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An Approach to Mimicking the Sesquiterpene Cyclase Phase by Nickel-Promoted Diene/Alkyne Cooligomerization

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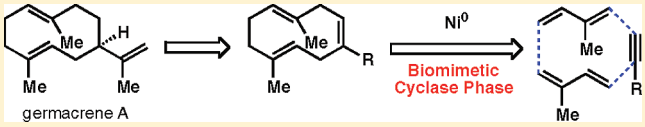
Supporting Information

ABSTRACT: Artificially mimicking the cyclase phase of terpene biosynthesis inspires the invention of new methodologies, since working with carbogenic frameworks containing minimal functionality limits the chemist's toolbox of synthetic strategies. For example, the construction of terpene skeletons from five-carbon building blocks would be an exciting pathway to mimic in the laboratory. Nature oligomerizes, cyclizes, and then oxidizes γ,γ-dimethylallyl pyrophosphate (DMAPP) and isopentenyl pyrophosphate (IPP) to all of the known terpenes. Starting from isoprene, the goal of this work was to mimic Nature's approach for rapidly building molecular complexity. In principle, the controlled oligomerization of isoprene would drastically simplify the synthesis of terpenes used in the medicine, perfumery, flavor, and materials industries. This article delineates our extensive efforts to cooligomerize isoprene or butadiene with alkynes in a controlled fashion by zerovalent nickel catalysis building off the classic studies by Wilke and co-workers.



INTRODUCTION

In perhaps the most dramatic example of divergent synthesis, Nature utilizes simple five-carbon (C_5) building blocks to fashion tens of thousands of natural products,[1] known collectively as terpenes and possessing a diverse array of physical and biological properties (for selected examples of terpene structures, see Figure 1).[2,3] Terpenes have long been utilized as flavors and fragrances, from floral to citrus and peppermint. The direct use of isoprene in the form of natural rubber, *poly*isoprene (**1**, Figure 1), by the ancient Mesoamericans dates back to as early as 1600 B.C.[4] Today the majority of isoprene is obtained from the C_5 cracking fractions of petroleum refining and is mostly used in the production of synthetic polymers.[5]

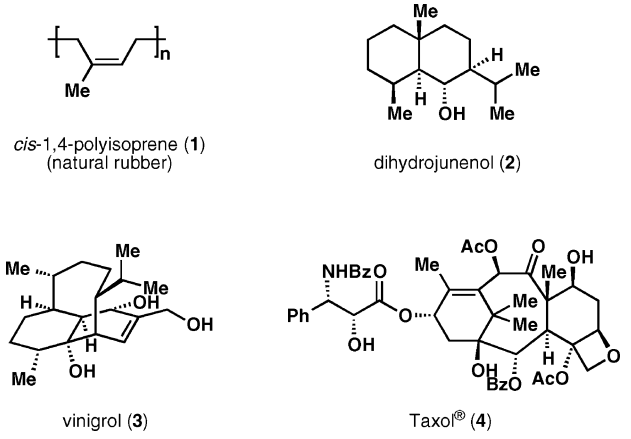


Figure 1. Selected examples of terpene natural products: polyisoprene (natural rubber, **1**), dihydrojunenol (**2**), vinigrol (**3**), and Taxol (**4**).

Organic chemists have held a long-term fascination with terpenoids because of their structural diversity, challenging molecular frameworks, and opportunities for the invention of methods and strategies in organic synthesis.[1,6] In Nature, γ,γ-dimethylallyl pyrophosphate (DMAPP, **5**) and isopentenyl pyrophosphate (IPP, **6**) are first oligomerized to relatively simple linear precursors like geranyl pyrophosphate (**7**) and farnesyl pyrophosphate (**8**, Scheme 1). Additional oligomerizations with IPP (**6**) can lead to higher order linear terpenes.[7] Following prenyl chain extension, carbocationic cyclizations can afford monocyclic compounds, such as β-bisabolene (**9**), germacrene A (**10**), and humulene (**11**, Scheme 1). After building the carbocyclic skeleton, Nature employs both oxidase enzymes and nonenzymatic oxidation processes to take the unadorned carbocycles to various oxidation states.

In contrast, a recapitulation of the biosynthetic route in the laboratory setting remains an unmet challenge. As a modest step in that direction, our laboratory recently outlined a two-phase biomimetic approach to terpenes consisting of the efficient construction of a minimally oxidized terpenoid followed by stepwise, chemoselective oxidations (Figure 2, left).[8,9] The full development of this approach may be broadly applied to the synthesis of terpene natural products, and as such, studies have been initiated to probe artificial versions of both "cyclase" and "oxidase" phase.

Although our previous approach to the eudesmane sesquiterpenes (e.g., pygmol (**12**) and dihydrojunenol (**2**)) is efficient and scalable (Figure 2, left),[9,10] it is strategically inferior to Nature's union of simple five-carbon building blocks. In further contrast to biosynthesis, the target-oriented synthesis used to access dihydrojunenol (**2**) from ketone **13** and

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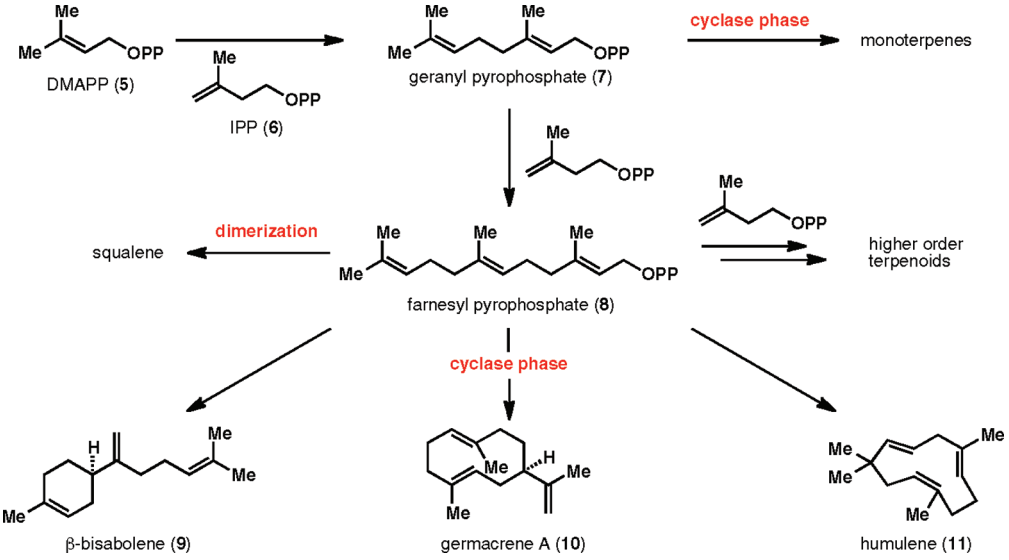
Scheme 1. Biosynthesis of Terpenoid Natural Products



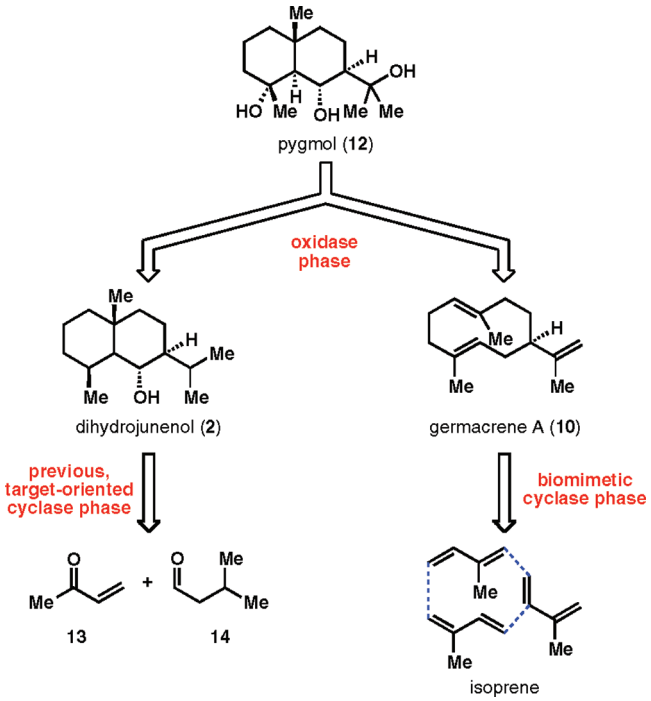


Figure 2. Retrosynthetic analysis of eudesmane natural products utilizing a two-phase approach to terpenes: direct comparison between the previously published, target-oriented method (left) and the proposed biomimetic route (right).

aldehyde **14** does not permit divergent entry to numerous scaffolds. Thus, a route from a simple C_5 unit, isoprene, to macrocyclic terpene natural products was pursued. Such a plan would rapidly forge the all-carbon germacrane skeleton (**10**), in the lowest possible oxidation state (Figure 2, right). In principle, such a structure could then be processed to a multitude of different terpenes, including the eudesmanes. This strategy would represent an ideal entry to many terpene families, as it does not require the divergent prefunctionalization of a five-carbon fragment (like the conversion of mevalonic acid pyrophosphate into DMAPP (**5**) and IPP (**6**) in Nature[11]) but would rely on the feedstock chemical isoprene as the sole starting material. Attempts to achieve this goal through a closely related diene/alkyne cooligomerization are described in this article.

Planning and Historical Context.

"[Nickel] catalysis may also be expected to be used in the partial syntheses of natural products (e.g. terpenes from isoprene)." Paul Heimbach, 1973[12]

Isoprene is underutilized in terpene total synthesis, often because more advanced terpenoid starting materials are available (e.g., limonene, farnesol, or steroid skeletons). Additionally, there is a lack of methods to rapidly process isoprene into synthetically useful building blocks. The initial inspiration for harnessing the reactivity of isoprene arose from the well-established fact that dienes react with a variety of transition metals through an oxidative cyclization to form metallacyclopentenes. These metallacycles are known to be key intermediates in the oligomerization of dienes. If successfully controlled, a cyclo-oligomerization approach could rapidly furnish macrocyclic terpene natural products, like the simple sesquiterpenes germacrene[6] or humulene,[13] which currently require multistep total syntheses.

Identification of the metal−ligand system with the best precedence for rapidly building medium-sized rings was the first priority. In principle, any metal capable of two-electron redox chemistry with a high affinity for π-donating ligands would be able to catalyze isoprene oligomerization. Indeed, a plethora of transition metals have been used to promote diene oligomerization,[14,15] the most prominent of which are Pd,[16−22] Fe,[23−25] Co,[23,26] Cr,[27−29] Ti,[28−31] Ru,[32] and Zr.[30]

Eventually, the chemistry of Wilke and Heimbach using zerovalent nickel for the oligomerization of dienes piqued our interest.[12,33−35] Utilizing dienes, Wilke and co-workers have established methods for the creation of 4,[36−38] 5,[39−41] 6,[42] 8,[36−38] 10,[43−45] 12,[46] and >12-membered rings[12,47] (Scheme 2A). In particular, the synthesis of 10-membered ring systems by cooligomerization with a C_2 component, either alkenes[48,49] or alkynes,[44,45,50,51] has been developed in great detail (vide infra). There have been extensive studies on the effects of solvent, temperature, pressure, ligands, and substrates (for both the diene and cooligomerization partner).[52] In the case of cyclo-cooligomerization with ethylene, Wilke was able to achieve 78% crude

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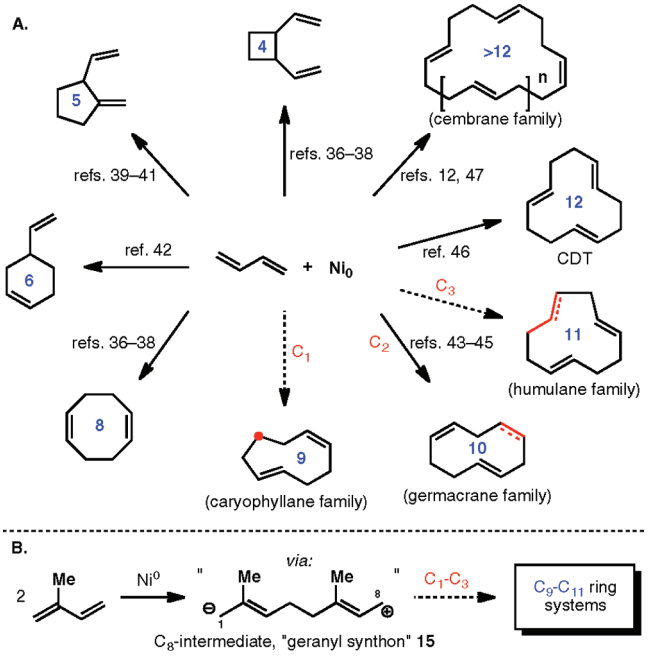
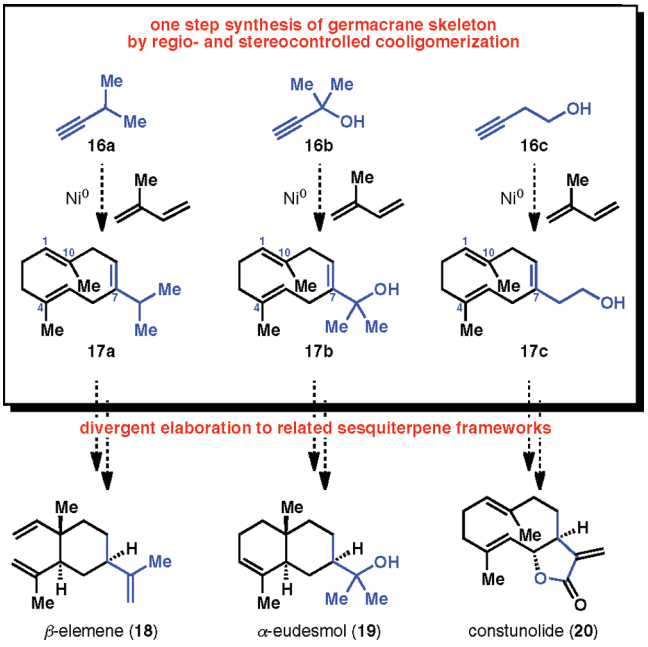
Scheme 2. (A) Synthesis of Monocyclic Carbon Skeletons from Butadiene by Nickel Catalysis and (B) the Nickel-Bound C_8-Intermediate 15 as a "Geranyl Synthon"



Scheme 3. Development of a Controlled Ni^0-Catalyzed Cooligomerization of Isoprene: Rapid Access to Germacrene-Derived Natural Products



yield on multikilogram scale.[53] This seems ideal, as all of the skeletons targeted in this research program would be carried on to further oxidase-phase studies that require scalable access to the lowly oxidized germacrene scaffold. Heimbach's striking quote above was particularly inspiring in this regard. To our knowledge, despite Wilke's and Heimbach's pioneering studies on the Ni^0-catalyzed cyclo-oligomerization, chemists have not explored this prospect in the context of natural product synthesis.[54−57]

To further expand the concept of alkyne/diene cooligomerization, the catalytically formed metal-bound C_8-intermediate **15** (Scheme 2B) was identified as a reactive building block with differentiated termini[58] with the potential to be intercepted by a variety of C_1, C_2, and C_3 units to selectively access caryophyllane, germacrane, and humulane frameworks, respectively (Scheme 2A). Establishing such a cooligomerization as a method for terpene synthesis would require a great expansion of Wilke's methodology—already well worked out for butadiene—by judicious choice and fine-tuning of both the catalytic system and cooligomerization components.

Zerovalent nickel stands out for its pronounced tendency to form medium-sized rings due to its innate size.[59] In the absence of ligands, Ni^0 will engage three butadiene molecules and rapidly form 1,5,9-*trans*,*trans*,*trans*-cyclododecatriene (CDT) catalytically and in greater than 80% yield.[60,61] Although handling Ni^0 complexes requires an inert atmosphere, there are reasonably stable zerovalent nickel sources such as $Ni(cod)_2$ which can be purchased or easily prepared in multigram quantities.[62] In addition, the respective Ni^{II} precursors (e.g., $Ni(acac)_2$) are air-stable, inexpensive, and are easily converted in situ to catalytically active Ni^0 species by a variety of common reducing agents.[63]

If successfully adapted to isoprene, the application of this method employing simple alkynes **16a−c** could produce the germacrane skeleton in a single step (**17a−c**, Scheme 3). Sophisticated choice of the alkyne "coupling" partner should afford different functional handles on the terpenoid backbone and thus allow access to related sesquiterpenes like *β*-elemene (**18**), *α*-eudesmol (**19**), or constunolide (**20**) within a minimum number of synthetic manipulations.

The field of catalytic C−C coupling processes has undergone a stunningly rapid development since the early work of Wilke and his co-workers. Thus, a reinvestigation to overcome some of the limitations that have to date precluded the application of Ni^0-catalyzed ring-forming processes of isoprene to significantly more complex terpenoid frameworks was pursued. Several issues needed to be addressed in order to realize this plan; these are highlighted within the catalytic cycle of cooligomerization proposed by Wilke and co-workers (Scheme 4).[64] In the first step, two isoprene units must be oxidatively dimerized regioselectively, in a head-to-tail fashion, as found in Nature. In an experiment with stoichiometric nickel, Wilke has shown that the regioselectivity in the formation of **21** can be altered by employing a suitable ligand. Strikingly, the use of PMe_3 led to a 50:50 mixture of tail-to-tail and head-to-tail dimers, while changing the phosphine ligand to PPh_3 or P^iPr_3 yielded exclusively the desired coupling product with head-to-tail connectivity.[64,65] Similarly, van Leeuwen et al. have demonstrated modest control of regioselectivity in the cyclodimerization of isoprene through extensive exploration of phosphine ligands.[66]

Second, the hapticity in the key intermediate **22** (previously characterized by X-ray diffractometry[40,67−69]) has to be controlled since it determines the regioselective outcome of the alkyne incorporation.[65,70] The Ni^0 intermediate **22** has been shown to exist as the η^1,η^3-complex (as drawn) *irrespective* of the nature of the phosphine ligand.[64] Since the two reactive positions in key intermediate **22** are clearly differentiated—both sterically and electronically[58]—regioselective incorporation of unsymmetrically disubstituted alkynes was deemed a worthy pursuit.

The most serious drawback of the alkyne/diene cooligomerization as originally reported by Wilke is that the

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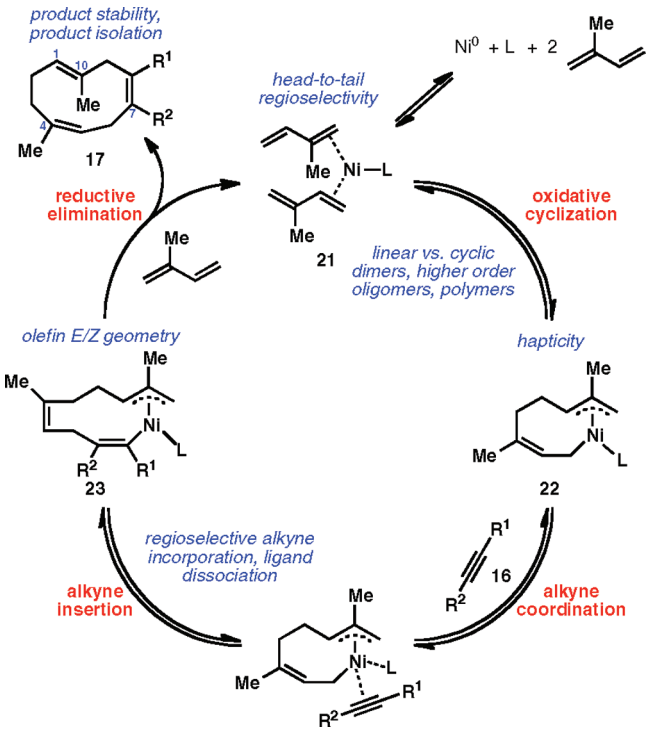
Scheme 4. Catalytic Cycle as Proposed by Wilke, and Challenges (blue) Associated with the Co-oligomerization of Isoprene and Alkynes



cyclodecatrienes are always obtained as the 4*Z*,7*Z*,10*E* isomers,[71] whereas most naturally occurring germacrenes feature two endocyclic 4*E*,10*E* double bonds.[72] It was conjectured that fine-tuning the catalytic system using modern ligands capable of stabilizing low-valent transition metals and/or the addition of suitable additives might resolve this issue.[73] As an alternative, the possibility of delaying the olefin isomerization to a subsequent transformation was considered.[74,75]

Additionally, if intermediate **23** reenters the catalytic cycle, the cooligomerization reaction has the potential to produce higher-order oligomers and polymers, both linear and cyclic.[76] For simple systems, Wilke was able to optimize the ligand, temperature, and reactant ratio in order to partially suppress such nonproductive pathways.[44,45,77]

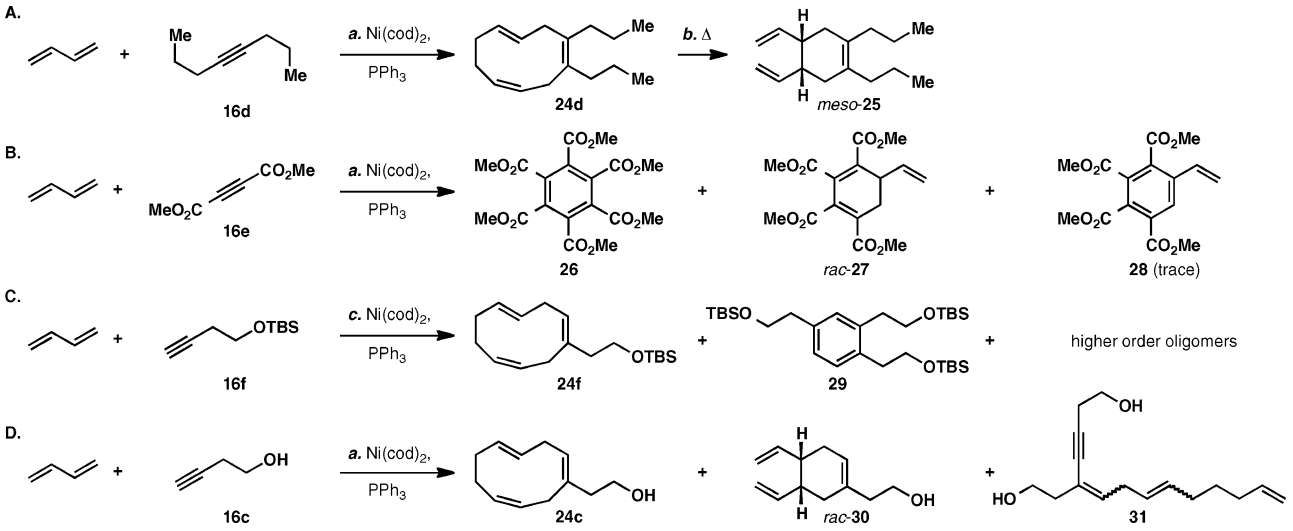
Finally, germacrene sesquiterpenes are notoriously unstable to acidic conditions (leading to cyclized products) and thermal conditions (leading to Cope rearrangements)[78] and can often exist as conformationally stable isomers at ambient temperatures.[79−81]

All of the above issues lead to further serious, albeit technical obstacles since the copolar nature of the products creates problems with regard to purification of crude reaction mixtures and subsequent analysis of inseparable mixtures of isomers. Because Heimbach conducted most of his work with butadiene (instead of isoprene) and *symmetric* alkynes, many of the above difficulties were avoided. Furthermore, his research group often simplified the resulting mixture of crude products by hydrogenation or Cope rearrangement.[82,83] Our proposal, utilizing isoprene and *unsymmetrical* alkynes, and accounting for all possible combinations of *E* and *Z* olefins, leads to 32 possible isomers[84] (as opposed to only six possible isomers for the cooligomerization of symmetric alkynes with butadiene). While Wilke and co-workers usually purified complex product mixtures by gas chromatography and/or spinning-band distillation on preparative scale,[43,51] this was deemed unsuitable for the synthesis of terpenoid natural products in multigram quantities. Despite these tremendous obstacles, the benefits of such a simple and rapid synthesis were still enticing, and thus research endeavors were carried out.

RESULTS AND DISCUSSION

Butadiene Cooligomerizations. Initial forays utilized butadiene as a means to probe the scope of alkyne substitution. Wilke's reported procedure[45] was repeated at first: $Ni(cod)_2$ (3.4 mol %), PPh_3 (3.4 mol %), butadiene (5 equiv), and 4-octyne (**16d**), neat, and sealed in a pressure vessel at room temperature for ∼18 h (Scheme 5A). With similar dialkyl alkynes, Wilke reported a ∼90% yield of 10-membered rings based on GC which was immediately distilled to afford the respective Cope products.[85] In our hands, macrocycle **24d**

Scheme 5. Major Products of Selected Butadiene/Alkyne Cooligomerization Reactions[a]



[a]Reagents and conditions: (a) 5:1 butadiene/alkyne, $Ni(cod)_2$ (10 mol %), PPh_3 (10 mol %), 16 h, 83%; (b) 120 °C, 1 h, quant; (c) 40:1 butadiene/alkyne, $Ni(cod)_2$ (10 mol %), PPh_3 (10 mol %), 16 h.

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could be isolated (along with trace impurities) by silica gel chromatography, eluting with hexanes, in 83% yield. As anticipated, 4*Z*,7*Z*,10*E*-cyclodecatriene **24d** was conformationally flexible at room temperature and required low-temperature NMR for reliable structure elucidation; this turned out to be a recurring issue for the analysis of any 4*Z*,7*Z*,10*E*-cyclodecatriene system. Compound **24d** underwent quantitative Cope rearrangement at 120 °C to give divinylcyclohexene **25**.[86] It was found that simply increasing the catalyst loading from 3.4 mol % to 10 mol % shortened the necessary reaction time. The use of a pressure vessel was essential for the reaction to proceed quickly and with good conversion, as previously demonstrated by Wilke. Unfortunately, the calibrated and heatable glass autoclave routinely used by Wilke to monitor internal pressure, volume loss, and temperature over the course of the reactions was not available to us.[37,44,51,87] Although volume loss was observed during the reactions, its quantification was not possible. To obtain comparable results, reactions were typically stopped after ∼16−20 h.

After a preliminary substrate screen, several interesting, albeit undesired, side products that plagued these reactions were identified. Specifically, the use of alkynes with conjugated electron-withdrawing groups (e.g., **16e**) gave exclusively [2 + 2 + 2], Reppe-type cycloadducts (e.g., **26**, Scheme 5B).[88,89] This well-precedented cycloaddition demonstrates one background reaction that occurred with many different substrates (cf. formation of **29**, Scheme 5C). Many reactions also afforded hetero-[2 + 2 + 2] products, in which two alkynes and a single butadiene molecule had reacted (e.g., *rac*-**27** and **28**, Scheme 5B). In addition, linear products were observed repeatedly (e.g., **31**, Scheme 5D). As expected, the isolation and structure elucidation of these repeatedly occurring motifs was challenging, but their characterization enabled the establishment of guidelines for the analysis of the conducted cyclo-cooligomerization reactions (Figure 3). Because product purification was extraordinarily tedious, rapid analysis of crude reaction mixtures by means of GC−MS and/or crude NMR according to the flowchart shown in Figure 3 was crucial.

Immediately, after running the reactions, crude GC/MS analysis quickly showed if the reaction fit into category A or B: no reaction at all or too complex to be practical. In both of these cases, the reactions were abandoned at that point. If the reaction appeared to show a limited number of major products, but the desired product was not the main component by gas chromatography (category C), the reaction was worked up. The crude reaction mixture was first analyzed by ^{1}H and ^{13}C

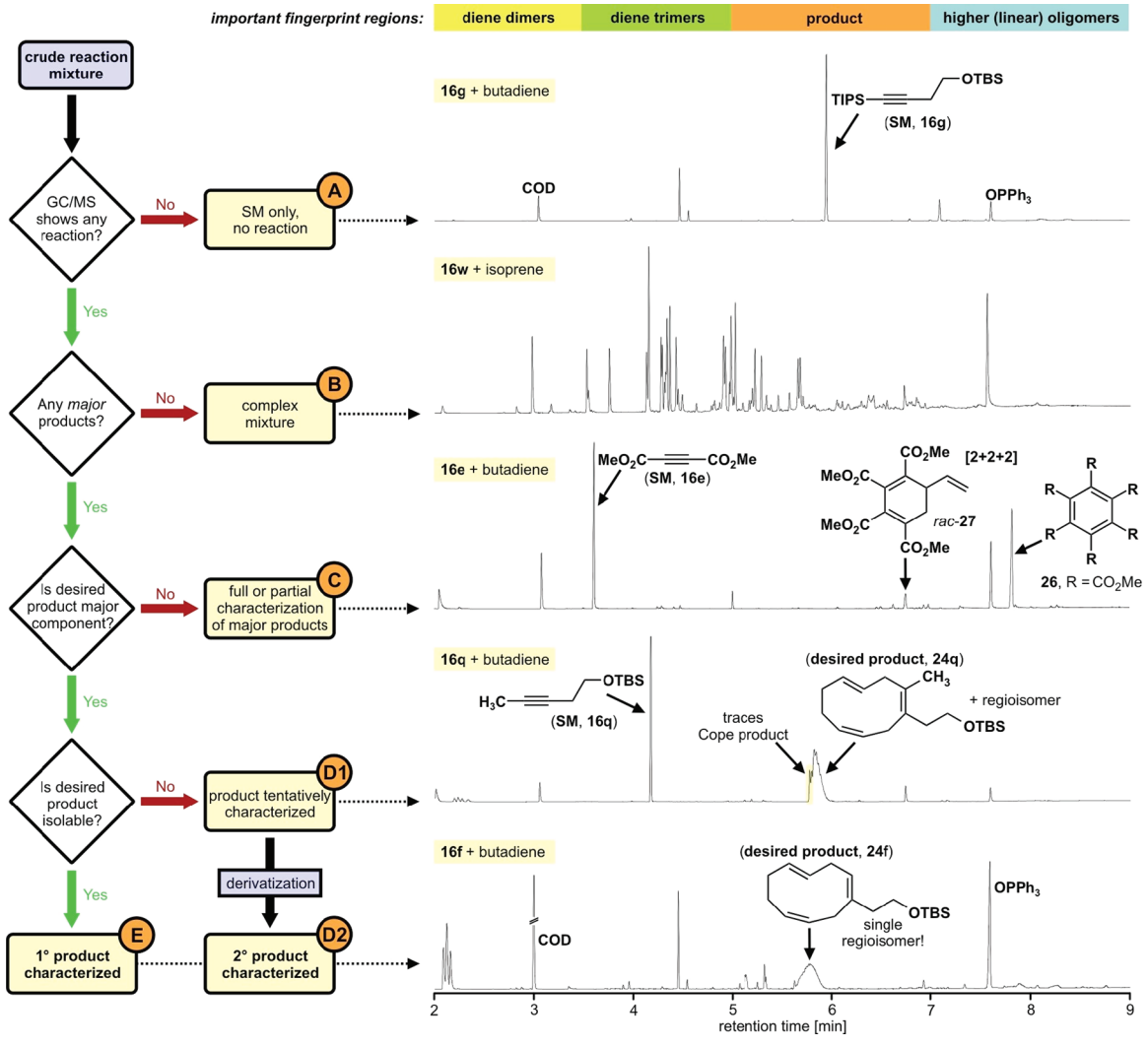

Figure 3. Flowchart that demonstrates the method of reaction analysis, illustrated with selected gas chromatograms representative for reactions belonging to categories A−E.

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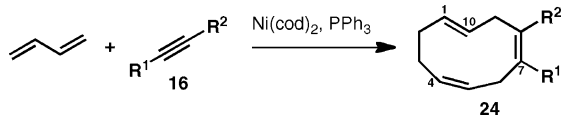
Table 1. Ni^0-Catalyzed Butadiene/Alkyne Cooligomerization[a]



entry	alkyne	R^1	R^2	product	outcome[b]
1	**16g**	CH_2CH_2OTBS	TBS	**24g**	A
2	**16h**	CH_2CH_2OTBS	TBDPS	**24h**	A
3	**16i**	CH_2CH_2OTBS	TIPS	**24i**	A
4	**16j**	$(CH_2)_4CO_2H$	H	**24j**	A
5	**16k**	$CH_2CH{=}CH_2$	H	**24k**	B
6	**16e**	CO_2Me	CO_2Me	**24e**	C[c]
7	**16l**	CO_2Et	H	**24l**	C[c]
8	**16m**	CH_2CH_2Cl	H	**24m**	C[c]
9[d]	**16b**	$C(CH_3)_2OH$	H	**24b**	C[c]
10	**16n**	$C(CH_3)_2OTMS$	H	**24n**	C[c]
11[d]	**16n**	$C(CH_3)_2OTMS$	H	**24n**	C[e]
12	**16c**	CH_2CH_2OH	H	**24c**	C[f]
13[g]	**16d**	^{n}Pr	^{n}Pr	**24d**	D2, E[h]
14	**16o**	^{n}Hex	H	**24o**	D2
15	**16a**	^{i}Pr	H	**24a**	D2
16	**16p**	CH_2CH_2OTBS	Me	**24p**	D1
17	**16q**	CH_2CH_2OTBS	TMS	**24q**	D1
18[g]	**16f**	CH_2CH_2OTBS	H	**24f**	D2, E[h]

[a]Reagents and conditions: 5:1 butadiene/alkyne, $Ni(cod)_2$ (10 mol %), PPh_3 (10 mol %), rt, 16 h. [b]Refer to Figure 3 for reaction outcomes. [c]Main product: [2 + 2 + 2] adducts. [d]20:1 butadiene/alkyne. [e]Main product: Cope; GC/MS shows traces of 10-membered ring. [f]Main product: linear coupling products (**31**, cf. Scheme 5d). [g]40:1 butadiene/alkyne. [h]The macrocyclic product was characterized both directly and after derivatization.

NMR. If crude analysis was insufficient and separation was possible by silica gel chromatography, purification was undertaken and the obtained products were reanalyzed. Frequently, isomeric mixtures were still inseparable and were analyzed in a "semi-pure" state by 1D and 2D NMR, as well as HRMS.

In the event that the product was the major component after crude analysis (categories D1, D2, and E), purification was attempted by silica gel chromatography and preparative thin-layer chromatography, often in combination and repeatedly. It is worth noting that the selection of alkyne substrate was at least partially influenced by the projected facility of purification. Nonpolar alkynes such as isopropylacetylene (**16a**) could rapidly lead to germacrene (**10**), but unless the reaction performed perfectly—in terms of yield, regio- and stereoselectivity—completely intractable mixtures of nonpolar compounds would result. In addition, distillation was hampered by the facile [3,3]-Cope rearrangement. On the other hand, 10-membered ring systems with polar functional groups were more easily handled and separated. Nevertheless, even for these more polar products, secondary derivatization (e.g., removal of the protecting group from protected alcohol **24f**) was often necessary for purification (category D2).

With a working reaction in hand, namely butadiene/4-octyne (**16d**, Scheme 5A), the substrate scope was explored (Table 1). It was quickly determined that bulky substituents on the alkyne inhibited the reaction, presumably due to steric clash around the metal center (**16g–i**, entries 1–3, Table 1). Carboxylic acid **16j** did not react (entry 4, Table 1), perhaps due to either chelation to Ni^0 or the instability of zerovalent nickel in the presence of protic substrates. Allylic alkyne **16k** resulted in a complex, inseparable mixture (entry 5, Table 1). As briefly stated above, alkynes with electron-withdrawing substituents (**16e** and **16l**, entries 6 and 7, Table 1) reacted exclusively in [2 + 2 + 2] fashion, which is well documented in the literature.[88] Under standard conditions, substrates **16b**, **16m**, and **16n** (entries 8–10, Table 1) also primarily underwent [2 + 2 + 2] cyclotrimerization. This was not entirely unexpected, as Reppe-type trimerizations were generally observed as a background reaction. The use of excess butadiene (20 equiv) with protected alcohol **16n** (entry 11, Table 1) suppressed the [2 + 2 + 2] reaction. Unfortunately, the primary 10-membered ring was only observed in trace amounts by GC–MS; instead, the follow-up Cope product predominated. In the presence of homopropargyl alcohol (**16c**, entry 12, Table 1) the primary product was found to be a linear adduct between two alkynes and a single butadiene (**31**, Scheme 5d). This may be due to the ability of the free alcohol to coordinate to the nickel center bringing two alkynes closer to the reactive metal.[90,91] Simple alkyl alkynes **16a**, **16d**, or **16o** are incorporated efficiently into 10-membered rings, as previously demonstrated by Wilke (entries 13–15, Table 1). In the case of 1-octyne (**16o**), the crude mixture was distilled directly and analyzed as its respective Cope-rearranged product (structure not shown, see the Experimental Section). It is worth mentioning that the reaction with 1-octyne (**16o**) is the first reported case of successful incorporation of a *terminal* alkyne into a 10-membered ring system under Wilke's reported conditions. Utilizing isopropylacetylene (**16a**), the product was isolated following derivatization by cycloaddition with 1,1-dibromoformaldoxime (see the Experimental Section). To the best of our knowledge, α-branched alkyl alkynes have not been previously used in the Ni^0-catalyzed cooligomerization with dienes. To fully suppress the formation of linear side products (cf. entry 12, Table 1), the unsymmetrically disubstituted alkynes **16p** and **16q** were investigated (entries 16 and 17, Table 1). In each case, the desired product was obtained, and crude analysis of the reaction mixture was sufficient for structural elucidation. Product **24p** (entry 16, Table 1) was isolated as a 1.6:1 mixture of regioisomers (with respect to the alkyne incorporation) as determined by low-temperature 2D-NMR.[92] This encouraging result indicated that regiochemical incorporation of the alkyne might be even more effectively controlled by judicious choice of the substrate.

Although surprising at first glance, it was observed that disubstituted products **24p** and **24q** (entries 16 and 17, Table 1) underwent Cope rearrangement at unusually low temperatures. It is difficult to deduce simple rules for the propensity of the 10-membered macrocycles to rearrange, but there are two trends, both of which are supported by theses from the Heimbach group.[49] First, 4*Z*,7*Z*,10*E*-cyclodecatrienes undergo Cope rearrangement at a lower temperature (room temperature to 60 °C) than 4*Z*,10*E*-cyclodecadienes (~150 °C). Second, the ease of [3,3]-rearrangement correlates with increasing bulkiness and number of the substituents on the olefinic carbons. This is, however, extremely dependent on the position of the substituents. These trends are a result of the orbital overlap of the π-systems as determined by the conformation of the macrocycle, which is strongly influenced by the substitution pattern of the 10-membered ring. A significant driving force for the rearrangement is the strain release of the macrocycle.

On the basis of the above results, terminal alkyne **16f** (entry 18, Table 1) appeared to be an ideal cooligomerization partner

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since: (1) The alkyne is electronically and sterically more differentiated than **16p** and **16q** (entries 16 and 17, Table 1) and was thus expected to be incorporated with higher regioselectivity; (2) the respective 10-membered ring **24f** is less prone to undergo Cope rearrangement under the reaction conditions, therefore enabling its isolation; and (3) the desired product **24f** would contain a suitably functionalized side chain for elaboration into terpene natural products when applied to a cooligomerization reaction with isoprene.

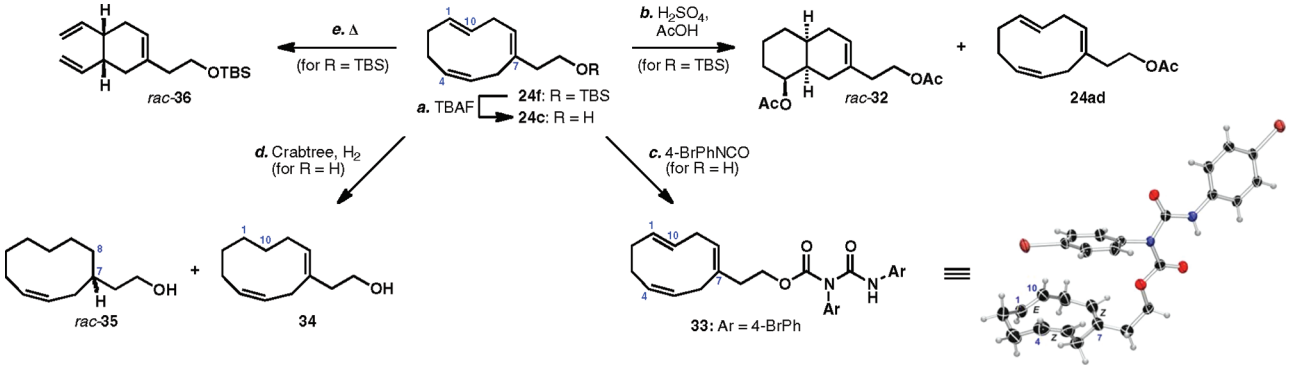
Under the standard conditions, the desired product **24f** was observed, albeit with a substantial number of higher order oligomeric side products and Reppe-type cycloadducts. In order to suppress these side reactions, optimization of the butadiene/alkyne **16f** cooligomerization was carried out. An extensive ligand screen including mono- and bidentate phosphines (e.g., P(2-furyl)$_3$, PBu$_3$, SPhos, and *rac*-BINAP), amines (NPh$_3$), NHCs (e.g., 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride), and arsines (AsPh$_3$) led to either inhibition or no significant improvement when compared to the routine ligand (PPh$_3$). However, two general trends were deduced: (1) The only ligands that afforded the desired product were derivatives of PPh$_3$ (e.g., P(3-MeOPh)$_3$ or P(4-ClPh)$_3$) and (2) the use of bidentate ligands (e.g., dppp or *rac*-BINAP) showed no consumption of alkyne. Changing the reaction temperature from room temperature to 40 °C led to a more complex mixture, while decreasing it to 4 °C led to a lowered reaction rate without improving the reaction outcome. Finally, the diene/alkyne ratio was modulated in the hope of inhibiting the formation of both [2 + 2 + 2] products and other nonproductive pathways. A decreased ratio of 2:1 resulted in reduced formation of 10-membered ring and more side products, while a 40:1 stoichiometry sufficiently suppressed side reactions involving multiple alkynes. Similarly, diluting the reaction with toluene, Et$_2$O, or THF (5:1 diene/alkyne, concentration: 0.5 M) led to comparable results. Finally, the optimized conditions (vide supra) afforded the desired product **24f** in 23% isolated yield (980 mg product). Most remarkably, macrocycle **24f** was shown to be a single regioisomer by 1D and 2D NMR studies, demonstrating the excellent selectivity of the alkyne insertion step (see **22** → **23**, Scheme 4). With this result, it was anticipated that substrate **16f** could lead to terpene natural products if cooligomerized with isoprene instead of butadiene.

Innate Reactivity of 4*Z*,7*Z*,10*E*-Cyclodecatrienes. With 4*Z*,7*Z*,10*E*-cyclodecatriene **24f** in hand, some of its general reactivity was explored. Macrocycle **24f** was first deprotected with TBAF to generate free alcohol **24c** (Scheme 6). From this common intermediate, various derivatizations were carried out. A transannular cyclization in acetic acid afforded the 6,6-fused bicyclic system *rac*-**32**. While the constitution of macrocycle **24f** had been fully elucidated, the regiochemical outcome of the alkyne insertion remained unclear due to the complexity of the NMR spectra, even employing low temperature experiments. After extensive efforts to synthesize crystalline derivatives of **24c** or **24f** (e.g., by epoxidation with excess *m*-CPBA and esterification with various substituted benzoyl chlorides), single crystals suitable for X-ray crystallographic analysis were finally obtained from the dibrominated derivative **33** (Scheme 6). The crystal structure confirmed the constitution, previously determined by NMR experiments (see the Supporting Information), and unambiguously proved the regiochemical outcome of the alkyne insertion. Thus, the macrocycles **24c** and **24f** are 4*Z*,7*Z*,10*E*-cyclodecatrienes with a side chain in the 7-position.

Crabtree's catalyst effected a selective hydrogenation, unexpectedly reducing the most strained 10*E*-olefin rather than the olefin proximal to the alcohol to yield diene **34**. Continued hydrogenation led to the expected 7*Z*-double bond being reduced, affording macrocycle *rac*-**35**. In contrast, Wilke had demonstrated the reduction of both disubstituted olefins with H$_2$/Raney-Ni.[45] Not surprisingly, under thermal conditions, the 10-membered ring **24c** underwent [3,3]-Cope rearrangement to give divinylcyclohexene *rac*-**36**. Additionally, Heimbach and co-workers have shown that 4*Z*,7*Z*,10*E*-cyclodecatrienes can be further processed to saturated hydrocarbons and diketones by selective hydrogenation and ozonolysis, respectively.[82,83] As such, a variety of synthetically useful building blocks can be obtained from 4*Z*,7*Z*,10*E*-cyclodecatrienes, as exemplified by some selected reactions of macrocycle **24c** (Scheme 6).

Isoprene Cooligomerizations. The reaction of simple test substrate 4-octyne (**16d**) with isoprene afforded a crude mixture of 10-membered ring products, which was distilled to give two regioisomeric Cope products (*rac*-**37** and *meso*-**37**′, 1:1 ratio, Scheme 7A) as determined by ^{1}H, ^{13}C, and APT NMR. The structural elucidation of vinylcyclohexenes *rac*-**37** and *meso*-**37**′ provided indirect proof of the constitution of the

Scheme 6. General Reactivity of 4*Z*,7*Z*,10*E*-Cyclodecatriene 24c[a]



[a]Reagents and conditions (all yields unoptimized): (a) TBAF (1.1 equiv), THF, rt, 97%; (b) AcOH, H_2SO_4 (cat.), rt, 46% for **32**, 28% **24ad**; (c) 4-BrPhNCO (4.0 equiv), NEt$_3$ (6.0 equiv), DMAP (0.25 mol %), DCM, rt, 38%; (d) [Ir(cod)(PCy$_3$)(py)]PF$_6$ (5 mol %) H_2 (150 psi), EtOAc, rt, ~60% for **34**, ~30% for *rac*-**35**; (e) neat, 100 °C, 80%.

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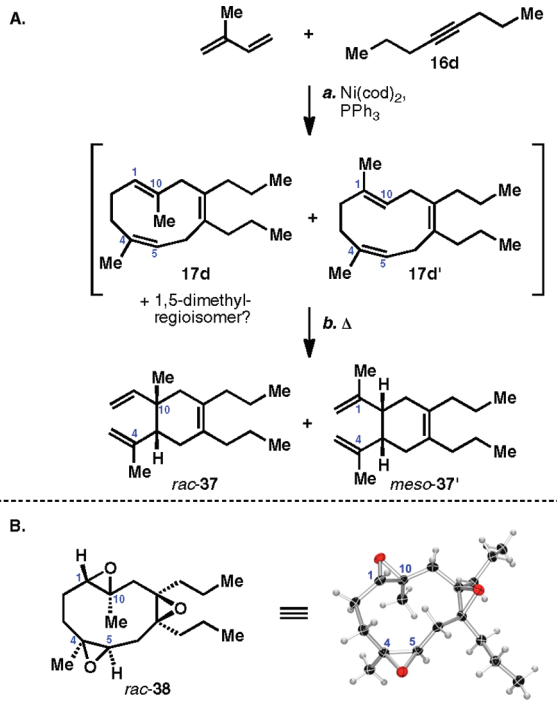
primary products: *rac*-**37** arises from the desired 4,10-dimethylcyclodecatriene **17d** (head-to-tail connectivity), while *meso*-**37′** traces back to the respective 1,4-regioisomer **17d′** (tail-to-tail connectivity). From the obtained data, the presence of the head-to-tail 1,5-dimethyl regioisomer cannot be excluded since it converges to yield the same Cope product (*rac*-**37**) as the 4,10-dimethylcyclodecatriene **17d**. The fact that the third possible regioisomer (i.e., with head-to-head coupled isoprene subunits) was not observed, demonstrated that the regioselectivity in the initial oxidative dimerization of two C_5 building blocks can indeed be controlled—at least to a certain extent.[93] The head-to-tail connectivity and 4*Z*,10*E*-geometry of **17d** was corroborated by exhaustive epoxidation of the crude reaction mixture and subsequent X-ray crystallographic analysis of triepoxide product (*rac*-**38**, Scheme 7B). The reaction of **17d** with

Scheme 7. (A) Isoprene Cooligomerization Model Study,[a] and (B) Crystal Structure of Triepoxide *rac*-38

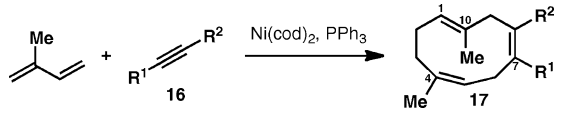


[a]Reagents and conditions: (a) 5:1 butadiene/alkyne, $Ni(cod)_2$ (10 mol %), PPh_3 (10 mol %), 16 h; (b) distillation.

excess *m*-CPBA afforded a mixture of three major components, two of which were determined to be diastereomers by X-ray crystallography, both arising from the desired head-to-tail coupled 10-membered ring **17d**.[94] At this point, the regioselectivity problem arising from the alkyne insertion was successfully overcome (cf. **24f**), and the formation of regioisomeric mixtures (head-to-tail selectivity) during the oxidative dimerization of isoprene was partially solved (cf. **17d**).

After successfully applying Wilke's reaction conditions to isoprene/4-octyne (**16d**), the substrate scope was explored in further detail (Table 2). Substrates **16r**–**u** (entries 1–4, Table 2) were not reactive under these standard conditions. This can be rationalized for the carboxylic acid and the diol, in agreement with the results obtained with butadiene (entries 4 and 12, Table 1): Coordination events and/or the presence of an acidic proton may inhibit or shut down the reactivity of the catalytically active nickel species. This hypothesis was substantiated by testing methyl ester **16v** which was fully consumed, but in unproductive fashion (entry 5, Table 2). As opposed to the observations for butadiene, simple

Table 2. Ni^0-Catalyzed Isoprene/Alkyne Cooligomerization[a]



entry	alkyne	R^1	R^2	product	outcome[b]
1	**16r**	TMS	H	**17r**	A
2	**16s**	TMS	TMS	**17s**	A
3[c]	**16t**	$(CH_2)_2CO_2H$	H	**17t**	A
4	**16u**	CH_2OH	CH_2OH	**17u**	A
5	**16v**	$(CH_2)_4CO_2Me$	H	**17v**	B
6	**16w**	Et	H	**17w**	B
7	**16o**	^{n}Hex	H	**17o**	B
8	**16a**	^{i}Pr	H	**17a**	B
9	**16x**	^{i}Pr	Et	**17x**	B
10	**16y**	Ph	Bu	**17y**	B[d]
11	**16n**	$C(CH_3)_2OTMS$	H	**17n**	B
12	**16z**	CH_2OTHP	H	**17z**	B
13	**16aa**	CH_2CH_2OTHP	H	**17aa**	B
14	**16ab**	CH_2CH_2OMe	H	**17ab**	B
15	**16ac**	CH_2CH_2OTMS	H	**17ac**	B
16	**16q**	CH_2CH_2OTBS	TMS	**17q**	B
17[e]	**16l**	CO_2Et	H	**17l**	C[f]
18[g]	**16b**	$C(CH_3)_2OH$	H	**17b**	C[f]
19	**16p**	CH_2CH_2OTBS	Me	**17p**	C[h]
20[e,g]	**16f**	CH_2CH_2OTBS	H	**17f**	C[f,i]
21	**16d**	^{n}Pr	^{n}Pr	**17d**	D2

[a]Reagents and conditions: 5:1 isoprene/alkyne, $Ni(cod)_2$ (10 mol %), PPh_3 (10 mol %), 60 °C, 16 h. [b]Refer to Figure 3 for reaction outcomes. [c]Toluene was used as a cosolvent (0.5 M). [d]A trace of Cope product was observed. [e]Alkyne was added dropwise; not under pressure. [f]Main product: [2 + 2 + 2] adduct. [g]40:1 butadiene/alkyne. [h]Main product: Cope product (see the Experimental Section). [i]Main product: linear trimer (see the Experimental Section).

terminal alkyl alkynes **16a**, **16o**, and **16w** (entries 6–8, Table 2) typically resulted in complex mixtures. Similarly, alkyl, phenyl, and oxygenated unsymmetrically disubstituted alkynes (**16n**, **16q**, and **16x**-**16ac**, entries 9–16, Table 2) were consumed, but also resulted in inseparable mixtures. As expected from the results obtained for butadiene (cf. Table 1), substrates **16l** and **16b** (entries 17 and 18, Table 2) showed [2 + 2 + 2] adducts as the primary products. Disappointingly, the substrates which had provided the most promising results for butadiene, namely alkynes **16p** and **16f** (entries 19 and 20, Table 2), yielded mixtures of [2 + 2 + 2], linear, Cope, and other unidentifiable products. Protected alcohol **16p** (entry 19, Table 2) afforded a Cope product as the major component (see the Experimental Section), demonstrating the intermediacy and thermal instability of the desired 10-membered ring. Being aware that dilution had significantly improved the butadiene/**16f** cooligomerization, a dropwise addition of protected alcohol **16f** was undertaken (entry 20, Table 2). As expected, the reaction performed poorly in the absence of a pressure vessel, but there was a noticeable increase in product formation by GC/MS analysis. Unfortunately, the mixture was still too complex to allow for isolation, and further attempts to improve the reaction were met with failure. In order to amend these results, a variety of additives were screened, including Brønsted (e.g., AcOH, Montmorillonite K10) and Lewis acids

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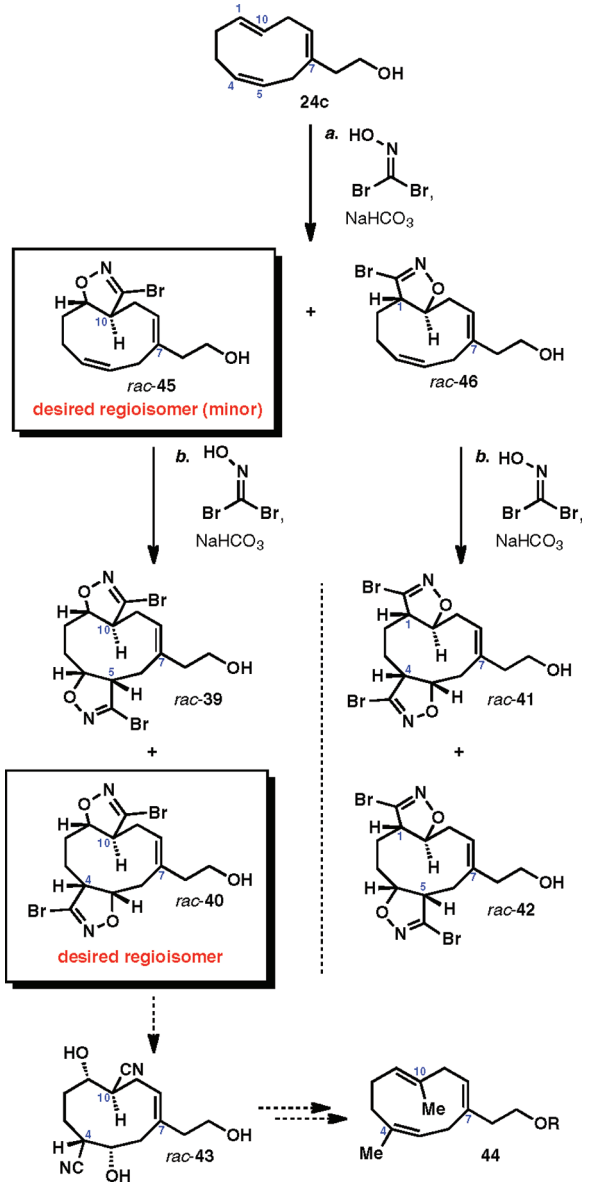
(e.g., $MgBr_2{\cdot}Et_2O$, $TiCl_2(^iOPr)_2$), bases (e.g., DBU, Cs_2CO_3), cometals (e.g., $PtCl_4$, $AgNO_3$), solvents (e.g., DMSO, hexafluoro-2-propanol), and salts (e.g., KI, Bu_4NBr). However, none of these led to any improvement in the reaction.

Despite all of the substrates and conditions explored, none of the cooligomerizations employing isoprene proceeded with sufficient selectivity. Even when utilizing the conditions optimized for butadiene (vide supra), the isoprene/alkyne **16f** cooligomerization resulted in a complex mixture. Furthermore, the reaction of isoprene with one of the *simplest* substrates, 1-octyne (**16o**), revealed a general limitation: While the butadiene/1-octyne (**16o**) system had provided a clean reaction to form the desired 10-membered ring, the outcome was completely different with isoprene, in which case the desired macrocyclic product **17o** was not observed. Instead, formation of different isomers of the rearranged Cope product predominated. This showcases an *inherent* problem related to the use of isoprene as the cooligomerization partner, since substituted 4,10-dimethyl-4*Z*,7*Z*,10*E*-cyclodecatrienes—the desired products—can be expected to undergo Cope rearrangement under the reaction conditions (60 °C). For this reason, any optimization cannot overcome the main obstacle: The thermal instability of substituted 4,10-dimethyl-4*Z*,7*Z*,10*E*-cyclodecatrienes. While significantly lowering the reaction temperature may preclude Cope rearrangement, the rate of the reaction would then become the limiting factor and would prevent its synthetic utility.

Delayed Installation of C_1 Units onto 4*Z*,7*Z*,10*E*-Cyclodecatriene 24c. With the inherent flaw in the isoprene/alkyne cooligomerization revealed, the butadiene system **24c** (obtained by deprotection of macrocycle **24f**, Scheme 6) was reevaluated. It was envisioned that subsequent installation of the "missing" methyl groups on macrocycle **24c** could still enable access to germacrene natural products (Scheme 8). Most importantly, this transformation would have to proceed with high regio- and chemoselectivity to afford only one out of four possible regioisomers (*rac*-**39**–*rac*-**42**, Scheme 8). Epoxidation followed by subsequent S_N2 reaction with a methyl nucleophile was ruled out because backside attack on the σ^* orbitals is blocked by the macrocycle. Utilizing a cycloaddition strategy would install the necessary carbon atom while maintaining the oxidation state of the endocyclic olefin. Cycloadditions with 1,1-dibromoformaldoxime have been shown to proceed with high regioselectivity at room temperature,[95] which was crucial to avoid Cope rearrangement. The intended endgame would then involve fragmentation of the resulting isoxazoline moieties to the bis-β-hydroxynitrile *rac*-**43** with Raney-Ni[96,97] or TMSCl/NaI.[98] Following elimination of the secondary alcohols, a vinyl nitrile cross-coupling based closely on the work of Dankwardt could be employed in order to access the lowly oxidized germacrene skeleton **44**.[99]

In practice, 1,1-dibromoformaldoxime afforded the desired isoxazoline *rac*-**45**, unfortunately as the minor regioisomer (2.7:1 ratio, Scheme 8). Regioisomers *rac*-**45** and *rac*-**46** were separated and subjected to the same [3 + 2]-cycloaddtion conditions.[100] In both cases the respective diadducts (*rac*-**39**–*rac*-**42**) were formed with no observed regioselectivity (1:1 ratio). Although good chemoselectivity was achieved (i.e., the trisubstituted olefin remained intact), it proved impossible to alter the regioselectivity in either cycloaddition by changing the solvent, temperature, or base. Thus, the dicycloadducts were not elaborated to natural products because of a lack of regiocontrol during the dipolar cycloaddition. More importantly, this sequence deviated significantly from the initial proposal of an ideal approach, namely utilizing isoprene for the total synthesis of terpenes.

Scheme 8. Attempted Installation of Missing Germacrene Carbons on a Macrocycle Derived from Butadiene[a]



[a]Reagents and conditions (all yields unoptimized): (a) 1,1-dibromoformaldoxime (excess), $NaHCO_3$ (excess), EtOAc, rt, 21% for *rac*-**46**, 58% for *rac*-**47**; (b) 1,1-dibromoformaldoxime (excess), $NaHCO_3$ (excess), EtOAc, rt, 47% for *rac*-**39**:*rac*-**40** (1:1 ratio by NMR) and 41% for *rac*-**41**:*rac*-**42** (1:1 ratio by NMR).[101]

CONCLUSION

In summary, this full account has traced our extensive studies aiming to mimic Nature's cyclase phase of terpene synthesis. Wilke's and Heimbach's pioneering studies in both diene oligomerization and organonickel chemistry were vital in our efforts. In this publication, a comprehensive list of their original publications related to diene (co)oligomerization, many of which are not easily available, was compiled and efforts to translate and summarize details from the original German texts

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were made. Reinvestigating their work in a more modern context, an attempt was made to push the limits of their methods to the total synthesis of terpene natural products. The ambitious goal was to establish a preparatively useful method for the creation of simple, yet synthetically challenging terpenes such as the germacrenes, in two to three steps by a controlled Ni^0-mediated isoprene/alkyne cooligomerization. Lasting lessons from these studies include:

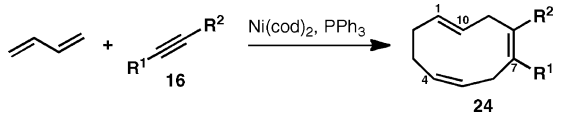
1 It was realized through experimental findings that the vision of terpene synthesis from isoprene/alkyne cooligomerization, in the present form, is inherently flawed. Most significantly, the products, 4*Z*,7*Z*,10*E*-cyclodecatrienes, are thermally unstable under the reaction conditions. The number of regio- and stereoisomers and inseparable side products led to tedious and often impossible separations that resulted in serious analytical issues.
2 Despite the complexity of the reaction mixtures, several repeatedly occurring side products from the diene/alkyne cooligomerization were isolated and fully elucidated. This allowed for the establishment of a rapid qualitative analysis of crude reaction mixtures.
3 In spite of intense efforts, the outcome of the diene/alkyne cooligomerization was only minimally tunable by variation of the reaction conditions. For example, the ligand was incapable of significantly altering the outcome of the reaction—in terms of both olefin geometry and regioselective incorporation of isoprene or alkyne. Ultimately, it was observed that the reaction is contingent primarily upon the alkyne substrate.
4 With respect to butadiene, notable advances in substrate scope were achieved. For the first time, both terminal and α-branched alkynes were successfully incorporated into the 4*Z*,7*Z*,10*E*-cyclodecatriene frameworks. Most remarkably, full regiocontrol was obtained in the incorporation of the unsymmetrical alkyne **16f**, as unambiguously established by the crystallographic analysis of macrocycle **33**.
5 Despite its propensity to undergo Cope rearrangement, a crystal structure of 4,10-dimethyl-4*Z*,7*Z*,10*E*-cyclodecadiene **17d** was obtained, as the triepoxide *rac*-**38**. This directly confirmed the product structure, solid-state conformation, and olefin geometry for the first time.

Although, ultimately, terpenes could not be produced from isoprene due to several intractable factors, the cooligomerization of alkynes with butadiene may still be useful for total syntheses in a different context. Such studies, as well as the utilization of the bulk chemical isoprene as a building block for terpene synthesis, continue to be of interest in our laboratory.

EXPERIMENTAL SECTION

General Methods. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), triethylamine (NEt_3), toluene, dichloromethane (DCM), and diethyl ether (Et_2O) were obtained by passing commercially available predried, oxygen-free formulations through activated alumina columns. Reagents were purchased at the highest commercial quality and used without further purification unless otherwise stated. Dibromoformaldoxime was synthesized according to a literature-known procedure.[102] Reactions were monitored by thin-layer chromatography (TLC), carried out on 0.25 mm silica gel plates (60F-254) using UV light as visualizing agent and either (1) *p*-anisaldehyde in ethanol/aqueous H_2SO_4/CH_3CO_2H or (2) 2% $KMnO_4$ in 4% aqueous sodium bicarbonate and heat as developing agents. Nuclear magnetic resonance (NMR) spectra were calibrated using residual undeuterated solvent signals as an internal reference ($CHCl_3$: 7.26 ppm for ^1H NMR, 77.16 ppm for ^{13}C NMR). 1D and 2D NMR spectra were recorded at room temperature unless otherwise stated. All NMR peak assignments given in the Supporting Information were determined by ^1H, ^{13}C, APT, COSY, HMQC, and/or HMBC experiments. The following abbreviations were used to assign NMR signal multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High-resolution mass spectra (HRMS) were recorded on an LC/MSD TOF mass spectrometer by electrospray ionization time-of-flight reflectron experiments (ESI-TOF). For IR spectra the major absorbance bands are reported in wavenumbers. Melting points (m.p.) are uncorrected. GC/MS analyses were carried out applying the following method: Agilent 19091S-433 column (30 m × 320 μm × 0.25 μm); H_2 30 mL/min, air 400 mL/min, He 25 mL/min; 50 °C for 2.25 min, ramp to 300 °C (60 °C/min), and hold at 300 °C for 4 min.

Preparation of Bis(1,5-cyclooctadiene)nickel(0).[62] Since the outcome of the $Ni(cod)_2$ formation is strongly dependent on the quality of $Ni(acac)_2$, the latter was first azeotropically distilled in refluxing toluene (130 °C) with a Dean–Stark apparatus to remove trace amounts of water. The flask was cooled to ~90 °C and filtered through Celite while hot. Toluene was removed in vacuo to afford anhydrous $Ni(acac)_2$ (forest green solid). Freshly dehydrated $Ni(acac)_2$ (2.0 g, 7.78 mmol) were dissolved in toluene (4.8 mL, if not fully soluble the azeotropic distillation should be repeated) in a flame-dried Schlenk flask. 1,5-cyclooctadiene (4.78 mL, 38.9 mmol, 5 equiv) was added and the mixture degassed by either three freeze–pump–thaw cycles or by sonication for 15 min with concomitant vigorous argon bubbling. The degassed homogeneous mixture was cooled to −78 °C and butadiene (~0.5 mL, 5.91 mmol, 0.76 equiv) was condensed into the flask. The solution was warmed to −10 °C and $AlEt_3$ (0.9 M solution in toluene, 19.5 mL, 2.25 equiv) added dropwise. The reaction was then allowed to come to room temperature and stirred overnight (8–10 h). The resulting red-brown suspension was cooled to −30 °C and the supernatant carefully removed by cannula to give a yellow solid, which was washed with degassed Et_2O (the suspension was allowed to equilibrate to −30 °C between washings). Analytically pure $Ni(cod)_2$ (1.24 g, 4.51 mmol, 58%) was obtained as an air-sensitive yellow solid, dried in vacuo in the Schlenk flask and stored under argon (preferentially inside a glovebox) at low temperatures. In general, yields ~60% $Ni(cod)_2$ were obtained on up to 10 g scale: ^1H NMR (C_6D_6, 400 MHz) δ = 4.30 (s, 8 H), 2.08 (s, 16 H) ppm; ^{13}C NMR (C_6D_6, 400 MHz) δ = 89.7 (CH), 30.9 (CH_2) ppm.



General Procedure for Ni^0-Catalyzed Cooligomerization of Butadiene and Alkynes 16. A 35 mL pressure vessel and stir bar were flame-dried and brought into a glovebox. Freshly prepared $Ni(cod)_2$ (79.0 mg, 0.29 mmol, 10 mol %) and PPh_3 (75.0 mg, 0.29 mmol, 10 mol %) were added to the reaction flask.[103] The vessel was sealed with a septum, brought out of the glovebox, connected to a Schlenk line and cooled to −78 °C. Under an argon atmosphere, 1,3-butadiene (~1.25–10 mL, 14.4–115 mmol, 5–40 equiv) was condensed into the flask, and the alkyne **16** (2.87 mmol) was added. Under a steady flow of argon, the septum was rapidly exchanged with a screw cap. The reaction was allowed to come to room temperature and stirred for 18 h. For safety reasons the reactions were conducted behind an explosion-proof blast shield. The reaction mixture was cooled to −78 °C, uncapped, and excess 1,3-butadiene was allowed to evaporate at room temperature. Subsequently, the reaction was worked up according to one of the following two methods:

(A) Wilke's Standard Workup Procedure. The residue was taken up in EtOAc (50 mL) and washed subsequently with 5 M HCl, 5%

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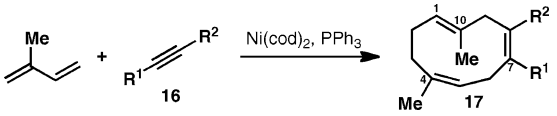
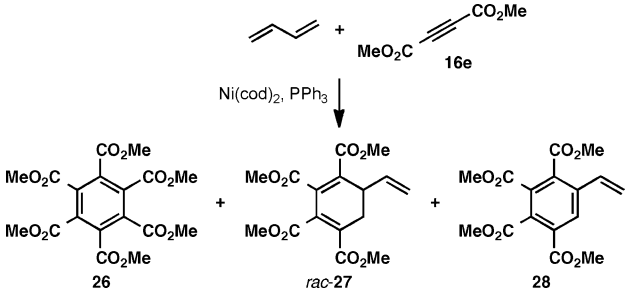
aqueous H_2O_2, saturated aqueous sodium bicarbonate solution, water, and finally brine. The organic phase was dried over magnesium sulfate, filtered, and concentrated in vacuo. Purification by flash chromatography then followed, if necessary and if the crude mixture was deemed separable (i.e., categories C, D1, D2, and E[104]).

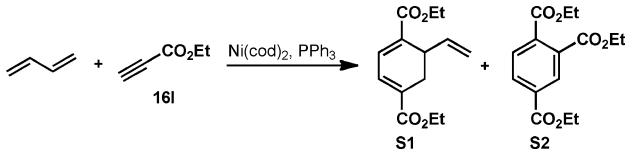
(B) Modified Workup Procedure. The residue was suspended in hexanes, loaded directly onto a plug of silica gel, and eluted sequentially with hexanes or appropriate hexanes/EtOAc mixtures. The solvent was removed in vacuo, and the crude mixture thus obtained was further purified by flash chromatography, if necessary and if it was deemed separable (i.e., categories C, D1, D2, and E[106]).



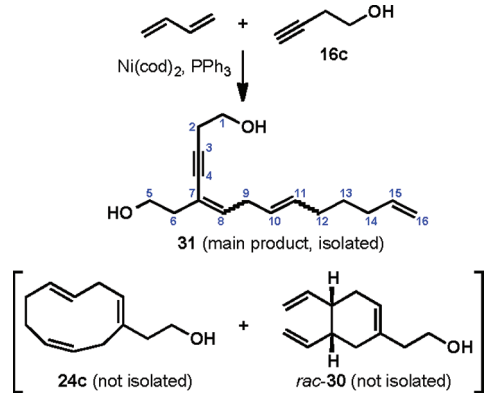
General Procedure for Ni^0-Catalyzed Cooligomerization of Isoprene and Alkynes 16. A 35 mL pressure vessel equipped with a stir bar was flame-dried. In a glovebox freshly prepared $Ni(cod)_2$ (79.0 mg, 0.29 mmol, 10 mol %) and PPh_3 (75.0 mg, 0.29 mmol, 10 mol %) were added to the reaction flask. The vessel was sealed with a septum, brought out of the glovebox, and connected to a Schlenk line. Under an argon atmosphere, isoprene (1.5–12 mL, 14.4–115 mmol, 5–40 equiv) and alkyne **16** (2.87 mmol) were added.[103] Under a steady flow of argon, the septum was rapidly exchanged with a screw cap, the mixture heated to 60 °C and stirred for 18 h. The reaction mixture was then cooled to room temperature and excess isoprene was allowed to evaporate under a flow of nitrogen. The remaining crude material was subsequently worked up by either method A or B (vide supra).



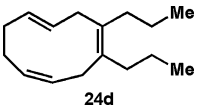
Synthesis of 10-Membered Ring Systems: Isolation and Characterization of Primary Macrocycles, Secondary Derivatives, and Undesired Side Products. Isolation of [2 + 2 + 2] Cycloadducts from the Reaction of Alkyne 16e and Butadiene (Category C[104]). The standard procedure was followed using dimethyl acetylenedicarboxylate (**16e**, 1.62 g, 11.5 mmol) and 1,3-butadiene (~5 mL, 57.3 mmol, 5.0 equiv) to give a brown viscous oil. GC/MS analysis of the obtained crude mixture allowed for the tentative assignment of the above three homo- and hetero-[2 + 2 + 2] cycloadducts **26**–**28** as the main products (for GC trace see the Supporting Information).



Isolation of [2 + 2 + 2] Cycloadducts S1 and S2 from the Reaction of Alkyne 16l and Butadiene (Category C[104]). The standard procedure was followed using alkyne **16l** (1.13 g, 11.5 mmol) and 1,3-butadiene (~5 mL, 57.3 mmol, 5.0 equiv) to give a yellow oil. The main components were isolated in analytically pure form by preparative TLC (silica gel, hexanes/EtOAc, 12:1). GC/MS analysis and ^{1}H NMR of the obtained products allowed for the unambiguous assignment of the [2 + 2 + 2] cycloadducts **S1** and **S2** (GC trace given in the Supporting Information).



Isolation of the Linear Cooligomer 31 (Category C[104]). The reaction was performed according to the standard procedure, however, with altered stoichiometry: Homopropargyl alcohol **16c** (806 mg, 0.87 mL, 11.5 mmol), 1,3-butadiene (~5.0 mL, 57.3 mmol, 5.0 equiv), $Ni(cod)_2$ (106 mg, 0.39 mmol, 3.3 mol %), PPh_3 (100 mg, 0.39 mmol, 3.3 mol %). Workup A afforded a pale yellow oil. TLC of the obtained crude mixture showed four major components along with several minor side products. This was confirmed by GC/MS analysis, which revealed a fairly clean and selective reaction with full consumption of starting material giving 1,5-cyclodecadiene, Cope product *rac*-**30**, traces macrocycle **24c** (the latter two were inseparable and were tentatively assigned by ^{1}H and ^{13}C NMR of a crude mixture), and one further, unknown compound. Subsequently, an aliquot (20 mg, crude) of the crude mixture was purified by preparative TLC (silica gel, EtOAc/hexanes, 1:1) yielding the main product, diol **31**, in analytically pure form. Its structure was fully elucidated by 2D NMR experiments. R_f = 0.76 (silica gel, hexanes/EtOAc, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.80 (ddt, J = 17.1, 10.4, 6.7 Hz, 1 H, H15), 5.71 (t, J = 7.3 Hz, 1 H, 8-H), 5.50–5.34 (m, 2 H, 10-H, 11-H), 4.99 (dd, J = 17.3, 1.3 Hz, 1 H, 16-H-*trans*), 4.94 (dt, J = 10.1, 1.1 Hz, 1 H, 16-H-*cis*) 3.79–3.73 (m, 4 H, 1-H, 5-H), 2.95 (t, J = 6.7 Hz, 2 H, 9-H), 2.63 (t, J = 6.2 Hz, 2 H, 2-H), 2.37 (t, J = 5.9 Hz, 2 H, 6-H), 2.00 (m, 4 H, 12-H, 14-H), 1.44 (dt, J = 14.4, 7.4 Hz, 2 H, 14-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 138.9 (C-15), 137.7 (C-8), 131.4 (C-11), 127.5 (C-10), 119.8 (C-7), 114.6 (C-16), 91.7 (C-3), 80.4 (C-4), 61.5 (C-5), 61.4 (C-1), 40.5 (C-6), 33.9 (C-9), 33.4 (C-14), 32.1 (C-12), 28.8 (C-13), 24.1 (C-2) ppm; IR (ATR, neat) ν_{max} 3335, 2923, 2853, 1640, 1455, 1431, 1377, 1329, 1260, 1178, 1090, 1041, 967, 909, 845, 801, 699 cm^{-1}; HRMS calcd for $C_{16}H_{24}O_2$ 249.1849 $[M + H]^+$, found (ESI-TOF) 249.1852.



Direct Characterization of 24d (Category E[104]). The standard procedure was followed using 4-octyne (**16d**, 316 mg, 0.42 mL, 2.87 mmol) and 1,3-butadiene (~10 mL, 115 mmol, 40 equiv) to give the colorless oil **24d** (518 mg, 2.37 mmol, 83%; this material contains 9% Cope product *meso*-**25** and 12% of unknown impurities according to GC/MS analysis) applying workup procedure B: R_f = 0.72 (silica gel, hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, −50 °C) δ = 5.47 (t, J = 10.2 Hz, 1 H), 5.28 (ddd, J = 15.1, 10.4, 4.5 Hz, 1 H), 5.18 (m, 2 H), 3.22 (t, J = 12.5 Hz, 1 H), 2.92 (dd, J = 15.1, 10.8 Hz, 1 H), 2.57 (d, J = 14.6 Hz, 1 H), 2.22 (ddd, J = 24.6, 12.0, 5.8 Hz, 2 H), 2.11–1.95 (m, 3 H), 1.91 (dd, J = 23.0, 11.5 Hz, 1 H), 1.79 (m, 1 H), 1.63 (td, J = 11.9, 4.0 Hz, 1 H), 1.52 (q, J = 11.5 Hz, 1 H), 1.41–1.27 (m, 3 H), 1.24–1.17 (m, 1 H), 0.91–0.84 (m, 6 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, −50 °C) δ = 134.5, 132.5, 132.4, 131.8, 129.4, 122.8, 38.7, 37.7, 35.6, 32.2, 31.4, 26.2, 22.4, 21.7, 14.9, 14.5 ppm; IR (ATR, neat) ν_{max} 3007, 2956, 2928, 2867, 1453, 1376, 1202, 1183, 1123, 1088, 970, 950, 911, 842, 813, 738, 704 cm^{-1}; HRMS calcd for $C_{16}H_{26}$ 219.2107 $[M + H]^+$, found (ESI-TOF) 219.2107.

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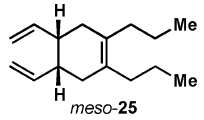
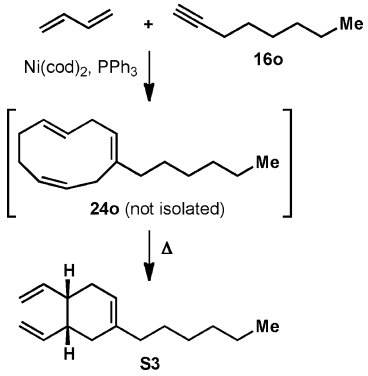
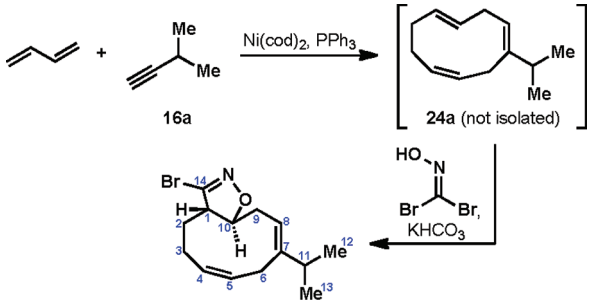


meso-**25**

Characterization of 24d in Form of Its Respective Cope Product (*meso*-25, Category D2[104]). Macrocycle **24d** (10.0 mg, 45.8 μmol) was heated neat to 120 °C for 1 h. The reaction afforded the clear yellow oil, divinylcyclohexene *meso*-**25** in quantitative yield (9.90 mg, 45.3 μmol, 99%): R_f = 0.66 (silica gel, hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.79 (ddd, J = 17.0, 10.6, 7.5 Hz, 2 H), 5.01 (ddd, J = 8.6, 2.0, 0.8 Hz, 2 H), 4.98 (d, J = 0.8 Hz, 2 H), 2.41 (dd, J = 11.8, 4.9 Hz, 2 H), 2.17−1.87 (m, 8 H), 1.44−1.32 (m, 4 H), 0.88 (t, J = 7.3 Hz, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 140.6, 128.7, 114.4, 41.9, 35.2, 33.5, 21.7, 14.4 ppm; IR (ATR, neat) ν_{max} 3075, 2957, 2929, 2900, 2871, 1639, 1465, 1455, 1434, 1377, 994, 967, 910, 719 cm^{-1}; GC/MS calcd for $C_{16}H_{26}$ 218.2035 $[M]^{\bullet+}$, found (FID[105]) 218.2.

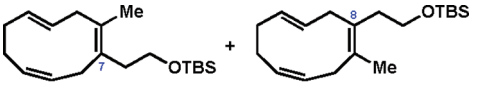


Characterization of 24o after Cope Rearrangement (Category D2[104]). The standard procedure was followed using 1-octyne (**16o**, 316 mg, 0.42 mL, 2.87 mmol) and 1,3-butadiene (~1.25 mL, 14.4 mmol, 5.0 equiv). After workup A, the crude mixture containing **24o** was distilled directly to afford the Cope product **S3** (racemic mixture) as a pale yellow oil (564 mg, 2.58 mmol, 70% over two steps): R_f = 0.66 (silica gel, hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.85−5.76 (m, 2 H), 5.38−5.35 (m, 1 H), 5.04−4.98 (m, 4 H), 2.49−2.37 (m, 2 H), 2.22−2.19 (m, 1 H), 2.18−2.15 (m, 1 H), 2.06−1.82 (m, 4 H), 1.43−1.22 (br m, 8 H), 0.88 (t, J = 6.9 Hz, 3 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 140.5, 140.4, 136.5, 119.0, 114.5, 114.5, 41.7, 41.2, 37.9, 32.3, 31.9, 29.3, 29.2, 27.8, 22.8, 14.3 ppm; IR (ATR, neat) ν_{max} 3076, 2956, 2925, 2856, 1639, 1457, 1437, 1378, 994, 910, 819, 722 cm^{-1}; GC/MS calcd for $C_{16}H_{26}$ 218.2035 $[M]^{\bullet+}$, found (FID[105]) 218.2.



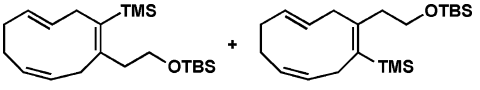
dihydroisoxazole derivative **S4**

Characterization of 24a in Form of Its Dihydroisoxazole Derivative S4 (Category D2[104]). The standard procedure was followed using alkyne **16a** (196 mg, 0.29 mL, 2.87 mmol) and 1,3-butadiene (~1.25 mL, 14.4 mmol, 5.0 equiv) to afford a crude mixture (486 mg) containing **24a** after workup A. An aliquot of this mixture (35 mg) was brought up in EtOAc (2.0 mL), and $NaHCO_3$ (100 mg, 1.19 mmol, excess) and dibromoformaldoxime (40 mg, 0.20 mmol, approximately 1.0 equiv) were added sequentially. The reaction was stirred at room temperature for 30 min and additional dibromoformaldoxime (40 mg, 0.20 mmol, approximately 1.0 equiv) was added. The reaction mixture was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. Preparative TLC (silica gel, hexanes/EtOAc 20:1) afforded the above dihydroisoxazole derivative **S4** (racemic mixture) as the only isolable regioisomer (colorless oil, 11.3 mg, 37.9 μmol, 18% estimated yield over two steps based on alkyne **16a**):[106] R_f = 0.50 (silica gel, hexanes/EtOAc, 20:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 5.77 (ddd, J = 10.8, 6.6, 6.0 Hz, 1 H, H-5), 5.34−5.24 (m, 2 H, H-4, H-8), 4.43 (d, J = 13.9 Hz, 1 H, H-10), 3.21 (t, J = 12.0 Hz, 1 H, H-6), 3.09 (t, J = 12.7 Hz, 1 H, H-1), 2.83 (t, J = 12.7 Hz, 1 H, H-9), 2.71−2.64 (m, 1 H, H-9), 2.44−2.31 (m, 3 H, H-3, H-6, H-11), 2.12−2.07 (m, 1 H, H-3), 1.93 (t, J = 13.9 Hz, 1 H, H-2), 1.59−1.53 (m, 1 H, H-2), 1.07−1.03 (m, 6 H, H-12, H-13) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 150.4 (C-7), 146.8 (C-14), 129.7 (C-5), 128.1 (C-4), 114.6 (C-8), 89.6 (C-10), 49.8 (C-1), 34.5 (C-11), 30.3 (C-2), 29.9 (C-9), 27.5 (C-6), 23.7 (C-3), 23.1 (C-12), 22.0 (C-13) ppm; IR (ATR, neat) ν_{max}: 3011, 2959, 2924, 2866, 1611, 1571, 1466, 1447, 1381, 1356, 1294, 1251, 1130, 1100, 1082, 1045, 1009, 999, 963, 919, 878, 825, 799, 758, 705 cm^{-1}; HRMS calcd for $C_{14}H_{20}BrNO$ 298.0801 $[M + H]^+$, found (ESI-TOF) 298.0799.



24p: Inseparable mixture of regioisomers

Direct Characterization of 24p in Crude Form (Category D1[104]). The standard procedure was followed using alkyne **16p** (569 mg, 2.87 mmol) and 1,3-butadiene (~10 mL, 115 mmol, 40 equiv). In order to establish the constitution of the isolated component(s), the following protocol was undertaken: After the standard workup procedure A, GC/MS analysis of the crude mixture revealed a fairly clean reaction, with almost all starting material consumed after 18 h. Based on the GC/MS chromatogram, it was determined that the reaction contained 10-membered ring **24p** (t_R = ~6.0 min, broad) and traces of Cope products (t_R = ~5.9 min). Column chromatography (silica gel, silica gel, hexanes → hexanes/EtOAc 100:1) afforded the main product of the reaction, **24p** (576 mg, 1.89 mmol, 66%), as an inseparable mixture of two components. ^{13}C and APT NMR excluded the presence of Cope product (no olefinic methylene groups with a characteristic chemical shift of ~115 ppm). Evidence for the formation of 10-membered ring was demonstrated by the resolution of the ^{1}H NMR at −54 °C: Upon cooling the sample, the broad signals of the CH_2 groups of the ring system became sharp due to the slowed down molecular motion of the conformationally flexible macrocycle. Observing two methylene carbons adjacent to an oxygen, two methyl groups joined to sp^2 carbons, and twelve olefinic carbons, the reaction was determined to be a 1.6:1 mixture (cf. integrals of the two methyl groups attached to olefinic carbons C-7 or C-8) of regioisomers, which coeluted during column chromatography and GC analysis. Further characterization of the ring system and partial assignment of substructures of the two regioisomers was possible by full 2D NMR analysis (COSY, HMQC, HMBC) at low temperature. Chromatograms and spectra are included in the Supporting Information. **24p** (mixture of two regioisomers): R_f = 0.75 (silica gel, DCM/Et_2O, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$, −54 °C) δ = 5.48 (dt, J = 11.3, 10.4 Hz, 1 H), 5.12−5.34 (m, 3 H), 3.53 (t, J = 6.5 Hz, 2 H), 3.20−3.40 (m, 2 H), 2.90−3.03 (m, 1 H), 2.57 (q, J = 13.5 Hz, 3 H), 2.17−2.41 (m, 3 H), 1.85−2.14 (m, 4 H), 1.69 (s, 3 H), 1.52 (q, J = 11.5 Hz, 1 H), 0.86 (s, 9 H), 0.043 (br s, 6 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$, rt) δ = 132.1, 131.7, 130.1, 129.8, 128.0, 123.3, 62.5, 41.0, 40.3, 38.2, 34.9, 32.8, 26.5, 26.1 (two signals), 22.6, −5.1 (two signals) ppm; IR (ATR, neat) ν_{max} 3007, 2952, 2928, 2895, 2857, 1471, 1462, 1445, 1382, 1361, 1253, 1089, 1005, 971, 937, 913, 833, 812, 773, 731, 703, 661 cm^{-1}; HRMS calcd for $C_{19}H_{34}OSi$ 307.2452 $[M + H]^+$, found (ESI-TOF) 307.2449.



24q: Inseparable mixture of regioisomers and coeluting Cope products (not shown)

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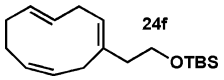
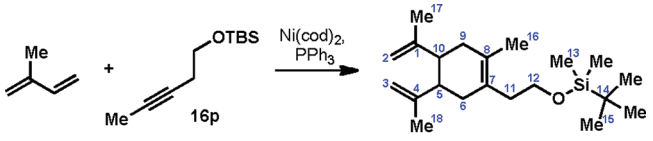
Direct Characterization of 24q in Crude Form (Category D1[104]). The standard procedure was followed with alkyne **16q** (736 mg, 2.87 mmol) and 1,3-butadiene (~1.25 mL, 14.4 mmol, 5.0 equiv). Different from the standard procedure the reaction mixture was stirred for 96 h (due to the slower reaction rate for the sterically more demanding alkyne) with monitoring by GC/MS, the final alkyne **16q** (t_R = 4.62 min) to product **24q** (t_R = 6.20 min, broad) ratio being ~65:35. The GC/MS analysis of the crude mixture revealed at least four peaks showing product mass (m/z = 307.2, [M − ^{t}Bu]$^+$). Following workup A, the crude material was subjected to column chromatography (silica gel, hexanes → hexanes/EtOAc 9:1) to remove unreacted starting material, PPh_3, and PPh_3O. The obtained mixture was analyzed by ^{1}H and ^{13}C NMR. ^{1}H NMR revealed traces of Cope product (characteristic olefinic methylene groups with a chemical shift of ~115 ppm) as well as the typical broadening associated with the conformational flexibility of the desired 10-membered ring system. The ^{13}C NMR showed at least four methylene carbons bonded to oxygen, indicating four major products which incorporated alkyne **16q**. Further, unambiguous identification and assignment proved unsuccessful, but based on the obtained data it is likely that the main components comprise the two regioisomers (with regard to the alkyne incorporation) of the expected macrocycle **24q** and the follow-up Cope product. The obtained spectral data and GC traces are provided in the Supporting Information.



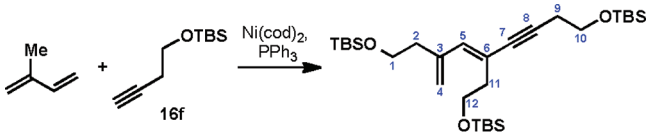
Direct Characterization of 24f (Category E[104]). The standard procedure was followed with $Ni(cod)_2$ (395 mg, 1.44 mmol, 10 mol %), PPh_3 (377 mg, 1.44 mmol, 10 mol %), alkyne **16f** (2.65 g, 14.4 mmol), and 1,3-butadiene (~50 mL, 576 mmol, 40 equiv) to afford crude **24f** (after workup B), which was further purified by flash chromatography (silica gel, hexanes → hexanes/EtOAc 100:1). After removal of traces 1,5-cyclooctadiene by application of vacuum overnight analytically pure **24f** was obtained as a colorless oil (980 mg, 3.35 mmol, 23%): R_f = 0.69 (silica gel, DCM/Et_2O, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$, −54 °C) δ = 5.46 (t, J = 10.9 Hz, 1 H), 5.39−5.28 (m, 2 H), 5.24−5.15 (m, 2 H), 3.65 (td, J = 9.5, 5.0 Hz, 1 H), 3.56 (q, J = 8.9 Hz, 1 H), 3.25 (t, J = 12.5 Hz, 1 H), 2.79−2.63 (m, 2 H), 2.29−2.23 (m, 2 H), 2.21−2.14 (m, 1 H), 2.08−1.99 (m, 2 H), 1.94 (q, J = 11.6 Hz, 1 H), 1.54 (q, J = 11.6 Hz, 1H), 0.84 (s, 9 H), 0.02 (s, 6 H) ppm; ^{13}C NMR (125 MHz, CDCl3, −54 °C) δ = 138.7, 131.4, 131.4, 129.4, 123.8, 123.6, 62.7, 41.9, 32.6, 31.4, 31.0, 30.4, 25.9, 18.5, −5.4 ppm; IR (ATR, neat) ν_{max} 3007, 2928, 2894, 2856, 1471, 1462, 1435, 1387, 1360, 1253, 1091, 1005, 970, 932, 914, 833, 811, 772, 742, 706, 664 cm^{-1}; HRMS calcd for $C_{18}H_{32}OSi$ 293.2295 [M + H]$^+$, found (ESI-TOF) 293.2289.

Characterization of 24f after Deprotection To Form 24c (Category D2[104]). Protected alcohol **24f** (760 mg, 2.60 mmol) was dissolved in THF (15 mL, 0.17 M). TBAF in THF (1.0 M, 2.86 mL, 2.86 mmol, 1.1 equiv) was added dropwise over 15 min at room temperature. The reaction was stirred at room temperature until it was judged to be complete by TLC (ca. 30 min). The mixture was neutralized with 1.0 N HCl and extracted with Et_2O. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude material was purified by column chromatography (silica gel, hexanes → DCM/hexanes 2:1) to give **24c** as a colorless oil (448 mg, 2.51 mmol, 97%): R_f = 0.25 (silica gel, DCM); ^{1}H NMR (500 MHz, $CDCl_3$, −50 °C) δ = 5.49−5.41 (m, 2 H), 5.35 (ddd, J = 15.3, 10.4, 4.7 Hz, 1 H), 5.27−5.18 (m, 2 H), 3.71−3.54 (m, 2 H), 3.28 (t, J = 12.6 Hz, 1 H), 2.85−2.68 (m, 2 H), 2.33−2.23 (br m, 3 H), 2.18 (br s, 1 H), 2.11−2.02 (m, 2 H), 1.95 (dd, J = 11.9, 11.5 Hz, 1 H), 1.56 (q, J = 11.6 Hz, 1 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, −50 °C) δ = 138.3, 131.2, 131.1, 129.6, 125.3, 124.0, 59.7, 41.4, 32.7, 31.0, 29.5, 25.9 ppm; IR (ATR, neat) ν_{max} 3335, 3007, 2928, 2885, 2856, 1471, 1437, 1361, 1252, 1194, 1041, 869, 833, 773, 706, 666 cm^{-1}; HRMS calcd for $C_{12}H_{18}O$ 179.1430 [M + H]$^+$, found (ESI-TOF) 179.1429.



S6, only isolated component from complex mixture

Isolation of the Main Product S6 from the Reaction of Alkyne 16p with Isoprene (Category C[104]). The standard procedure was followed with alkyne **16p** (569 mg, 2.87 mmol) and isoprene (1.5 mL, 14.4 mmol, 5.0 equiv). Workup A afforded a complex product mixture showing >10 products by TLC, while GC revealed the crude material to contain ~20 components. Despite the complexity of the crude mixture, isolation of the title compound was achieved by column chromatography (silica gel, hexanes/EtOAc, 250:1) followed by ^{1}H NMR analysis of single column fractions. The constitution of the Cope product **S6** was unambiguously established by 2D NMR experiments (see the Supporting Information):[106] ^{1}H NMR (600 MHz, $CDCl_3$) δ = 4.76 (s, 2 H, H-2, H-3), 4.64 (d, J = 9.2 Hz, 2 H, H-2, H-3), 3.61 (t, J = 7.5 Hz, 2 H, H-12) 2.51−2.44 (m, 2 H, H-6, H-10), 2.33−2.27 (m, 1 H, H-11), 2.26−2.20 (m, 1 H, H-11), 2.17−2.06 (m, 4 H, H-5, H-9), 1.73 (s, 3 H, H-18), 1.72 (s, 3 H, H-17), 1.65 (s, 3 H, H-16), 0.89 (s, 9 H, H-15), 0.05 (s, 6 H, H-13) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 148.1 (C-1, C-4), 127.5 (C-8), 125.9 (C-7), 110.3 (C-2, C-3), 61.9 (C-12), 42.8 (C-5), 42.5 (C-10), 37.2 (C-11), 36.1 (C-9), 34.1 (C-6), 26.1 (C-15), 23.9 (C-18), 23.8 (C-17), 19.0 (C-16), 18.5 (C-14), −5.1 (C-13) ppm; IR (ATR, neat) ν_{max} 3084, 2954, 2928, 2857, 1643, 1462, 1375, 1361, 1253, 1087, 1005, 887, 834, 811, 775, 733, 662 cm^{-1}; HRMS calcd for $C_{21}H_{38}OSi$ 335.2765 [M + H]$^+$, found (ESI-TOF) 335.2763.



S7, only isolated component from complex mixture

Isolation of a Main Component S7 from the Reaction of Alkyne 16f with Isoprene (Category C[104]). Reaction performed as in standard procedure with altered stoichiometry: Protected alcohol (**16f**, 2.11 g, 11.5 mmol), isoprene (5.7 mL, 57.3 mmol, 5.0 equiv), $Ni(cod)_2$ (106 mg, 0.39 mmol, 3.3 mol %), PPh_3 (100 mg, 0.39 mmol, 3.3 mol %).[107] Workup A afforded a brown oil, which was judged to be a mixture of >6 components by TLC and GC analysis. An aliquot (20 mg) of the crude material was purified by preparative TLC (silica gel, hexanes, plate run three times; then hexanes/EtOAc, 150:1, plate run three times) yielding **S7** as the only product that could be isolated in analytically pure form: R_f = 0.21 (silica gel, 2% EtOAc in hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.04 (s, 1 H, H-5), 5.37 (s, 1 H, H-4), 5.02 (s, 1 H, H-4), 3.79−3.67 (m, 6 H, H-1, H-10, H-12), 2.63 (t, J = 7.0 Hz, 2 H, H-11), 2.57 (t, J = 7.4 Hz, 2 H, H-9), 2.35 (t, J = 6.9 Hz, 2 H, H-2), 0.90−0.88 (m, 36 H), 0.07 (s, 6 H), 0.05 (s, 6 H), 0.04 (s, 6 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 142.5 (C-6), 136.7 (C-5), 118.5 (C-3), 118.0 (C-4), 94.1 (C-8), 81.3 (C-7), 63.0 (C-12), 62.2 (C-1), 62.0 (C-10), 43.3 (C-2), 38.8 (C-11), 26.8 (^{t}Bu), 26.7 (^{t}Bu), 24.3 (C-9), 18.5, −5.1 ppm; IR (ATR, neat) ν_{max} 2955, 2926, 2855, 1724, 1463, 1380, 1361, 1253, 1096, 1005, 938, 834, 812, 775, 721, 667 cm^{-1}; HRMS calcd for $C_{30}H_{60}O_3Si_3$ 553.3923 [M + H]$^+$, found (ESI-TOF) 553.3912.

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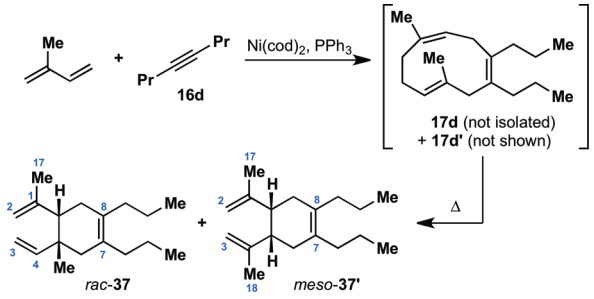
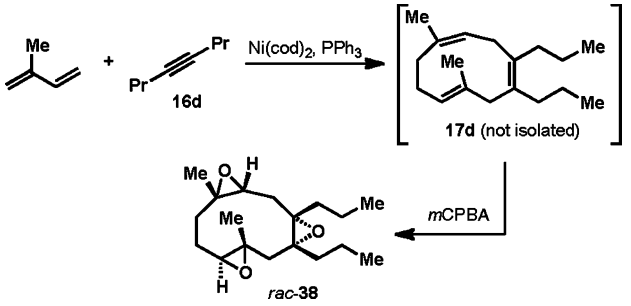
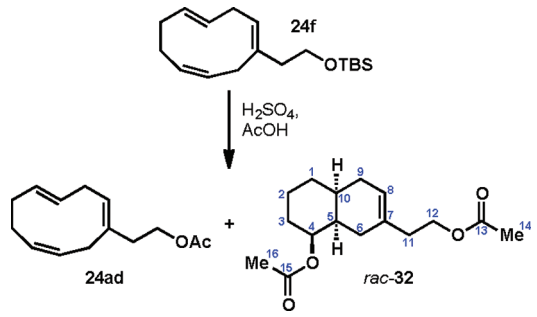


Characterization of 17d after Cope Rearrangement To Form *rac*-37 and *meso*-37′ (Category D2[104]). The standard procedure with workup A was followed using alkyne **16d** (316 mg, 0.42 mL, 2.87 mmol) and isoprene (~1.5 mL, 14.4 mmol, 5.0 equiv). The obtained crude material containing macrocycle **17d** was distilled directly to afford a 1:1 mixture of *rac*-37 and *meso*-37′ as determined by analysis of ^{1}H, ^{13}C, and APT NMR. In the following only the characteristic proton NMR signals are listed (full spectral data provided in the Supporting Information): R_f = 0.67 (silica gel, hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.02 (dd, J = 17.1, 11.4 Hz, 1 H, H-4 in *rac*-37), 4.97 (s, 1 H), 4.94 (dd, J = 8.0, 1.7 Hz, 1 H), 4.80–4.75 (m, 3 H), 4.71 (d, J = 2.4 Hz, 1 H), 4.67 (s, 2 H), 1.74 (s, 6 H, H-17, H-18 in *rac*-37′), 1.71 (s, 3H, H-17 in *rac*-37) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 148.3, 147.8, 144.0 (CH, C-4 in *rac*-37), 129.6, 129.5, 128.6, 112.2, 112.0, 110.2 (CH_2, C-2, C-3 in *meso*-37′), 51.6, 44.5, 42.7, 38.5, 35.3, 35.1, 34.9, 33.6, 26.1, 23.9, 23.0, 21.8, 21.7 (two signals), 14.5, 14.4 ppm; IR (ATR, neat) ν_{max} 3082, 2957, 2930, 2870, 1639, 1454, 1374, 1006, 910, 888, 738 cm^{-1}; GC/MS calcd for $C_{18}H_{30}$ 246.2348 $[M]^{\bullet+}$, found (FID[105]) 246.3.



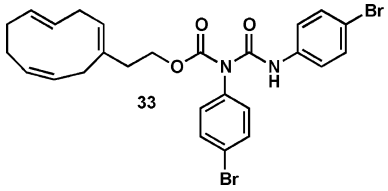
Characterization of 17d after Exhaustive Epoxidation Yielding Triepoxide *rac*-38 (Category D2[104]). The standard procedure was followed with alkyne **16d** (316 mg, 0.42 mL, 2.87 mmol) and isoprene (~1.5 mL, 14.4 mmol, 5.0 equiv). After workup A, an aliquot of the crude mixture containing **17d** (500 mg, crude) was brought up in DCM (20 mL) and 70% *m*-CPBA (3.00 g, 12.2 mmol, ~6.0 equiv) was added. The reaction was allowed to stir overnight at room temperature. Excess *m*-CPBA was quenched with saturated aqueous NaS_2O_3, and the mixture was extracted with DCM. The organic layer was washed with half-saturated aqueous $NaHCO_3$, H_2O, brine, and dried over $MgSO_4$. The crude material was purified by column chromatography (silica gel, hexanes/EtOAc, 9:1) to afford triepoxide *rac*-**38** (105 mg, 0.36 mmol; fully characterized) along with a second diastereomer (characterized by X-ray, see the Supporting Information). Crystals suitable for X-ray diffraction were obtained by slow evaporation of solution of *rac*-**38** in Et_2O layered with hexanes: R_f = 0.25 (silica gel, 15% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.81 (d, J = 8.4 Hz, 1 H), 2.70 (d, J = 14.9 Hz, 1 H), 2.65 (dt, J = 8.0, 2.4 Hz, 1 H), 2.45 (d, J = 15.6 Hz, 1 H), 2.19–2.11 (m, 2 H), 2.02 (ddd, J = 14.1, 10.5, 5.2 Hz, 1 H), 1.72–1.34 (m, 11 H), 1.33 (s, 3 H), 1.26 (s, 3 H), 1.01–0.97 (m, 6 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 69.9, 65.9, 65.4, 61.7, 61.4, 58.6, 44.7, 37.1, 33.9, 32.2, 30.3, 24.2, 22.8, 18.2, 17.9, 17.1, 14.6, 14.5 ppm; IR (ATR, neat) ν_{max} 2962, 2932, 2872, 1458, 1383, 1289, 1255, 1158, 1135, 1109, 1066, 1045, 1006, 958, 912, 872, 842, 798, 762, 731, 670 cm^{-1}; HRMS calcd for $C_{18}H_{30}O_3$ 295.2268 $[M + H]^+$, found (ESI-TOF) 295.2265.



Divergent Derivatization of 24f and 24c. Ring Fusion To Yield a 6,6-Bicyclic System (*rac*-32). Macrocycle **24f** (50.0 mg, 0.17 mmol) was dissolved in glacial acetic acid (1 mL, 0.17 M), and H_2SO_4 (1 drop) was added. The mixture was stirred at room temperature for 18 h, diluted with H_2O, neutralized with saturated aqueous $NaHCO_3$, and extracted with DCM. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude material by preparative TLC (silica gel, DCM:hexanes, 3:2) afforded the fused 6,6-bicyclic system *rac*-**32** as a colorless oil (22.0 mg, 78.5 μmol, 46%) and uncyclized macrocycle **24ad** as an oil (10.4 mg, 47.2 μmol, 28%).

rac-**32**: R_f = 0.10 (DCM/hexanes, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.37 (dd, J = 2.0, 1.5 Hz, 1 H, H-8), 4.89 (dt, J = 11.0, 5.0 Hz, 1 H, H-4), 4.14 (t, J = 7.0 Hz, 2 H, H-12), 2.30–2.21 (m, 4 H, H-5, H-9, H-11), 2.03 (s, 6 H, H-14, H-16), 1.85–1.67 (m, 5 H, H-3, H-6, H-9, H-10), 1.57 (ddd, J = 24.0, 12.5, 4.5 Hz, H-3), 1.41–1.18 (m, 3 H, H-1, H-2) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 171.2 (C-13), 170.7 (C-15), 130.8 (C-7), 121.7 (C-8), 75.6 (C-4), 63.1 (C-12), 36.9 (C-11), 36.0 (C-5), 33.2 (C-10), 31.5 (C-9), 25.9 (C-1), 25.6 (C-3), 24.1 (C-6), 23.8 (C-2), 21.5 (C-14), 21.1 (C-16) ppm; IR (ATR, neat) ν_{max} 2924, 2857, 1736, 1435, 1363, 1240, 1092, 1031, 973, 910 cm^{-1}; HRMS calcd for $C_{16}H_{24}O_4$ 281.1747 $[M + H]^+$, found (ESI-TOF) 281.1742.

24ad: R_f = 0.38 (DCM/hexanes, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.52–5.44 (m, 1 H), 5.43–5.33 (m, 2 H), 5.32–5.19 (m, 2 H), 4.13 (t, J = 7.0 Hz, 2 H), 3.30 (br s, 1 H), 2.76 (br s, 2 H), 2.35–2.10 (m, 4 H), 2.04 (s, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 171.2, 131.4, 131.3, 131.2, 129.8, 124.5, 124.1, 63.5, 38.0, 32.9, 31.0, 26.4, 21.1 ppm; IR (ATR, neat) ν_{max} 3007, 2957, 2925, 2855, 1741, 1436, 1381, 1364, 1236, 1036, 971, 913, 842, 793, 708 cm^{-1}; HRMS calcd for $C_{14}H_{20}O_2$ 221.1536 $[M + H]^+$, found (ESI-TOF) 221.1536.



Preparation of the Crystalline Derivative 33. Et_3N (0.23 mL, 1.68 mmol, 6.0 equiv) and DMAP (8.6 mg, 0.07 mmol, 25 mol %) were added to a solution of **24c** (50 mg, 0.28 mmol) in DCM (3 mL, 0.09 M). 4-Bromobenzyl isocyanate (221 mg, 1.12 mmol, 4.0 equiv) was added, and the resulting suspension was stirred for 18 h at room temperature. The mixture was acidified with 1 N HCl and extracted with DCM and EtOAc. The organic layers were washed with 1 N HCl, H_2O, and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the crude product by preparative TLC (silica gel, DCM/hexanes, 1:1) afforded **33** (61.0 mg, 0.11 mmol, 38%) as a white foam. Single crystals suitable for X-ray crystallographic analysis were obtained by slow evaporation of a solution of **33** in Et_2O/hexanes (1:1): R_f = 0.41 (silica gel, DCM/hexanes, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 10.87 (br s, 1 H), 7.55 (d, J = 7.0 Hz, 2 H), 7.43 (s, 4 H), 7.07 (d, J = 7.5 Hz, 2 H), 5.37–5.26 (m, 2 H), 5.24–5.17 (m, 2 H), 5.13 (t, 4.5 Hz, 1 H), 4.21 (br s, 2 H), 3.19 (br s, 2 H), 2.68 (br s, 2 H), 2.22 (t, J = 5.0 Hz, 2 H), 2.02 (br s, 4 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 155.6, 151.3, 136.8, 136.0, 132.4, 132.1, 131.2, 130.6, 125.3, 124.3, 122.6, 121.6, 116.8, 66.3, 37.9, 33.0, 30.5, 26.3 ppm; IR

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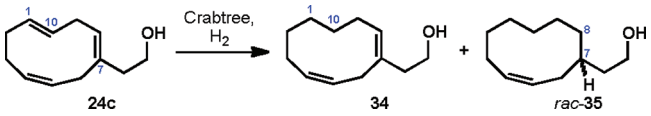
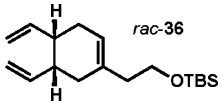
(ATR, neat) ν_{max} 3220, 3104, 3002, 2924, 2855, 1720, 1688, 1598, 1541, 1487, 1439, 1397, 1378, 1312, 1300, 1270, 1238, 1183, 1133, 1115, 1103, 1072, 1016, 1004, 993, 969, 925, 904, 833, 774, 743, 705, 688 cm^{-1}; HRMS calcd for $C_{26}H_{26}Br_2N_2O_3$ 573.0383 $[M + H]^+$, found (ESI-TOF) 573.0395.



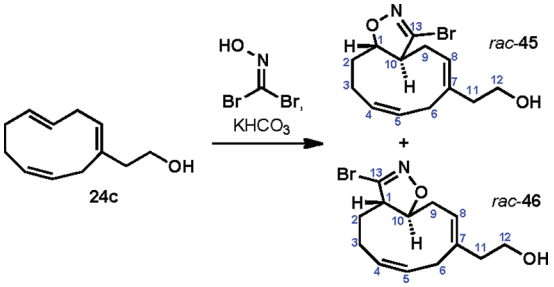
Hydrogenation of 24c To Afford 34 and *rac*-35. $[Ir(cod)(PCy_3)(py)]PF_6$ (4.50 mg, 5.59 μmol, 10 mol %) was added to a solution of macrocycle **24c** (10.0 mg, 56.1 μmol) in DCM. The reaction vessels was placed in a hydrogenation apparatus, charged with H_2 (150 psi), and stirred at room temperature for 18 h. The crude mixture was filtered through a silica plug (eluting with DCM) and the organic phase evaporated to dryness. Preparative TLC (silica gel, DCM) afforded analytically pure **34** (6.1 mg, 33.8 μmol, 60%) and *rac*-**35** (3.1 mg, 17.0 μmol, 30%).

34: R_f = 0.43 (silica gel, DCM); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 5.74 (app q, J = 9.3 Hz, 1 H, H-5), 5.29 (app dd, J = 9.4, 8.9 Hz, 1 H, H-4), 5.08 (t, J = 8.4 Hz, 1 H, H-8), 3.72 (d, J = 5.7 Hz, 2 H, H-12), 2.78 (d, J = 8.4 Hz, 2 H, H-6), 2.38–2.30 (m, 6 H, H-3, H-9, H-11), 1.56–1.50 (m, 2 H), 1.27–1.22 (m, 4 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 136.1 (C-7), 130.7 (C-4), 127.7 (C-8), 127.5 (C-5), 60.4 (C-12), 40.8 (C-11), 30.4, 30.1, 28.3 (C-9), 27.9 (C-6), 27.4 (C-3), 20.6 ppm; IR (ATR, neat) ν_{max} 3335, 3007, 2958, 2921, 2852, 1465, 1443, 1377, 1044, 1025, 935, 877, 864, 796, 761, 710 cm^{-1}; HRMS calcd for $C_{12}H_{20}O$ 181.1587 $[M + H]^+$, found (ESI-TOF) 181.1592.

rac-**35**: R_f = 0.43 (silica gel, DCM); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 5.47–5.38 (m, 2 H), 3.75–3.68 (m, 2 H), 2.35 (br s, 1 H), 2.14 (br s, 2 H), 1.76 (br d, J = 6.6 Hz, 1 H), 1.62–1.37 (m, 12 H), 1.24 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 131.2, 128.1, 61.6, 37.4, 32.9, 30.3, 29.9, 27.9, 27.5, 26.1, 25.7, 20.9 ppm; IR (ATR, neat) ν_{max} 3333, 2957, 2922, 2853, 1463, 1377, 1048, 888, 789, 722 cm^{-1}; HRMS calcd for $C_{12}H_{22}O$ 183.1743 $[M + H]^+$, found (ESI-TOF) 183.1752.



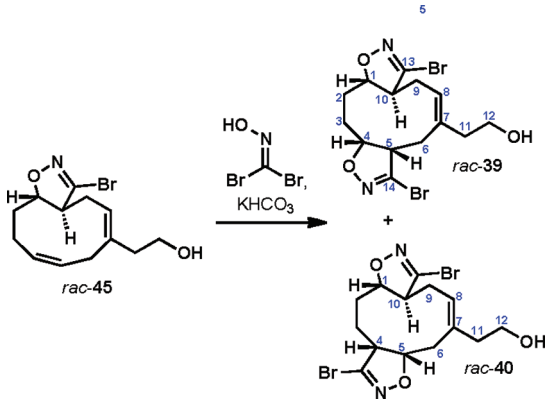
Cope Rearrangement to Divinylcyclohexene *rac*-36. Macrocycle **24f** (20.0 mg, 68.4 μmol) was heated neat to 100 °C in a sealed tube for 3 h. After purification of the crude mixture by column chromatography (silica gel, hexanes/EtOAc, 99:1) *rac*-**36** was obtained as a clear, pale yellow oil (16.0 mg, 54.7 μmol, 80%): ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.84–5.74 (m, 1 H), 5.41 (s, 1 H), 5.03–4.98 (m, 3 H), 3.66 (t, J = 7.0 Hz, 2 H), 2.48–2.36 (m, 2 H), 2.23–2.10 (m, 4 H), 2.01–1.89 (m, 2 H), 0.89 (s, 9 H), 0.05 (s, 6 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 140.3 (two signals), 133.5, 121.2, 114.6, 114.5, 62.4, 41.6, 41.2, 41.1, 32.8, 29.5, 26.1, 18.5, −5.1 ppm; IR (ATR, neat) ν_{max}: 3076, 2955, 2928, 2889, 2857, 1639, 1472, 1463, 1436, 1387, 1361, 1254, 1094, 995, 911, 833, 812, 774, 717, 661 cm^{-1}; HRMS calcd for $C_{18}H_{32}SiO$ 293.2295 $[M + H]^+$, found (ESI-TOF) 293.2287.



Delayed Installation of C_1 Units onto 24c. Monocycloadducts *rac*-45 and *rac*-46. Macrocycle **24c** (100 mg, 0.56 mmol) was dissolved in EtOAc (5.6 mL, 0.1 M). $NaHCO_3$ (282 mg, 3.36 mmol, 6.0 equiv) followed by dibromoformaldoxime (115 mg, 0.56 mmol, 1.0 equiv) were added at room temperature and the reaction was stirred under ambient atmosphere. Additional dibromoformaldoxime (115 mg, 0.56 mmol, 1.0 equiv) and $NaHCO_3$ (94.0 mg,1.12 mmol, 2.0 equiv) were added in intervals of 1 h until TLC analysis indicated full consumption of starting material.[108] The reaction was quenched with H_2O and extracted with EtOAc. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography (silica gel, DCM/Et_2O, 100:1→10:1) afforded the desired monocycloadduct *rac*-**45** (35 mg, 21%) and its undesired regioisomer *rac*-**46** (98 mg, 58%).

rac-**45**: R_f = 0.48 (silica gel, DCM/Et_2O, 10:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 5.68 (td, J = 10.7, 6.4 Hz, 1 H, H-5), 5.44 (td, J = 11.0, 5.5 Hz, 1 H, H-4), 5.11 (dd, J = 11.4, 5.7 Hz, 1 H, H-8), 4.30 (ddd, J = 13.9, 11.5, 2.4 Hz, 1 H, H-1), 3.78–3.70 (m, 2 H, H-12), 3.29 (t, J = 11.9 Hz, 1 H-6), 3.24 (ddd, J = 13.8, 5.4, 2.4 Hz, 1 H, H-10), 2.87 (ddd, J = 14.9, 11.4, 5.6 Hz, 1 H, H-9), 2.59 (ddd, J = 14.9, 5.8, 2.6 Hz, 1 H, H-9), 2.53–2.44 (m, 1 H, H-3), 2.39–2.27 (m, 3 H, H-6, H-11), 2.14 (ddd, J = 13.3, 8.5, 4.1 Hz, 1 H, H-3), 2.08 (tt, J = 13.8, 2.4 Hz, 1 H, H-2), 1.88 (dddd, J = 13.8, 10.8, 4.2, 3 Hz, 1 H, H-2) ppm; ^{13}C (150 MHz, $CDCl_3$) δ = 145.5 (C-13), 140.5 (C-7), 129.6 (C-4), 126.8 (C-5), 120.2 (C-8), 83.3 (C-1), 60.5 (C-12), 56.7 (C-10), 40.0 (C-11), 32.1 (C-2), 27.7 (C-6), 26.7 (C-9), 22.8 (C-3); IR (ATR, neat) ν_{max} 3410, 3014, 2957, 2922, 2853, 1715, 1644, 1571, 1466, 1377, 1289, 1180, 1118, 1107, 1084, 1045, 979, 916, 887, 802, 760, 720 cm^{-1}; HRMS calcd for $C_{13}H_{18}BrNO_2$ 300.0594 $[M + H]^+$, found (ESI-TOF) 300.0602.

rac-**46**: R_f = 0.38 (silica gel, DCM/Et_2O, 10:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 5.78 (td, J = 10.8, 6.3 Hz, 1 H, H-5), 5.38–5.29 (m, 2 H, H-4, H-8), 4.43 (dt, J = 13.5, 2.8 Hz, 1 H, H-10), 3.75 (dd, J = 8.1, 3.6 Hz, 2 H, H-12), 3.26 (t, J = 11.9 Hz, 1 H, H-6), 3.08 (t, J = 12.0 Hz, 1 H, H-1), 2.86 (ddd, J = 15.0, 11.1, 3.6 Hz, 1 H, H-9), 2.70 (ddd, J = 14.9, 5.2, 2.0 Hz, 1 H, H-9), 2.43–2.31 (m, 4 H, H-3, H-6, H-11), 2.15–2.09 (m, 1 H, H-3), 1.95 (t, J = 13.9 Hz, 1 H, H-2), 1.56 (m, 1 H, H-2) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 146.9 (C-13), 140.6 (C-7), 129.0 (C-4), 128.4 (C-5), 119.8 (C-8), 89.3 (C-10), 60.6 (C-12), 49.9 (C-1), 40.0 (C-11), 30.1 (C-2), 29.9 (C-9), 27.9 (C-6), 23.8 (C-3) ppm; IR (ATR, neat) ν_{max}: 3390, 3010, 2922, 2862, 1719, 1657, 1572, 1466, 1379, 1305, 1251, 1128, 1072, 1043, 1007, 927, 879, 798, 772, 720 cm^{-1}; HRMS calcd for $C_{13}H_{18}BrNO_2$ 300.0594 $[M + H]^+$, found (ESI-TOF) 300.0597.



Dicycloadducts *rac*-39 and *rac*-40. Monocycloadduct *rac*-**45** (30.1 mg, 0.10 mmol) was dissolved in EtOAc (1 mL, 0.1 M). $NaHCO_3$ (33.6 mg, 0.40 mmol, 4.0 equiv) was added to the reaction followed by dibromoformaldoxime (41.6 mg, 0.20 mmol, 2.0 equiv). Repeated additions of base (16.8 mg, 0.20 mmol, 2.0 equiv) and dibromoformaldoxime (20.8 mg, 0.10 mmol, 1.0 equiv) were continued over 22 h until the reaction was judged to be complete by TLC.[108] The mixture was diluted with H_2O and extracted with EtOAc. The organic was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Preparative TLC (silica gel, DCM/Et_2O, 9:1) afforded a 1:1 mixture (by ^{1}H NMR) of the two cycloadducts *rac*-**39** and *rac*-**40** (20.0 mg, 47.4 μmol, 47%). For full structural elucidation the crude mixture was further purified by preparative TLC (silica gel, DCM:Et_2O, 9:1): The seemingly single PTLC spot was arbitrarily split

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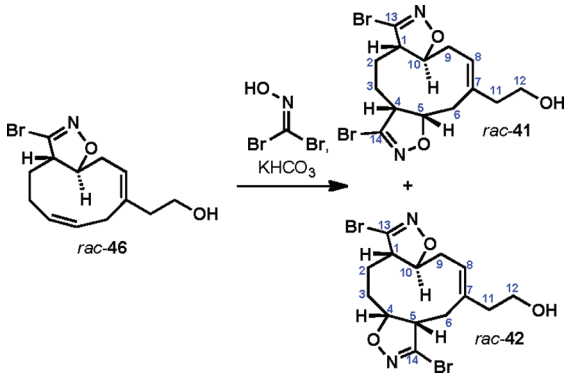
in half affording enriched samples of the two regioisomers *rac*-**39** and *rac*-**40** which allowed for full assignment by 2D NMR.

rac-**39**: R_f = 0.41 (silica gel, DCM/Et_2O, 9:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 5.21 (t, J = 8.5 Hz, 1 H, H-8), 4.51 (t, J = 9.1 Hz, 1 H, H-4), 4.19 (t, J = 12.8 Hz, 1 H, H-1), 3.84−3.74 (m, 2 H, H-12), 3.26 (d, J = 13.3 Hz, 1 H, H-10), 3.01 (t, J = 6.9 Hz, 1 H, H-5), 2.78 (dd, J = 15.3, 6.0 Hz, 1 H, H-6), 2.70 (m, 2 H, H-9), 2.45 (dt, J = 13.1, 4.0 Hz, 1 H, H-11), 2.37 (dt, J = 14.9, 7.4 Hz, 1 H, H-11), 2.30 (dd, J = 14.0, 5.3 Hz, 1 H, H-3), 2.14 (m, 2 H, H-2, H-3), 2.05 (m, 1 H, H-2), 1.84 (d, J = 15.6 Hz, 1 H, H-6) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 145.6 (C-14), 145.0 (C-13), 139.6 (C-7), 122.1 (C-8), 87.3 (C-4), 82.1 (C-1), 60.4 (C-12), 56.1 (C-10), 52.7 (C-5), 39.0 (C-11), 30.7 (C-2), 26.5 (C-9), 24.9 (C-6), 22.6 (C-3) ppm; IR (ATR, neat) ν_{max} 3415, 2926, 2866, 1717, 1571, 1467, 1448, 1392, 1306, 1288, 1250, 1214, 1177, 1107, 1085, 1043, 1002, 952, 908, 872, 854, 800, 731 cm^{-1}; HRMS calcd for $C_{14}H_{18}Br_2N_2O_3$ 420.9757 $[M + H]^+$, found (ESI-TOF) 420.9752.

rac-**40**: R_f = 0.37 (silica gel, DCM/Et_2O, 9:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 5.26 (dd, J = 10.9, 6.0 Hz, 1 H, H-8), 4.70 (t, J = 9.8 Hz, 1 H, H-5), 4.23 (t, J = 12.7 Hz, 1 H, H-1), 3.83−3.72 (m, 2 H, H-12), 3.24 (d, J = 13.8 Hz, 1 H, H-10), 2.88 (t, J = 12.7 Hz, 1 H, H-6), 2.83 (m, 1 H, H-4), 2.74−2.68 (m, 2 H, H-9), 2.52 (d, J = 14.2 Hz, 1 H, H-6), 2.41−2.31 (m, 2 H-11), 2.12 (t, J = 14.5 Hz, 1 H), 1.98 (t, J = 15.1 Hz, 1 H), 1.66 (dd, J = 16.2, 3.6 Hz, 1 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 145.7, 145.6, 136.5 (C-7), 123.7 (C-8), 82.5 (C-5), 81.8 (C-1), 61.0 (C-12), 55.8 (C-10), 53.5 (C-4), 39.0 (C-11), 32.7, 28.3 (C-6), 26.5 (C-9), 20.7 ppm; IR (ATR, neat) ν_{max} 3432, 2923, 2855, 1718, 1570, 1467, 1448, 1379, 1287, 1270, 1253, 1214, 1176, 1108, 1085, 1044, 976, 952, 909, 877, 853, 801, 733 cm^{-1}; HRMS calcd for $C_{14}H_{18}Br_2N_2O_3$ 420.9757 $[M + H]^+$, found (ESI-TOF) 420.9738.



Dicycloadducts *rac*-41 and *rac*-42. Monocycloadduct *rac*-**46** (91.0 mg, 0.30 mmol) was dissolved in EtOAc (3 mL, 0.1 M). $NaHCO_3$ (101 mg, 1.20 mmol, 4.0 equiv) was added to the reaction followed by dibromoformaldoxime (122 mg, 0.60 mmol, 2.0 equiv). Repeated additions of base (51.0 mg, 0.60 mmol, 2.0 equiv) and dibromoformaldoxime (61.0 mg, 0.30 mmol, 1.0 equiv) were continued over 22 h until the reaction was judged to be complete by TLC.[108] The mixture was diluted with H_2O and extracted with EtOAc. The organic was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the crude mixture by column chromatography (silica gel, DCM:Et_2O, 50:1 → 2:1) afforded a 1:1 mixture (by ^{1}H NMR) of the two cycloadducts *rac*-**41** and *rac*-**42** (52.0 mg, 0.12 mmol, 41%). For full structural elucidation an aliquot of the crude mixture was further purified by preparative TLC (silica gel, DCM:Et_2O, 9:1): The seemingly single PTLC spot was arbitrarily split in half affording enriched samples of the two regioisomers *rac*-**41** and *rac*-**42** which allowed for full assignment by 2D NMR.

rac-**41**: R_f = 0.36 (silica gel, DCM/Et_2O, 9:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 5.53 (dd, J = 11.0, 5.5 Hz, 1 H, H-8), 4.74 (t, J = 10.0 Hz, 1 H, H-5), 4.45 (d, J = 13.4 Hz, 1 H, H-10), 3.84−3.74 (m, 2 H, H-12), 3.06 (t, J = 12.8 Hz, 1 H, H-1), 2.91−2.68 (m, 4 H, H-4, H-6, H-9), 2.54 (d, J = 14.2 Hz, 1 H, H-6), 2.43−2.33 (m, 2 H, H-11), 2.03−1.83 (m, 2 H, H-2, H-3), 1.70−1.57 (m, 2 H, H-2, H-3) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 145.8 (C-13), 145.4 (C-14), 135.9 (C-7), 123.7 (C-8), 88.3 (C-10), 82.7 (C-5), 61.1 (C-12), 53.2 (C-4), 49.6 (C-1), 38.9 (C-11), 30.5 (C-2), 29.6 (C-9), 28.4 (C-6), 21.6 (C-3) ppm; IR (ATR, neat) ν_{max} 3404, 2922, 2855, 1728, 1570, 1464, 1447, 1378, 1325, 1303, 1263, 1210, 1167, 1126, 1084, 1043, 1010, 964, 907, 884, 855, 829, 801, 729 cm^{-1}; HRMS calcd for $C_{14}H_{18}Br_2N_2O_3$ 420.9757 $[M + H]^+$, found (ESI-TOF) 420.9771.

rac-**42**: R_f = 0.40 (silica gel, DCM/Et_2O, 9:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 5.45 (dd, J = 11.1, 5.7 Hz, 1 H, H-8), 4.50−4.42 (m, 2 H, H-4, H-10), 3.87−3.75 (m, 2 H, H-12), 3.07 (t, J = 7.3 Hz, 1 H, H-5), 2.97 (t, J = 13.0 Hz, 1 H, H-1), 2.85−2.70 (m, 3 H, H-6, H-9), 2.50−2.44 (m, 1 H, H-11), 2.41 (q, J = 7.7 Hz, 1 H, H-11), 2.27−2.21 (m, 1 H, H-3), 2.14−2.06 (m, 2 H, H-2, H-3), 1.86 (d, J = 15.3 Hz, 1 H, H-6), 1.72 (m, 1 H, H-2) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 145.7 (C-14), 145.2 (C-13), 138.9 (C-7), 122.2 (C-8), 88.3 (C-10), 87.1 (C-4), 60.6 (C-12), 52.7 (C-5), 50.5 (C-1), 38.9 (C-11), 29.6 (C-9), 28.3 (C-2), 25.2 (C-6), 23.6 (C-3) ppm; IR (ATR, neat) ν_{max} 3421, 2922, 2854, 1730, 1571, 1464, 1378, 1301, 1254, 1127, 1088, 1047, 966, 948, 886, 853, 797, 728 cm^{-1}; HRMS calcd for $C_{14}H_{18}Br_2N_2O_3$ 420.9757 $[M + H]^+$, found (ESI-TOF) 420.9774.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of relevant 1D and 2D NMR spectra, gas chromatograms, and details of the crystal structure determinations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(85) No yield was given for the Cope rearrangements.
(86) The assignment of the *cis*-relationship of the substituents at the 5 and 10 positions is based on previous results from extensive studies in the Heimbach laboratory. See ref 51 and references cited therein.
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(104) For assignment of the categories of reaction outcome refer to Figure 3.
(105) The compound did not ionize under ESI-TOF conditions.
(106) In addition, several—partially inseparable—further components were obtained that could not be characterized due to a lack of material.
(107) Alternatively, the reaction was run with a dropwise addition of **16f** or with a 40:1 diene/alkyne ratio. Although there was a noticeable increase in macrocycle formation by GC/MS, the mixture was still too complex for isolation.
(108) The dipole, generated in situ, dimerizes and must be replenished for the reaction to go to completion.