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# Stereoselective Total Synthesis of Atractylodemayne A, a Conjugated 2(*E*),8(*Z*),10(*E*)-Triene-4,6-diyne

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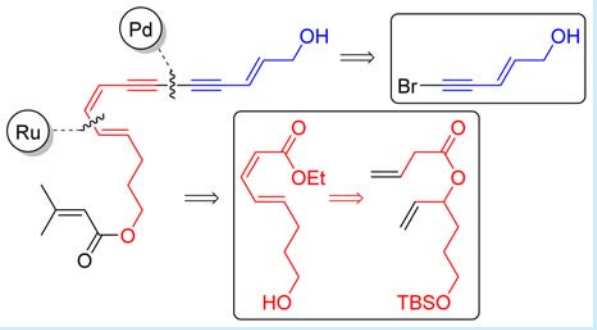
Supporting Information

**ABSTRACT:** The first total synthesis of the polyacetylene natural product atractylodemayne A is reported. Stereoselective construction of the conjugated 8(*Z*),10(*E*)-diene moiety was achieved through a tethered ring-closing metathesis approach, comprising a Ru-catalyzed RCM followed by a base-induced elimination. A Pd-catalyzed Cadiot−Chodkiewicz coupling was used for the synthesis of the diyne. Overall, atractylodemayne A was synthesized in nine steps for the longest linear sequence.




Polyacetylenes[1] constitute a large family of natural products isolated from diverse biological sources such as plants,[2−4] fungi,[3,4] bacteria,[3] or marine organisms.[3,5] In particular, edible plants, such as vegetables, herbs,[6,7] and medicinal plants,[8] are rich sources of polyacetylenes. While this has been considered to be potentially problematic due to the known harmful effects of some polyacetylenes on human health, such as allergenicity and neurotoxicity,[8,9] or their contribution to the bitter off-taste of certain processed vegetable products,[10] more recently, the beneficial effects of polyacetylene phytochemicals have been emphasized. In addition to antifungal, antibacterial, and cytotoxic activities,[4] antiinflammatory activity has been established for several polyacetylenes. A particularly well-investigated polyacetylene in this regard is falcarindiol (Figure 1), which was found to inhibit the activity of inducible nitric oxide synthase (iNOS), thereby leading to a modulation of the endogeneous NO production.[11] Nitric oxide plays, apart from many other physiological functions, an important role in inflammatory processes and may have pro- and anti-inflammatory effects. However, an overproduction of NO will result in a preponderant pro-inflammatory effect, and inhibition of iNOS could therefore be a potential therapeutic concept for the treatment of inflammatory diseases.[12]

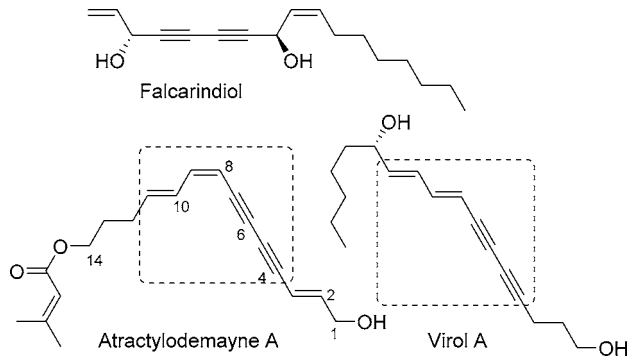



**Figure 1.** Diene−diyne polyacetylenes falcarindiol, atractylodemayne A and virol A.

*Atractylodes* is a genus of the flowering plant of the Asteraceae family. The rhizomes of several species have been used in traditional Chinese medicine as remedies against various diseases. During pharmacological evaluation of crude drug extracts of some species, anti-inflammatory activity was detected; however, this activity was not correlated to specific secondary metabolites.[13] Three polyacetylenes were isolated from the species *Atractylodes macrocephala* Koidz.[14] In vivo tests revealed that they did indeed contribute to the anti-inflammatory activity.[15] Very recently, this species was reinvestigated using a bioactivity guided approach with the aim of identifying additional antiinflammatory compounds which act by inhibition of NO production in macrophages.[16] Seven new and eight known polyacetylenes were isolated during this study. They all share a linear 14-carbon chain and a 2-ene-4,6-diyne-8,10-diene arrangement of the C−C multiple bonds. The seven new compounds were named atractylodemaynes A−G.[16]

A fully conjugated diene−diyne sequence, as highlighted in the structural formulas of atractylodemayne A and the previously described virol A,[17] is not an uncommon structural element in polyacetylene natural products (Figure 1). In most cases, the diene moiety is *E*,*E*-configured. In this regard, the secondary metabolites isolated from *A. macrocephala* are remarkable, as five out of 15 polyacetylenes have an 8*Z*,10*E* configuration, as shown

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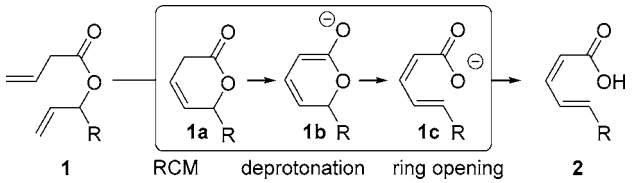
for atractylodemayne A. It is in line with the predominant *E,E*-configuration of the natural products that most synthetic efforts have also addressed this configuration.[18] For example, (*E*)-dihaloethenes have been elaborated into *E,E*-configured diene−diynes with retention of the configuration through successive Pd-catalyzed cross-coupling reactions.[17,19−21] A rare example for the stereoselective synthesis of an *E,Z*-diene−yne sequence was published by Taylor and co-workers in the course of a synthesis of the marine polyacetylene metabolite carduusyne A. Construction of the *E,Z*-diene was achieved through a sequence of nucleophilic addition to a pyrylium salt and electrocyclic ring opening.[22]

Herein, we report a highly stereoselective total synthesis of atractylodemayne A using a Ru-catalyzed tethered ring-closing metathesis[23] for the simultaneous and stereoselective construction of both C−C-double bonds and a Pd/Cu-catalyzed Cadiot−Chodkiewicz coupling[24,25] for connecting both alkyne moieties. The tethered RCM reaction used here was recently developed by us. It requires allylbutenoates **1** as starting materials, which undergo RCM to lactones **1a** and a base-induced elimination (**1b** → **1c**) in a one-pot fashion to yield, after protonation of the carboxylates **1c**, 2(*Z*),4(*E*)-dienecarboxylic acids **2**.[26−28] This transformation differs from other tethered RCM reactions, e.g., silicon-[29,30] or phosphate-tethered[31] RCM. Insofar as the tether remains in the molecule as a useful functional group, the double bond generated through olefin metathesis is shifted to an adjacent position, and a second double bond is generated via elimination (Scheme 1). Methods for the

**Scheme 1. Tethered RCM Ring Opening**

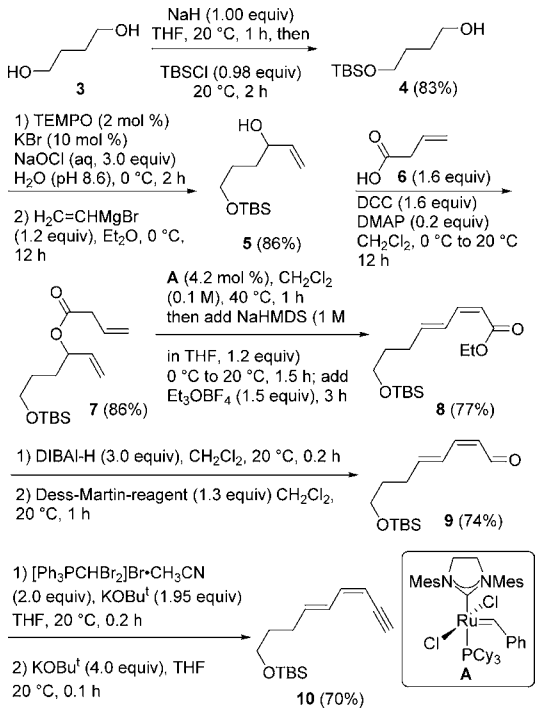



stereoselective synthesis of conjugated dienes have recently been reviewed.[32] An example for a stereoselective approach to 2(*Z*),4(*E*)-dienecarboxylic acids based on electrocyclic ring opening of cyclobutenes has been developed by Maulide and co-workers.[33−35]

Our synthesis of atractylodemayne A starts from 1,4-butanediol (**3**), which was first protected as the monosilyl ether **4**. Several protocols for the oxidation of **4** to the corresponding aldehyde were tested, but only Anelli's TEMPO-bromide-catalyzed oxidation with hypochlorite as oxidant gave satisfactory results.[36,37] Other oxidation methods, such as Swern oxidation, Dess−Martin reagent, or TPAP/NMO turned out to be impractical because isolation of the volatile aldehyde was required. Because of its instability and volatility, the aldehyde was not purified and characterized but reacted with vinylmagnesium bromide immediately after workup to give the allyl alcohol **5**. Steglich esterification[38] of **5** with carboxylic acid **6** resulted in the formation of allylbutenoate **7**, the precursor required for the tethered RCM−ring-opening sequence. We had previously synthesized 2(*Z*),4(*E*)-diene carboxylic acids via this sequence[26] but thought that for synthetic applications involving a reduction of the carboxyl group it might be more convenient to use esters instead of carboxylic acids. For these reasons, we investigated a modification of the original tethered RCM−ring-opening protocol that involved a trapping of the intermediate carboxylate **1c** with a suitable alkyl electrophile. To this end, the original sequence required some modification, but eventually cyclization of **7** was accomplished in $CH_2Cl_2$ with second-generation Grubbs' catalyst[39] (**A**) followed by deprotonation−ring opening induced by NaHMDS at ambient temperature and finally alkylation of the sodium carboxylate using Meerwein's salt.[40] Other alkylating agents were found to be inefficient. The desired ethyl ester **8** was isolated in good overall yield and as a single 2*Z*,4*E* isomer. The undesired 2*E*,4*E* isomer was not observed. Next, the aldehyde **9** was required as a starting material for a Corey−Fuchs-type homologation[41] to give diene−yne **10**. Conversion of **8** to **9** was accomplished in two steps by reduction of **8** with DIBAl-H to the corresponding primary alcohol and its subsequent oxidation to the aldehyde **9**. The primary alcohol was found to be surprisingly unstable when attempts to purify the crude product were made. In particular, double-bond isomerization appeared to be a major problem. For these reasons, the crude alcohol was immediately oxidized to dienal **9** using Dess−Martin periodinane.[42] Remarkably, this aldehyde is chemically and configurationally sufficiently stable to be isolated and fully characterized. In $CDCl_3$, a slow isomerization to the *E,E* isomer, presumably acid catalyzed, occurs, which is quantitative after 3 weeks. In the next step, the aldehyde to alkyne homologation was investigated. After some experimentation, we found that optimal results were obtained using Wolkoff's reagent[43] $[Ph_3PCHBr_2]Br\cdot CH_3CN$ in combination with $KOBu^t$ as a base. Isolation of the *gem*-dibromoalkene intermediate could be circumvented by adding additional $KOBu^t$ to the reaction mixture immediately after completion of the dibromomethylenation.[44] In spite of the strongly basic conditions, the diene−yne **10** was isolated in good yield and without concomitant double-bond isomerization or notable polymerization (Scheme 2).

For the construction of the diyne part, we envisaged a Cadiot−Chodkiewicz coupling of the C6−C14 fragment **10** and iodoacetylene **12a**. The latter had previously been synthesized

**Scheme 2. Synthesis of C6−C14 Fragment**



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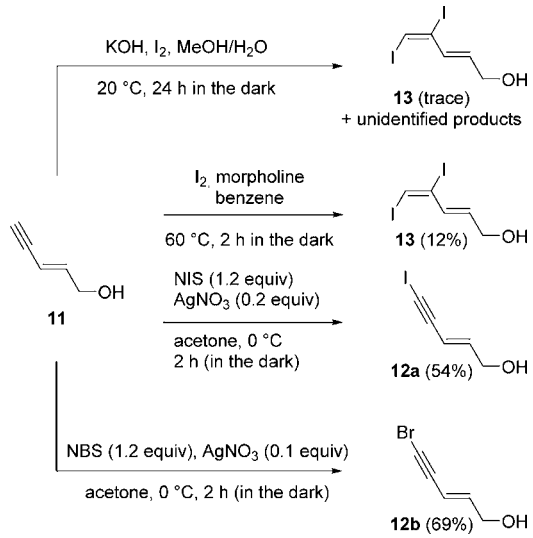
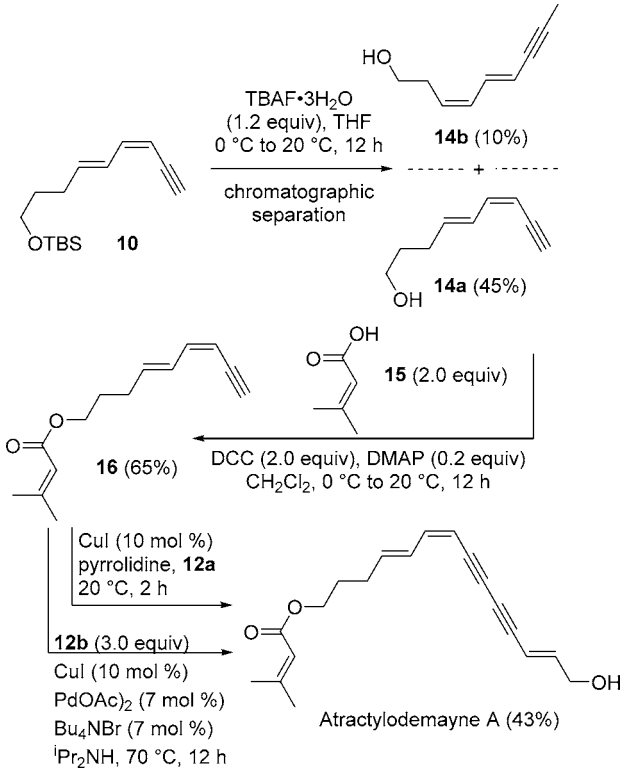
from the enyne **11**, which is commercially available, or can be synthesized in five steps from methylpropiolate.[45] One reported method for the synthesis of **12a** from **11** proceeds by electrophilic iodination/elimination, using iodine in the presence of KOH.[45] In our hands, these conditions led to a complex mixture of products with formation of trace amounts of the diiodocompound **13**. Treatment of **11** with iodine in the presence of morpholine[17] resulted again in the formation of **13**, but this time in isolable quantities, albeit in extremely low yield. Iodoacetylene **12a** was eventually obtained by treatment of **11** with *N*-iodosuccinimide (NIS) in the presence of a catalytic amount of $AgNO_3$, following a procedure published by Rossi and co-workers.[46] The bromo analogue **12b** was synthesized via the same procedure, using *N*-bromosuccinimide (NBS), in slightly higher yield.[45,46] All syntheses of haloalkynes **12a,b** and their further transformations should be carried out in the absence of light (Scheme 3).

**Scheme 3. Synthesis of Cadiot–Chodkiewicz Coupling Partners**




We decided to remove the TBS protecting group from compound **10** and replace it by the senecioyl (3-methylbut-2-enoyl) group required for the target molecule before the Cadiot–Chodkiewicz coupling. A reversed order of synthetic steps would require exposure of the fully conjugated diene–diyne–ene system to nucleophiles or acids to cleave the TBS ether. In addition, the regioselective introduction of the senecioyl group would become very difficult due to the presence of two primary alcohols. We tested first TBAF-trihydrate as a reagent for the desilylation of **10**. Cleavage of the TBS ether was quantitative but occurred with concomitant partial isomerization of the diene–yne moiety to **14b**. Assignment of the 3*Z*,5*E* configuration of **14b** was based on the $^3J(H^3–H^4)$ value of 10.6 Hz and the $^3J(H^5–H^6)$ value of 15.5 Hz. We are currently unable to propose a comprehensive mechanism for this rearrangement. Attempts to deprotect **10** with acetic acid to avoid this undesired reaction resulted in no conversion, while exposure of **10** to acetyl chloride–methanol resulted in quantitative decomposition. For these reasons, we returned to the TBAF trihydrate mediated deprotection and decided to separate **14a** and **14b** by column chromatography on silica, which was hampered by very similar polarities of the products. Eventually, a 45% yield of pure **14a** could be obtained, along with 10% of pure **14b** and a mixed fraction which accounts for 24% of the total yield. Pure **14a** was subjected to Steglich esterification with senecioylic acid (**15**) to furnish ester **16**, which was the starting material for the final Cadiot–Chodkiewicz coupling. An attempt to synthesize atractylodemayne A using a Cu-catalyzed coupling[17,47] with the iodoacetylene **12a** resulted in no conversion and a recovery of starting materials. However, with bromoacetylene **12b** as the coupling partner, $Pd(OAc)_2$ as catalyst, and CuI as cocatalyst,[48,49] the acetylenic coupling proceeded in 43% yield and high selectivity. In particular, no products resulting from *E*/*Z* isomerization or double-bond migration reactions were detected (Scheme 4).

**Scheme 4. Completion of the Total Synthesis**




In summary, we describe herein the first synthesis of the recently discovered polyacetylene natural product atractylodemayne A. Our synthesis proceeds in nine steps for the longest linear sequence and an overall yield of 2.9%. The crucial 8(*Z*),10(*E*)-diene moiety was constructed through a tethered RCM-base induced ring opening sequence, which is highly stereoselective. Acetylenic coupling to access the diyne was accomplished under Pd–Cu-co-catalyzed Cadiot–Chodkiewicz conditions. All analytical data obtained by us for synthetic atractylodemayne A match those reported by Yao and Yang[16] for the natural product very well.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00274.

Experimental procedures, analytical data, and $^1H$ and $^{13}C$ NMR spectra for all compounds (PDF)



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### Notes

The authors declare no competing financial interest.

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