding the use of protecting groups[14] and minimizing redox reactions.[15]

The synthesis of the tetralin fragment (Scheme 3) started with an enantioselective hydroxymethylation of allylic acetate **6** (prepared in two steps from 3,5-dimethoxybenzaldehyde; see the Supporting Information for more details) using iridium catalysis,[16] furnishing alcohol **18** in a very straightforward manner. The latter was protected with a TBDPS group, and the last carbon of the fragment was introduced by a cross-metathesis reaction with (*E*)-crotonaldehyde and Grubbs second-generation catalyst[17] to furnish enal **20**. Next, the alkene was reduced using a catalytic hydrogenation, and the aldehyde was treated with *p*TSA·H_2O to promote cyclization and dehydration of the alcohol intermediate, thus yielding

Scheme 2. Synthesis of the Terpenoid Fragment 3



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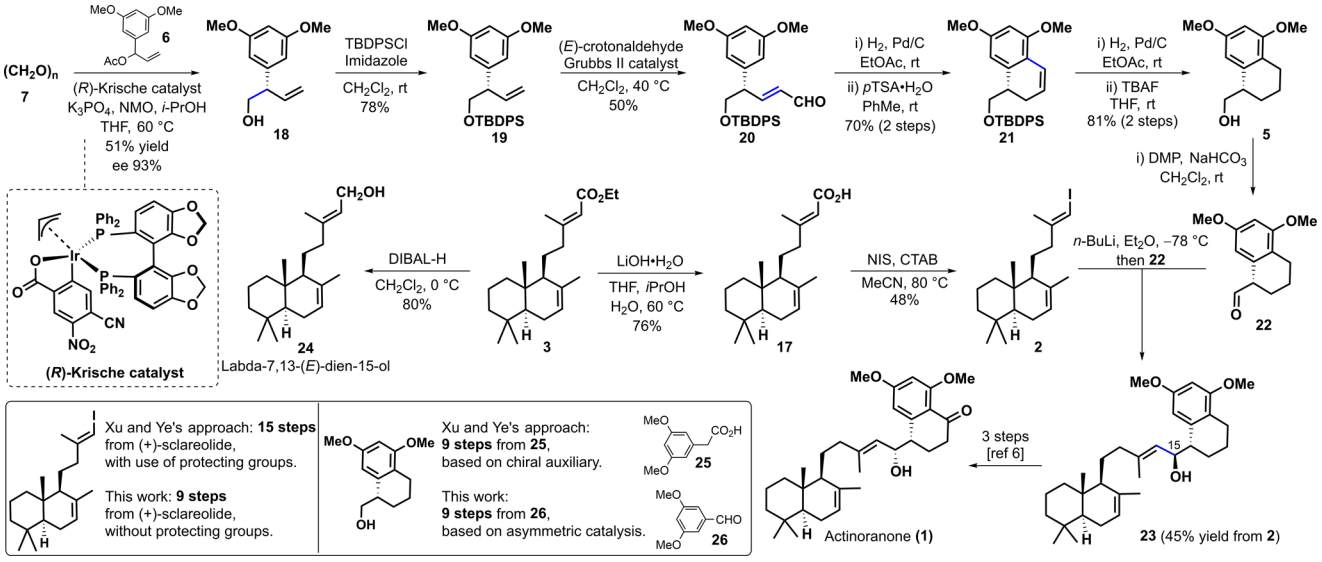
Scheme 3. Synthesis of Actinoranone



compound **21**. Finally, alcohol **5** was obtained after a second catalytic hydrogenation followed by removal of the protecting group. In our approach, the same number of steps were necessary to achieve **5**. However, while in the work of Xu and Ye the introduction of chirality was based on the use of a chiral auxiliary, our strategy relied on the use of catalytic transformations, including a recently developed enantioselective hydroxymethylation.

Finally, in order to join both terpenoid and tetralin fragments, alcohol **5** was oxidized with Dess–Martin periodinane, and after purification, aldehyde **22** was immediately used in the next step. Vinyl iodide **2** was subjected to a halogen–metal exchange with *n*-BuLi and treated with aldehyde **22**, leading to the formation of alcohol **23**[18] (Scheme 3), whose spectroscopic data were identical to those reported in the literature. According to the work of Xu and Ye, **24** could be converted to actinoranone (**1**) in three steps (Mitsunobu esterification, C–H oxidation and basic hydrolysis).

During the synthesis of the terpenoid fragment of actinoranone, we envisioned that the natural product labda-7,13-(*E*)-dien-15-ol (**24**)[19] could also be prepared from ester **3**. Thus, the synthesis of diterpene **24** was accomplished with a DIBAL-H reduction of ester **3**.

In summary, the formal total synthesis of actinoranone (**1**) was reported. The synthesis of the terpenoid fragment was based on the strategic epimerization at C8 of (+)-sclareolide (**4**) followed by a regioselective elimination reaction. Two sequences were evaluated to convert aldehyde **12** to ketone **14**. The carbon backbone of actinoranone (**1**) was forged by coupling two key fragments via a halogen–metal exchange of a vinyl iodide and treatment with an aldehyde. The first terpenoid fragment was obtained in nine steps from (+)-sclareolide (**4**), whereas the second fragment was prepared in nine steps from 3,5-dimethoxybenzaldehyde (**26**), employing a recently developed iridium catalyzed enantioselective hydroxymethylation and a ruthenium-catalyzed cross-metathesis reaction. The first asymmetric synthesis of labda-7,13-(*E*)-dien-15-ol (**24**) was also reported.

This work combines powerful classical and newly developed reactions and comes closer to a more efficient synthesis of actinoranone using step-count as the fundamental parameter on the evaluation of strategy efficiency.[20] Minimization of redox reactions, use of protecting groups, and reactions that do not contribute to enhance the complexity of the molecule must be seriously considered to approach an ideal synthesis of complex NPs.[21] Evaluation of the cytotoxic profile of actinoranone (**1**), labda-7,13-(*E*)-dien-15-ol (**24**), and compound **5**, which contains the polyketide scaffold, will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01287.

Experimental procedures, NMR spectra, GC/MS analyses (PDF)

X-ray data for compound **11** (CIF)

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Notes

The authors declare no competing financial interest.

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