

β -Hydroxy- γ -lactones as nucleophiles in the Nicholas reaction for the synthesis of oxepene rings. Enantioselective formal synthesis of (–)-isolaurepinnacin and (+)-rogioloxepane A†

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The enantioselective formal synthesis of (–)-isolaurepinnacin and (+)-rogioloxepane A has been achieved. The key steps are an intermolecular Nicholas reaction with a β -hydroxy- γ -lactone as the nucleophile, to form branched linear ethers, and an olefin ring-closing metathesis to obtain the oxepene core.

Medium-ring oxacycles are a common structural feature present in many ladder ether marine toxins, which have important implications with regard to their biological impact. Furthermore, medium-ring ethers are the structural skeletons of an important group of marine natural products, called lauroxanes. Lauroxanes are a series of nonterpenoid C₁₅-metabolites derived from fatty acid metabolism (acetogenins) that have been isolated from the *Laurencia* species of red algae, and those marine organisms which feed on them. These compounds display a wide range of biological activity including antitumor, antimicrobial, antifeedant, immunosuppressant, and pesticide activity.¹ Their fascinating structures and biological activities have stimulated the imagination and have been a challenge for synthetic chemists.² Seven-membered cyclic ethers are less common in lauroxanes and therefore synthetic approaches to them have been limited. The most representative examples of lauroxanes containing the oxepene ring are (+)-isolaurepinnacin (1) and (+)-rogioloxepane A (2) (Fig. 1).

Isolaurepinnacin (1) was isolated from *Laurencia pinnata* Yamada collected at Motsuta point, Hokkaido (Japan) in 1981 by Fukuzawa and Masamune.³ Rogioloxepane A (2) was isolated from *Laurencia microcladia* Yamada off the torrent II Rogiolo in the Mediterranean in 1992 by Pietra's group.⁴ Isolaurepinnacin (1) contains an

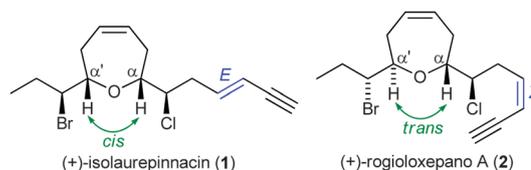


Fig. 1 Representative examples of lauroxepanes.

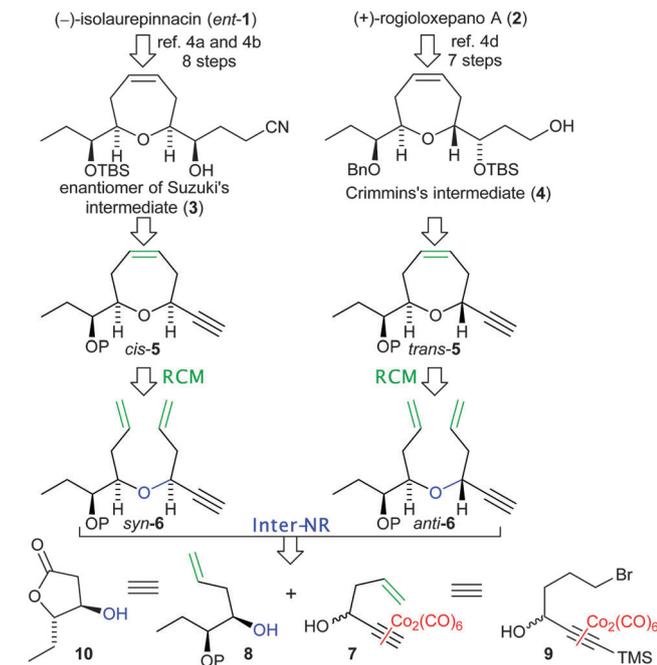
α, α' -*cis*-disubstitution oxepene ring and a conjugate *trans*-enyne unit, while rogioloxepane A (2) has an α, α' -*trans*-disubstitution pattern and a conjugate *cis*-enyne unit, both compounds having four stereogenic centers (Fig. 1). To date there is only one enantioselective synthesis and one stereoselective synthesis reported for each one of these natural products.⁵ As part of our continuing program directed at the synthesis of biologically active substances of marine origin⁶ and the development of new synthetic methodologies for the construction of medium-ring ethers,⁷ we embarked on the enantioselective formal synthesis of (–)-isolaurepinnacin (*ent*-1) and (+)-rogioloxepane A (2). Recently, we developed a new strategy for the synthesis of medium-ring oxacycles based on an intermolecular Nicholas reaction⁸ (interNR) to form unsaturated branched linear ethers and a ring closing olefin metathesis (RCM) to obtain the cobalt complex cyclic ethers. Using this approach we were able to obtain saturated cyclic ethers of seven, eight and nine members such as (+)-*cis*- and (–)-*trans*-lauthisan and (+)-*cis*- and (+)-*trans*-obtusan, whose structures represent the basic skeletons present in a number of these naturally occurring non-terpenoid seven-, eight-, and nine-membered ring ethers.⁹ Additionally, the methodology was exemplified by the formal synthesis of (+)-laurencin, a lauroxane with an eight-membered cyclic ether.^{9c}

Our initial synthetic approach is envisaged in Scheme 1. The key features of the route included: first, the synthesis of the branched linear ethers by an interNR using the acetylenic cobalt complex 9 as the electrophile and the enantioenriched monoprotected diol 8 as the nucleophile. It should be mentioned that bromide 9 is a very convenient synthetic equivalent of enyne 7 during the interNR coupling to avoid elimination of the alcohol.^{9c} Afterwards, we planned that the unsaturated branched ethers 6 would be obtained through a simple reaction sequence: decomplexation and elimination of

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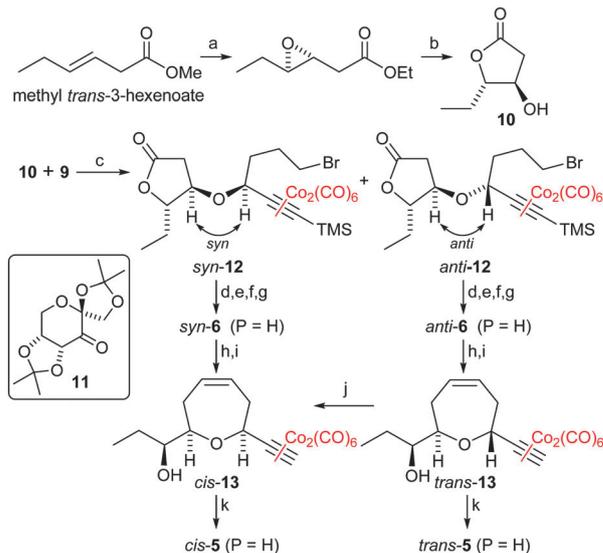
† Electronic supplementary information (ESI) available: Detailed experimental procedures and copies of ¹H and ¹³C NMR spectra of all compounds. See DOI: 10.1039/c4cc00389f



Scheme 1 Retrosynthetic analysis.

the bromide. Second, the RCM would provide the oxepenes **5**, which can be used as precursor for the synthesis of the compounds **3** and **4**. Oxepene **3** is the enantiomer of an advanced intermediate in the formal synthesis of (+)-isolaurepinnacin (**1**) reported by Suzuki and coworkers.^{5b} Furthermore, oxepene **4** is an advanced intermediate in the total synthesis of (+)-rogioloxepano A (**2**) developed by Crimmins and coworkers.^{5d}

After several fruitless attempts to achieve the interNR using monoprotected diol **8**, we pondered the use of β -hydroxy- γ -lactone **10** as its synthetic equivalent.¹⁰ Our thoughts were based on the hypothesis that **10** introduces the correct stereochemistry in two stereocenters and would be a less sterically hindered and more conformationally constrained nucleophile. The synthesis began with the commercially available methyl *trans*-3-hexenoate, which was subjected to a Shi asymmetric epoxidation.¹¹ Then, the obtained epoxide was treated with acid aqueous solution to afford the γ -lactone **10** in good yield, albeit with an enantiomeric ratio (er) of 87 : 13 (Scheme 2).¹² From the synthetic standpoint, the relatively low er of the compound **10** does not represent a major problem for the enantiomeric purity of the final products, because another asymmetric epoxidation has been planned at a later stage of the synthetic route (*vide infra*). The next step was the interNR between the γ -lactone **10** and the cobalt complex **9**^{9c} to afford in good yields the doubly branched ethers *syn*-**12** and *anti*-**12**, as an equimolar epimeric mixture in the newly created stereocenter. These hexacarbonyl dicobalt complexes were easily separated by column chromatography on silica gel. At this point of the synthesis, we were unable to determine which one was the *syn* complex, and which one was the *anti*. Therefore, the stereochemistry determination was postponed to more advanced intermediates. Decomplexation of the $\text{Co}_2(\text{CO})_6$ -complexes of *syn*-**12** and *anti*-**12** and further bromide elimination using a variant of the Grieco reaction provided

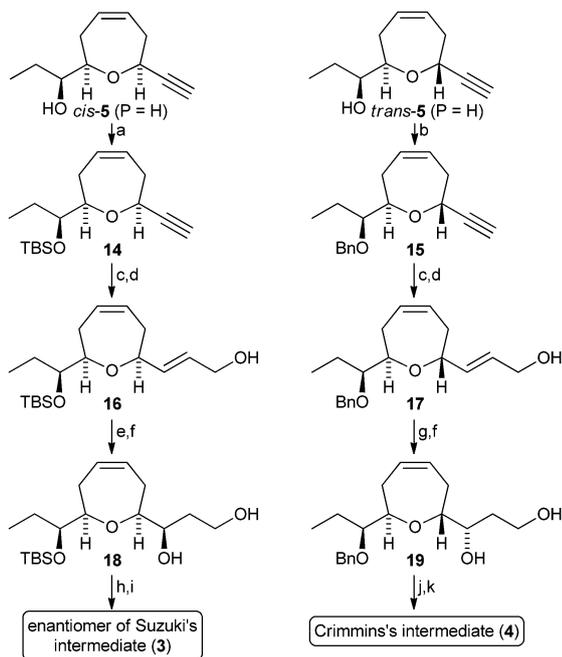


Scheme 2 Reagents and conditions: (a) Oxone, K_2CO_3 , CH_3CN /buffer pH = 10.5 (1 : 1), **11**, 0 °C; (b) 3% H_2SO_4 (aq), 81% after 2 steps; (c) $\text{BF}_3\cdot\text{OEt}_2$, CH_2Cl_2 , 0 °C, dr 1.0 : 1.0, 70%; (d) CAN, acetone, 0 °C, 97%; (e) (1) *o*- NO_2PhSeCN , NaBH_4 , EtOH, rt, (2) 30% H_2O_2 , 0 °C, quantitative; (f) DIBAL-H (1 equiv.), THF, -78 °C; (g) $\text{CH}_3\text{PPh}_3^+\text{Br}^-$, *n*-BuLi, THF, -78 °C \rightarrow -20 °C, 3 h, 89% after 2 steps; (h) $\text{Co}_2(\text{CO})_8$, CH_2Cl_2 , rt; (i) 2nd generation Grubbs' catalyst, CH_2Cl_2 , 40 °C, 84% after 2 steps; (j) $\text{BF}_3\cdot\text{OEt}_2$, CH_2Cl_2 , 0 °C, 94%; (k) CAN, acetone, 0 °C, 95%.

the terminal alkenes in one of the branches.¹³ The syntheses of the dienes *syn*-**6** (P=H) and *anti*-**6** (P=H) were accomplished by two consecutive steps: reduction with one equivalent of DIBAL-H and one-carbon homologation by the Wittig-olefination of the lactol obtained. Interestingly, when water was used to quench the Wittig reaction the TMS group was removed from the terminal alkyne.

Before the cyclization step by RCM, the complexation of the alkyne groups were carried out with $\text{Co}_2(\text{CO})_8$, affording the cobalt-complexes. This complexation generated a series of advantages: first, the cobalt complex should avoid the undesirable participation of the triple bond in the metathesis process,¹⁴ and second, the $\text{Co}_2(\text{CO})_6$ -alkyne can be used as a stereochemical control agent for an isomerization process. With the diene complexes in hand, closure of the oxepenes with the second-generation Grubbs' catalyst was performed. Thus, exposure of diene cobalt-complexes to 30 mol% of the catalyst in dichloromethane (0.004 M) at reflux, cleanly produced the desired and easily separable cycle-complexes *cis*-**13** and *trans*-**13** in excellent yields. Cleavage of the hexacarbonyl dicobalt from complexes *cis*-**13** and *trans*-**13** provided the oxepenes *cis*-**5** (P=H) and *trans*-**5** (P=H), which were used to establish the stereochemistry of both isomers by NOE studies.¹⁵ At this stage of the synthesis, we also pondered the possibility of performing an isomerization of the *trans*-isomer to the *cis*-isomer considering that such a stereoisomer is thermodynamically more stable. It was successfully performed under acidic conditions using boron trifluoride diethyl etherate as the acid.¹⁶

The next step was the protection of the secondary alcohol with the same protective groups present in the target molecules **3** and **4**, *i.e.* *t*-butyldimethylsilyl (TBS) and benzyl (Bn), obtaining the oxepenes **14** and **15**, respectively (Scheme 3). Once we had



Scheme 3 Reagents and conditions: (a) TBSOTf, imidazole, CH_2Cl_2 , rt, 92%; (b) NaH, BnBr, TBAI (cat), THF, 87%; (c) *n*-BuLi, THF, 15 min, then $(\text{CH}_2\text{O})_n$, -40°C to rt, 2 h, 93% for **14**, 94% for **15**; (d) LiAlH_4 , THF, rt, 92% for **14**, 95% for **15**; (e) (+)-DET, $\text{Ti}(\text{OPr-}i_4)$, *t*-BuOOH, 4 Å MS, CH_2Cl_2 , -20°C , 84%; (f) RedAl, THF, rt, 90% for **16**, 93% for **17**; (g) (–)-DET, $\text{Ti}(\text{OPr-}i_4)$, *t*-BuOOH, 4 Å MS, CH_2Cl_2 , -20°C , 84%; (h) TSCl, Et_3N , CH_2Cl_2 , DMAP (cat), rt, quantitative; (i) NaI, NaCN, CH_3CN , 80°C , 80%; (j) TBSOTf, imidazole, Et_3N , rt; (k) TFA, $\text{THF:H}_2\text{O}$, 0°C , 86% after 2 steps.

successfully built the left part of the advanced intermediates **3** and **4**, we focused our attention on the conversion of the terminal alkynes into the right side chains. The best approach found was the transformation of the terminal alkynes to the allylic alcohols **16** and **17** by coupling of the lithium salts of the alkynes with paraformaldehyde followed by reduction of the propargylic alcohols with LiAlH_4 . In order to introduce the secondary alcohol adjacent to the oxepene rings, Katsuki–Sharpless asymmetric epoxidations¹⁷ were performed with the allylic alcohols **16** and **17** using as chiral auxiliary (+)-diethyl tartrate¹⁸ and (–)-diethyl tartrate,¹⁸ respectively. Regioselective opening of the 2,3-epoxy-alcohols with Red-Al provided the two 1,3-diols **18** and **19** in excellent yields. The completion of the enantioselective formal synthesis of (–)-isolaurepinnacin (*ent*-**1**) from diol **18** dealt with the transformation of the primary alcohol into a cyano group. To achieve this goal, a one-carbon homologation of the primary alcohol was performed by a simple two-step sequence: selective tosylation and NaCN nucleophilic substitution. Finally, to achieve the enantioselective formal synthesis of (+)-rogioioxepane **2** the diol **19** was protected, as the bis-silyl ethers, followed by selective deprotection of the silyl ether of the primary alcohol with trifluoroacetic acid.

The iterative use of the $\text{Co}_2(\text{CO})_6$ acetylenic complex provides a powerful synthetic methodology to address the synthesis of seven-membered cyclic ethers. The strategy is based on two key steps: intermolecular Nicholas reaction using a β -hydroxy- γ -lactone as the nucleophile and a ring closing metathesis.

Using this strategy we performed, in few steps, the enantioselective formal synthesis of (–)-isolaurepinnacin and (+)-rogioioxepane **2**, two of the most representative lauroxanes with a seven-membered cyclic ether.

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- 18 The asymmetric epoxidation of the allylic alcohol provided two diastereoisomers, which were easily separated by column chromatography on silica gel. The major diastereomer (84% yield) has the correct configuration of all the stereocenters, and the other ($\approx 12\%$ yield) displays the correct configuration on the 2,3-epoxide, but the other three stereogenic centers are inverted, this is because the γ -lactone **10** is not optically pure. See ESI†.