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# Total Syntheses of the Marine Illudalanes Alcyopterosin I, L, M, N, and C

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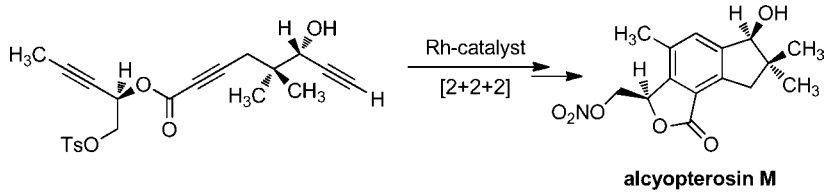
## ABSTRACT




**The combination of a modular assembly of enantiopure triynes and a powerful rhodium-catalyzed [2 + 2 + 2] alkyne cyclotrimerization reaction opens new and efficient entries to a set of alcyopterosins, including the first total synthesis of the alcyopterosins L, M, and C.**

Illudalane sesquiterpenes comprise a group of compounds being typical metabolites of both fungi and ferns.[1] Among these, the alcyopterosins represent a unique set of marine illudalanes isolated from the sub-Antartic deep sea soft coral *Alcyonium paessleri* (Figure 1).[2] More recently, other members of the alcyopterosin family were isolated from the Antarctic marine soft coral *Alcyonium grandis*.[3] Notably, the alcyopterosins represent the first ever reported illudalanes isolated from marine sources, and alcyopterosin E (**2**) and C (**4**) together with six other members of this family are the first nitrate esters to be found in any natural product. In vitro tests showed cytotoxicity toward the human larynx carcinoma cell line for alcyopterosin E (**2**), while alcyopterosin A (**1**) and C (**4**) were cytotoxic toward the HT-29 cell line.[2] Furthermore, remarkable DNA-binding properties have been described for alcyopterosin A (**1**) and its synthetic analogues.[4]

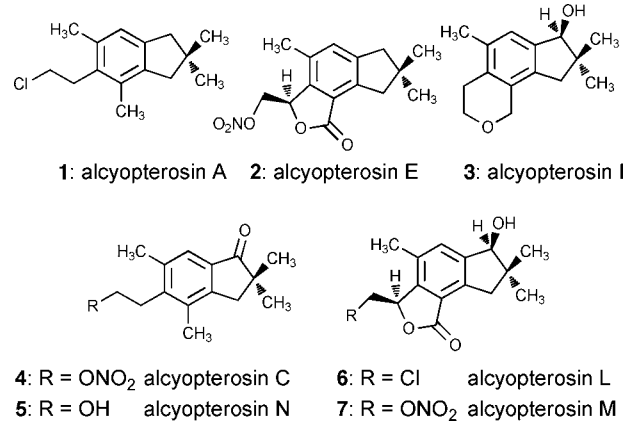



**Figure 1.** Alcyopterosins isolated from marine soft corals.

The total synthesis of some members of the alcyopterosin family has been reported already. The alcyopterosins A and N have been synthesized either by a classical multistep approach via the functionalization of a benzene core,[4] or by a titanium[5] or a palladium mediated cycloaddition reaction.[6] More recently, the synthesis of alcyopterosin I was reported within a study of rhodium-catalyzed intramolecular cyclizations of diynes with enones.[7] However, the asymmetric

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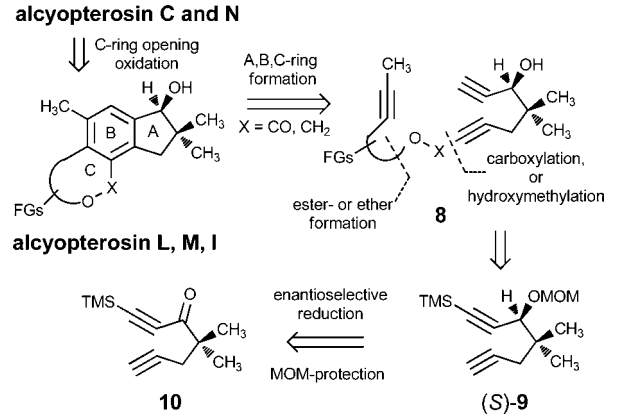
reduction of the thus obtained indanone proceeded only with poor enantioselectivity and therefore prevented a truly asymmetric approach to this set of natural products.

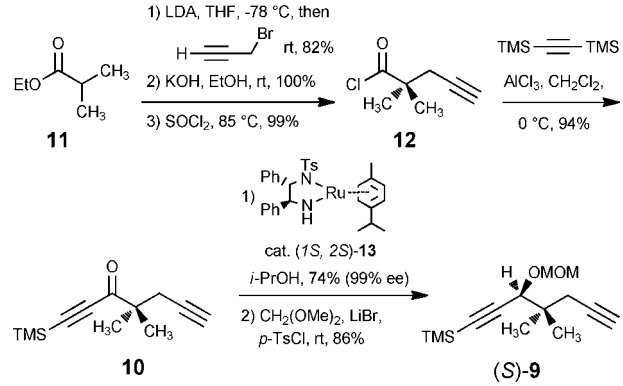
The transition metal catalyzed [2 + 2 + 2] alkyne cycloaddition is a powerful reaction for the construction of highly substituted benzenes.[8] However, despite its versatility and its atom- and step-economic features, applications of this capable catalytic method in natural product synthesis still remain rare.[9] One drawback of this methodology seems to be the often cumbersome synthesis of the functionalized triyne serving as the cyclotrimerization precursor. However, we have previously described the asymmetric synthesis of alcyopterosin E (**2**) that gains its advantage from the assembly of the triyne through a simple esterification.[9k]

We disclose here a synthetic strategy that is based on a modular approach to gain access to a set of alcyopterosins having either a tricyclic or a bicyclic core, and either one or two independent asymmetric centers. We envisaged that the alcyopterosin skeleton could be assembled through an ABC-ring formation approach based on transition metal catalyzed [2 + 2 + 2] cycloaddition reactions with suitable functionalized triynes **8** (Scheme 1). Depending on the tether lengths in **8**, this strategy should provide access to the angular fused [5−6−6]-, as well as the [5−6−5]-ring system of the targeted alcyopterosins. In turn the cyclotrimerization precursors, the triynes **8**, will be obtained via operational simple esterifications or ether formations. Furthermore, the overall synthetic strategy will take advantage of the use of chiral building blocks such as the diyne (*S*)-**9**, that should be received through an enantioselective reduction of the readily available ynone **10**.

**Scheme 1.** Retrosynthetic Analysis




**Scheme 2.** Preparation of the Key Building Block (*S*)-**9**




Scheme 2 summarizes the synthesis of the key building block (*S*)-**9**. Propargylation[10] of ethyl butyrate (**11**) with propargyl bromide was followed by saponification and conversion of the thus received carboxylic acid into the acid chloride **12** with thionyl chloride. Treatment of **12** with bis-trimethylsilyl acetylene in the presence of $AlCl_3$ resulted in a straightforward monoacylation of the bis-silylated acetylene[11] to give the ynone **10** (94% yield). Enantioselective transfer hydrogenation of **10** utilizing Noyori's catalyst[12] (1*S*,2*S*)-**13** in 2-propanol afforded the corresponding chiral alcohol with an excellent enantioselectivity (74% yield, 99% ee).[13] The thus obtained chiral propargylic alcohol was thereafter MOM-protected to provide the desired key building block (*S*)-**9** in 86% yield. Other enantioselective ketone reductions utilizing $LiAlH_4$/Darvon alcohol (46% yield, 31% ee),[14] or $BH_3-SMe_2$ in the presence of Garcia's (*S*)-oxazoborolidine (72% yield, 88% ee),[15] were less effective with **10**. These results confirm that Noyori's catalyst has

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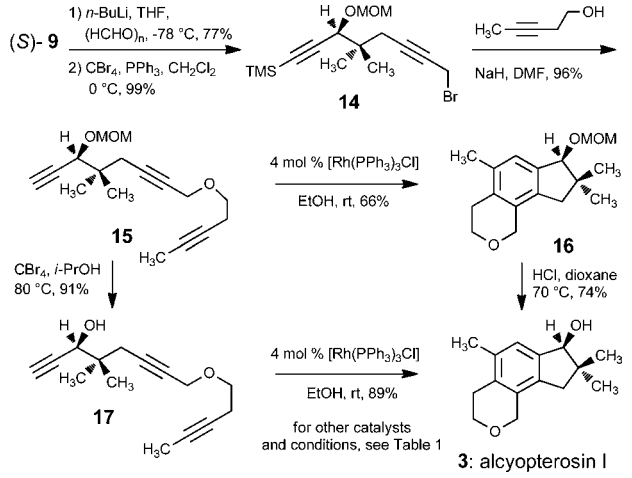
(13) The ee value was determined by chiral GC (CP-Chirasil-Dex CB) after its MOM-protection to give compound (*S*)-**9**.

outstanding reactivities and enantioselectivities toward sterically encumbered ynone substrates to furnish the corresponding propargylic alcohols.[16]

With the key building block (*S*)-**9** in hand, the synthesis of alcyopterosin I (**3**) was targeted (Scheme 3).

**Scheme 3.** Synthesis of Alcyopterosin I (**3**)




Hydroxymethylation of (*S*)-**9** followed by treatment with $CBr_4/PPh_3$ afforded the propargyl bromide **14**. Next, the triyne **15** was assembled in 96% yield via a simple ether formation between **14** and 3-pentyn-1-ol. At this stage, the construction of the angular fused [5−6−6]-ring system of alcyopterosin I via an ABC-ring formation approach was investigated.

The intramolecular [2 + 2 + 2] alkyne cyclotrimerization of **15** was performed in ethanol at room temperature with Wilkinson's complex ($[Rh(PPh_3)_3Cl]$) as a catalyst to give **16** in 66% yield. Subsequently, the targeted alcyopterosin I (**3**) was obtained via MOM-deprotection of **16** with HCl in dioxane. Alternatively, the total synthesis of the natural product **3** was accomplished by first removing the MOM protective group from triyne **15** to give **17** (91% yield), followed by the cyclotrimerization reaction utilizing Wilkinson's complex as a catalyst in ethanol (89% yield for **3**). Other catalysts for the transformation of **17** to **3** were examined and the results are listed in Table 1.

As can be seen, Wilkinson's complex (entry 1) as well as other cationic rhodium complexes (entry 6 and 7) served well for this purpose when the reactions were carried out in ethanol. Whereas the use of either [Cp*Ru(COD)Cl] or $[Ir(COD)Cl]_2$ in the presence of 2 equiv of diphenylphosphino ethane (DPPE) gave significantly lower yields.

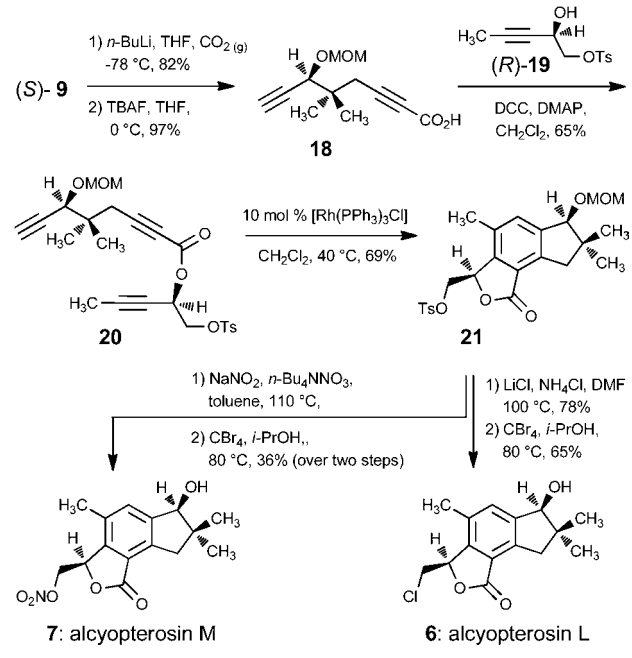
**Table 1.** Cyclotrimerization Studies of **17** To Give **3** in the Presence of 4 mol % of Catalyst

| entry | catalyst | solvent | temp (°C) | time (h) | yield (%) |
|---|---|---|---|---|---|
| 1 | $[Rh(PPh_3)_3Cl]$ | EtOH | 20 | 14 | 89 |
| 2 | $[Rh(PPh_3)_3Cl]$ | $CH_2Cl_2$ | 20 | 280 | 43 |
| 3 | $[Rh(PPh_3)_3Cl]$ | PhMe | 20 | 3 | 60 |
| 4 | [Cp*Ru(COD)Cl] | $CH_2Cl_2$ | 20 | 96 | 34 |
| 5 | [Cp*Ru(COD)Cl] | EtOH | 20 | 96 | 24 |
| 6 | $[Ir(COD)Cl]_2$/2 DPPE | EtOH | 60 | 160 | 30 |
| 7 | $[Rh(COD)_2BF_4]_2$/1 BINAP | EtOH | 20 | 4 | 90 |
| 8 | $[Rh(COD)_2BF_4]_2$/1 BINAP | $CH_2Cl_2$ | 60 | 264 | 46 |
| 9 | $[Rh(C_8H_{14})_2Cl]_2$/2 BINAP | EtOH | 60 | 120 | 71 |

The spectroscopic and analytical data of **3** were in agreement with those reported for alcyopterosin I isolated from the soft coral *Alcyonium paessleri*. The optical rotation of synthetic **3** ($[\alpha]^{25}_D$ +19.1 (*c* 2.39, $CHCl_3$)) was in conformity with that of the natural product ($[\alpha]^{25}_D$ +6.2 (*c* 2.59, $CHCl_3$))[2] and thereby verifying the absolute configuration not only of synthetic **3**, but also the absolute configuration of (*S*)-**9** obtained by the enantioselective transfer hydrogenation (Scheme 2).

With the aim to emphasize on the modular approach toward this set of natural products, the total synthesis of alcyopterosin L (**6**) and M (**7**) was investigated next (Scheme 4). Carboxylation of the terminal alkyne moiety of (*S*)-**9** was accomplished in 82% yield by its deprotonation with *n*-butyllithium at −78 °C followed by the addition of gaseous carbon dioxide. Subsequently, diyne **18** was obtained in 97%

**Scheme 4.** Synthesis of Alcyopterosin L (**6**) and M (**7**)

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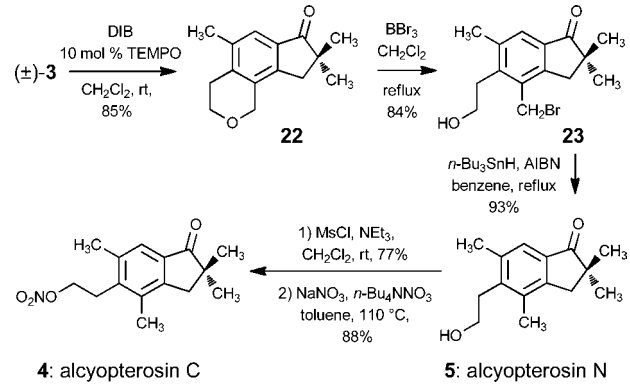
yield after removal of the trimethylsilyl protective group with tetrabutylammonium fluoride (TBAF) in THF. The dicyclohexylcarbodiimide (DCC) mediated esterification of **18** with the readily available propargylic alcohol (*R*)-**19**[17] proceeded with retention of the absolute configuration, to give the thus assembled enantiopure triyne ester **20** (65% yield).

Gratifyingly, the intramolecular cyclotrimerization of the exceedingly functionalized triyne ester **20** mediated by Wilkinson's catalyst proceeded at 40 °C and secured the assembly of the angular [5−6−5]-ring system of compound **21** (69% yield). The conversion of **21** into alcyopterosin L (**6**) commenced with the nucleophilic substitution of the tosyl ester against a chlorine atom using LiCl/$NH_4Cl$ in DMF. This was followed by cleavage of the MOM-ether with $CBr_4$ to furnish **6**, in 65% yield. Likewise, the total synthesis of alcyopterosin M (**7**) was accomplished in 36% yield over two steps by first displacing in **21** the tosyl ester against the nitrate ester functionality,[18] followed by a MOM-deprotection with $CBr_4$.

To examine the feasibility of the ABC-ring formation approach to gain access to the bicyclic members of the alcyopterosin family, we next focused on the synthesis of alcyopterosin N (**5**) and C (**4**) (Scheme 5). Therefore, (±)-**3** was oxidized to the indanone **22** (85% yield) by means of diacetoxy iodobenzene (DIB) and catalytic amounts of 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) at room temperature.[19] The use of the hypervalent iodine reagent in combination with TEMPO was chosen here as the environmentally benign alternative to heavy metal based oxidizers. The completely regiospecific cleavage of the C ring of **22** was achieved by using $BBr_3$ in $CH_2Cl_2$ to provide compound **23** in 84% yield. The reduction of the benzylic bromide moiety in **23** with tributyltin hydride gave alcyopterosin N (**5**) (93% yield). Finally, the first total synthesis of alcyopterosin C (**4**) was accomplished by converting **5** into its mesyl ester followed by nucleophilic displacement of the mesyl group against the nitrate ester functionality.

**Scheme 5.** Synthesis of Alcyopterosin N (**5**) and C (**4**)[20]




In conclusion, we have completed the enantioselective total synthesis of alcyopterosin I (**3**) within 11 steps (29% overall yield), as well as the first enantioselective total syntheses of alcyopterosin L (**6**) and M (**7**) within 12 steps each (10% and 6% overall yield, respectively). The efficiency of the synthetic sequences results from a modular assembly of the enantiopure triynes **17** and **20** and powerful metal-catalyzed intramolecular [2 + 2 + 2] cycloaddition reactions. This strategy was also successful for the total synthesis of the bicyclic alcyopterosins N (**5**) (14 steps, 19% overall yield) and C (**4**) (16 steps, 13% overall yield).

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**Supporting Information Available:** Experimental procedures and spectral data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Compound (*R*)-**19** was synthesized from (*S*)-2,3-*O*-isopropylidene glyceraldehyde in four steps, see: (a) Reference 9k. (*S*)-2,3-*O*-Isopropylidene glyceraldehyde is a widely used chiral building block that is accessible through a one-step preparation starting from commercially available (*R*)-2,3-*O*-isopropylideneglycerol, see: (b) Ermolenko, L.; Sasaki, N. A.; Potier, P. *Synlett* **2001**, 1565.

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(20) Racemic (±)-**3** was obtained by the same sequence as for (+)-**3** with the exception that **10** was reduced with $LiAlH_4$ to give (±)-**9** after MOM protection.