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Convergent and Stereospecific Synthesis of Complex Skipped Polyenes and Polyunsaturated Fatty Acids

Todd K. Macklin and **Glenn C. Micalizio***

Abstract

Skipped polyenes (i.e. 1,4-dienes and higher homologues) are stereodefined components of a vast array of biologically important natural products, including polyunsaturated fatty acids. While widespread in nature, these architectures are generally considered to represent significant barriers to efficient chemical synthesis. While partial reduction of skipped poly-ynes provides a pathway to a subset of such structures, general chemical methods for the preparation of skipped polyenes that contain varied stereochemistries and substitution patterns are lacking. Here, we describe a metal-promoted reductive cross-coupling reaction between vinylcyclopropanes and alkynes (or vinylsilanes) that provides stereoselective access to a diverse array of skipped polyenes through a process that establishes one C–C bond, generates up to three stereodefined alkenes, and can be used to introduce stereogenic centers at the central positions of the skipped polyene motif. We also demonstrate the significance of the present bond construction by preparing substituted and stereodefined polyunsaturated synthetic fatty acids.

Fatty acids are a subset of small molecules that are essential for life, playing not only central roles in compartmentalization and membrane function but also impacting cellular pathways that regulate blood pressure, clotting and lipid levels as well as the immune response and inflammation.(1–3) Polyunsaturated fatty acids (i.e. arachidonic acid, α-linoleic acid, γ-linoleic acid and eicosapentaenoic acid) are a subset of this large class of biomolecules that are present in all higher organisms and play critical roles in human health (Figure 1A).(4,5) These ubiquitous biomolecules share a common structural motif that imparts their unique properties – methylene interrupted polyenes (highlighted in blue). This central architectural feature is a stereodefined motif that is encountered throughout nature, with examples including structurally complex bioactive natural products from polyketide, terpene and alkaloid biosynthetic pathways. These more architecturally intricate molecules, identified as potent antibiotic, antifungal and cytotoxic agents, house skipped polyenes that contain

Correspondence and requests for materials should be addressed to G.C.M.

Author contributions

T.K.M. planned and carried out the experimental work. G.C.M. initiated and directed the project. The manuscript was written jointly by both authors.

Additional information

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stereochemically diverse di- and tri-substituted alkenes (i.e. ripostatin A, madangamine A).(6–10) Notably, more complex examples include secondary metabolites that house 1,4-dienes with stereogenic sp3 carbons at the central position of the isolated non-conjugated diene (i.e. jerangolid D and phorbasin C).(11–14)

The stereoselective preparation of these structural motifs remains a significant challenge in organic chemistry.(15–18) While methods based on carbonyl olefination, alkylation and partial reduction of acetylenes have been employed in numerous campaigns in stereoselective synthesis, these often multi-step processes are each plagued by significant limitations in scope, selectivity and efficiency. Here, we describe a titanium-mediated stereoselective fragment coupling reaction that delivers a variety of complex skipped polyenes by a process that establishes five unique stereochemical relationships across the skipped polyene backbone in concert with C–C bond formation (Figure 2). While defining a unique stereoselective transformation in organic chemistry, this convergent coupling reaction illuminates a powerful solution to the synthesis of a complex stereodefined structural motif observed throughout nature. In addition to presenting the basic reaction scope and selectivity of the process, we demonstrate the application of this reaction to the preparation of complex synthetic polyunsaturated fatty acids (PUFAs).

Results and Discussion

Reaction design

In designing a mode of reactivity suitable for the stereoselective construction of acyclic skipped polyenes, we were inspired by the well-established sigmatropic rearrangement chemistry of vinylcyclopropanes (Figure 3). In the case of cis-divinylcyclopropanes **1**, Cope rearrangement (**a**) is driven by the release of ring strain associated with the cyclopropane, and a cyclic 1,4-diene **2** is produced (Figure 3a).(19,20) In a mechanistically related rearrangement, cis-disubstituted vinylcyclopropanes (**3**) can undergo 1,5-hydrogen migration (**b**) to deliver acyclic 1,4-dienes (**4**) (Figure 3b).(21–24)

We speculated that a related six-electron process could ensue from an organometallic intermediate of general structure **5** (Figure 3c). Here, we reasoned that fragmentation would have the potential to proceed in a stereospecific manner, where the stereochemistry of the organometallic intermediate (**5**) could be translated directly to the stereochemistry of the skipped polyene product (**6**).

To prepare the required stereodefined metalated cyclopropanes (**5**), we speculated that a titanium-mediated, alkoxide-directed fragment union reaction between a substituted vinylcyclopropane **7** and a suitably functionalized coupling partner (i.e. **8**), could deliver tricyclic titanacyclopentane intermediates of general structure **9** (Figure 3d).(25) In addition to overcoming the sluggish reactivity of substituted alkenes in carbometalation chemistry, the hydroxy group of **7** would orchestrate encapsulation of the titanium center while establishing a rigid organometallic intermediate **9** suitably functionalized for the planned fragmentation. If rupture of the tricycle **9** proceeds in a stereospecific fashion, then the stereoselective annulation process (**7** + **8** → **10**) would lead, after hydrolysis, to the establishment of a stereodefined skipped polyene **11**. Overall, this reaction design would

define a convergent coupling reaction that has the potential to establish up to three stereodefined alkenes and one new stereogenic center (*), while generating a complex yet common stereochemically defined structural motif in nature. As synthetic approaches to stereodefined cyclopropanes of general structure **7** are readily available, we reasoned that the proposed coupling process would define a potentially powerful entry to skipped polyenes.

Exploring the reactivity of the vinylcyclopropane component

The feasibility of this proposal was first examined in coupling reactions of chlorodimethylvinylsilane with substituted vinylcyclopropanes, themselves derived from well-established cyclopropanation chemistry of allylic diazoacetates (i.e. **12–16**) (Table 1).(26,27) As depicted in entry 1, initial exploration provided support for the proposed stereoselective coupling process. Here, vinylcyclopropane **17** was converted to 1,4-diene **23** in 58% isolated yield (82% yield based on recovered starting material). While illustrating a useful reaction for the synthesis of a 1,4-diene bearing a central quaternary carbon, this reaction proceeded in a stereoselective manner and established a central (*E*)-disubstituted alkene (*E:Z* ≥ 20:1).

Similarly, conversion of vinylcyclopropane **18** to 1,4-diene **24** proceeded in 54% isolated yield (entry 2). Here, high *E*- selectivity (≥ 20:1) was accompanied by the generation of a 1 , 4-diene possessing a central chiral carbon. Entries 3 and 4 demonstrate that this coupling process is compatible with more highly substituted substrates. While conversion of **19** to the 1,4-diene **25** establishes a trisubstituted alkene, the trisubstituted vinylcyclopropane **20** is converted to a 1,4-diene that possesses a 1,1-disubstituted alkene and an allylic stereocenter (**26**). In both cases, high (*E*)-selectivity is observed in the formation of the central disubstituted alkene (≥ 10:1).

This coupling reaction can be used for the preparation of substituted skipped polyenes that house stereogenic centers at the 3-and 6-positions of the central 1,4-diene. As depicted in entries 5 and 6, vinylcyclopropanes **21** and **22** can be converted to stereodefined 1,4-dienes **27** and **28** in 55 and 52% yield, respectively. In each case, products were isolated as single isomers (dr ≥ 20:1, *E:Z* ≥ 20:1).

Probing stereospecificity

This complex coupling reaction appears to proceed in a stereospecific fashion. As depicted in entries 7 and 8 of Table 1, coupling of the isomeric vinylcyclopropanes **30** and **32** proceeds to deliver the skipped *Z,E*-diene **31** and *E,E*-diene **33**. While the establishment of the central *E*-trisubstituted alkene occurs with apparently high levels of stereoselectivity (≥20:1), the disubstituted alkene of these products is generated in a stereospecific fashion. On close spectroscopic analysis of the crude products from these coupling reactions, no evidence could be found for the production of minor products derived from conversion of **30** to **33** or from **32** to **31**. This intimate relationship between relative stereochemistry of the starting material and olefin geometry of the 1,4-diene product is consistent with a mechanistic proposal that follows from stereoselective formation of the tricyclic titanacyclopentanes **I** and **J**, followed by stereospecific fragmentation.

While defining a unique entry to stereodefined 1,4-dienes, to the best of our knowledge, this coupling reaction represents a unique transformation in organic chemistry. Alkoxide-directed metal centered [2+2+1] annulation enables stereoselective access to a fleeting organometallic intermediate (a configurationally defined cyclopropylcarbinyl anion) whose subsequent fragmentation occurs in a stereospecific manner.(28–34)

Skipped trienes from the reductive coupling of vinylcyclopropanes with alkynes

The titanium-mediated cross-coupling reaction of vinylcyclopropanes with alkynes enables direct stereoselective access to skipped trienes. As depicted in Figure 4a, reaction of vinylcyclopropane **34** with TMS-alkyne **35**, followed by desilylation (TBAF, THF) delivers complex triene **36** in 34% isolated yield over the two-step process (82% based on recovered starting material in the T i-mediated coupling reaction). While regioselective functionalization of the alkyne proceeds in a manner where C–C bond formation occurs distal to the TMS-substituent,(35) the sense of regio- and stereoselective functionalization of vinylcyclopropane **34** is consistent with the observations made during study of the vinylcyclopropane–vinylsilane coupling. Overall, this convergent coupling reaction establishes one C–C bond, sets three stereodefined alkenes, one sp3 stereogenic center, and delivers a complex skipped triene in a single step. Notably, each sp3 stereogenic center in this product is positioned between the alkenes of the skipped polyene, defining a product that contains five contiguous stereogenic relationships that span eight contiguous carbons.

Synthesis of novel polyunsaturated fatty acids (PUFAs)

As a test of our methodology, we targeted application to the synthesis of novel stereochemically complex polyunsaturated fatty acids. While polyunsaturated fatty acids define a region of natural product chemical space that is rich in biological function, the dearth of methods available for the efficient synthesis of stereodefined skipped polyenes has generally limited medicinal investigation. The targets selected to explore the utility of our vinylcyclopropane-based skipped polyene synthesis were fatty acids that display complex stereochemical features for which a general synthetic method has not been available. Specifically, we aimed to access polyunsaturated fatty acids that contain: 1) di- and tri-substituted alkenes, 2) *E*- and *Z*- olefins, and 3) contain stereochemistry at the central positions of the 1,4-diene motifs. Such features represent the most complex examples of skipped polyenes observed in bioactive natural products.

As illustrated in Figure 4b, a sequence involving 1) reductive cross-coupling of suitably substituted vinylcyclopropanes with TMS alkynes, 2) desilylation, and 3) oxidation provides polyunsaturated fatty acids in a highly stereoselective fashion. While equation 2 demonstrates this process is effective for the preparation of a simple C-14 skipped triene-containing fatty acid, equations 3 and 4 confirm that this synthetic sequence is equally effective for the generation of higher homologues that contain stereodefined tetra-enes (**39**) and branched alkyl substitution (**41**).

While serving as a platform to challenge our chemical technology, this exercise has delivered complex stereodefined synthetic fatty acids. Likely due to the difficulties associated with preparing such architectures with existing chemical methods, such structures

have never been reported. The mode of chemical reactivity described here provides a unique and powerful means to initiate investigations aimed at elucidating the physical and biological properties of complex and diverse polyunsaturated fatty acids.

Conclusion

Skipped polyenes are structural motifs present in organic molecules observed throughout nature and biology. Natural products that possess this motif are known to play key roles in compartmentalization and signal transduction, while others possess potent anticancer and antibiotic properties. Although recognized as a central stereodefined architectural feature of a variety of biologically significant natural products, skipped polyenes have remained as significant challenges in stereoselective chemical synthesis. We have described a chemical process that enables direct and stereoselective access to complex and diverse skipped polyenes by the direct union of vinylcyclopropanes with alkynes and vinylsilanes. While appearing complex, the vinylcyclopropane substrates for this process are available in a few steps from allylic diazoacetates by well-known cyclopropanation chemistry. Due to the previously established barriers associated with the preparation of this type of stereodefined architecture, and the relative ease with which the current method delivers these complex systems, we are looking forward to scientific advances that follow from this initial report.

Methods

General procedure for the reductive cross-coupling of vinylcyclopropanes with alkynes

To a round bottom flask (RBF) containing alkyne (2 mmol) and $ClTi(O\textit{i}\text{-}Pr)_3$ (2 – 2.5 mmol, 1.0 M in hexanes) in toluene (0.1 M) at −78 °C is added *c*-C_5H_9MgCl (4 – 5 mmol) by syringe and the mixture is warmed to −30 °C and stirred for 1 h (becoming deep brown in color). In a separate RBF containing a vinylcyclopropane carbinol (1 mmol) in diethyl ether (Et_2O) (<0.3 M) at −78 °C is added *n*-BuLi (1.2 mmol) by syringe and the mixture is warmed to 0 °C over 20 min and then added by cannula to the titanium complex that has been re-cooled to −70 °C. The mixture is then slowly warmed to RT over 2–3 h and treated with 1N HCl (~5 mL / mmol of vinylcyclopropane used) with rapid stirring. After 10 min the now colorless mixture is further diluted with ethyl acetate (EtOAc) and then filtered through a pad of silica rinsing with additional EtOAc. After concentration *in vacuo*, the non-polar product fractions are separated from the unreacted vinylcyclopropane by flash column chromatography (0 to 5% Et_2O in hexanes followed by flushing with EtOAc).

In the examples presented, subsequent functionalization by desilylation and/or oxidation was accomplished by the following protocols: To this crude product in a plastic vial dissolved in acetonitrile (MeCN) / dichloromethane (CH_2Cl_2) (5 mL, 1:1) at 0 °C is added HF • pyridine by plastic syringe in 1 mL / 5 min increments. When the reaction is complete (indicated by TLC), the reaction mixture is poured slowly into a plastic beaker containing stirred saturated aqueous $NaHCO_3$ (100 mL) at 0 °C, then diluted with Et_2O. The layers are separated, the aqueous phase extracted with Et_2O, organic extracts combined and filtered through $MgSO_4$, concentrated *in vacuo*, and purified by flash column chromatography (10 – 15% EtOAc in hexanes). The resultant alcohol, which could contain small amounts of reduction side products, was used directly in the following oxidation. The purified skipped polyene alcohol

(ie 0.5 mmol) in dimethylformamide (DMF) (3 mL) is added pyridinium dichromate (PDC) (2.0 mmol) and two drops of water at RT and the reaction is stirred for 12 h. The reaction mixture is then poured into brine (15 mL) and extracted three times with Et_2O, extracts combined, washed with brine, filtered through $MgSO_4$, concentrated *in vacuo*, and purified by flash column chromatography (20% EtOAc in hexanes) to yield the pure product.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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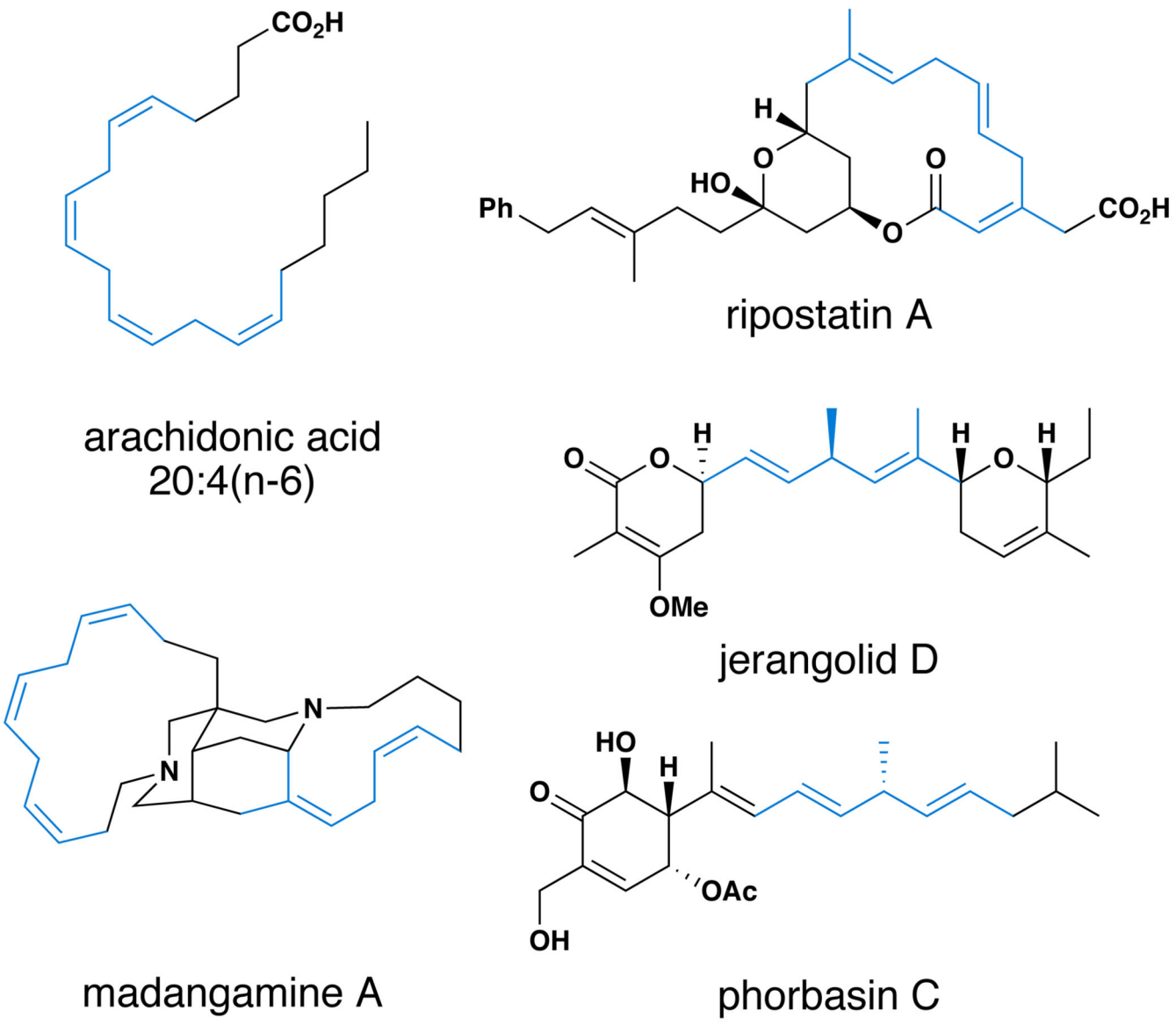

Figure 1. Stereodefined skipped polyenes are a structural motif found in diverse natural products

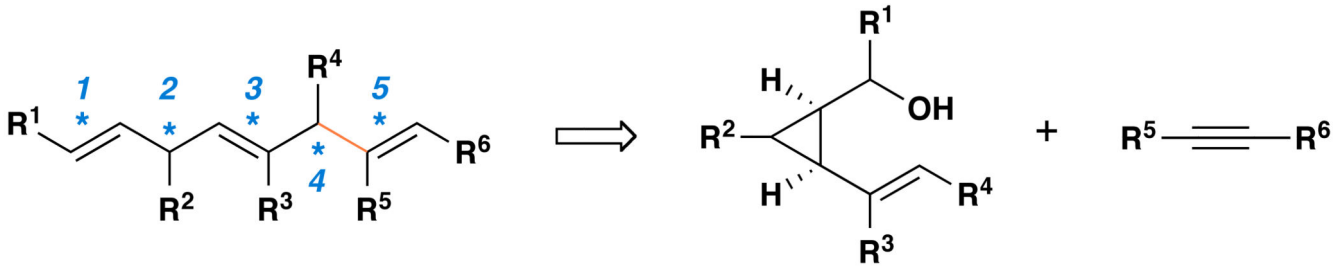

Figure 2. A route to stereodefined skipped polyenes by titanium-mediated reductive cross-coupling of vinylcyclopropanes with alkynes

* = Stereochemical relationships established in this skipped polyene synthesis; **1** = stereochemistry set in a stereospecific fashion (*E* or *Z*); **2** = stereochemistry retained from cyclopropane; **3** and **4** = stereochemistry set in a stereoselective fashion (≥20:1); **5** = stereochemistry is set as a function of the reaction mechanism. / = carbon–carbon bond formed in Ti-mediated cross-coupling.

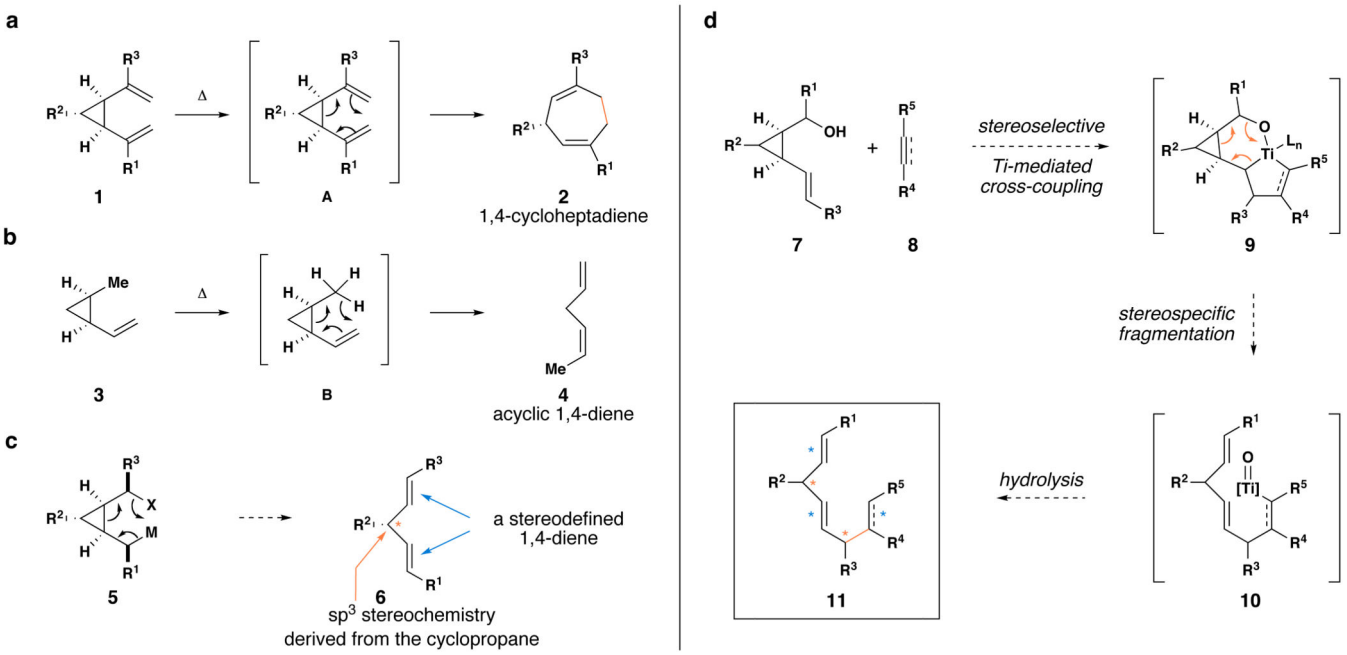

Figure 3. The design of a convergent coupling reaction suitable for the stereoselective synthesis of complex skipped polyenes

a, Cope rearrangement of cis-divinylcyclopropanes. **b**, 1,5-hydrogen migrations in cis-vinylcyclopropanes. **c**, A plausible 6-electron process for acyclic 1,4-diene synthesis – alkene geometry is set as a function of the stereochemistry of the intermediate and the mechanistic course of the fragmentation. **d**, Design of a cross-coupling/fragmentation cascade for preparation of stereodefined skipped polyenes. * = stereochemistry of up to three alkenes is established; * = this carbon–carbon bond forming process has the potential to establish 1,4-dienes bearing a central stereodefined C3-carbon; / = carbon–carbon bond formed in Ti-mediated cross-coupling; **M** = metal.

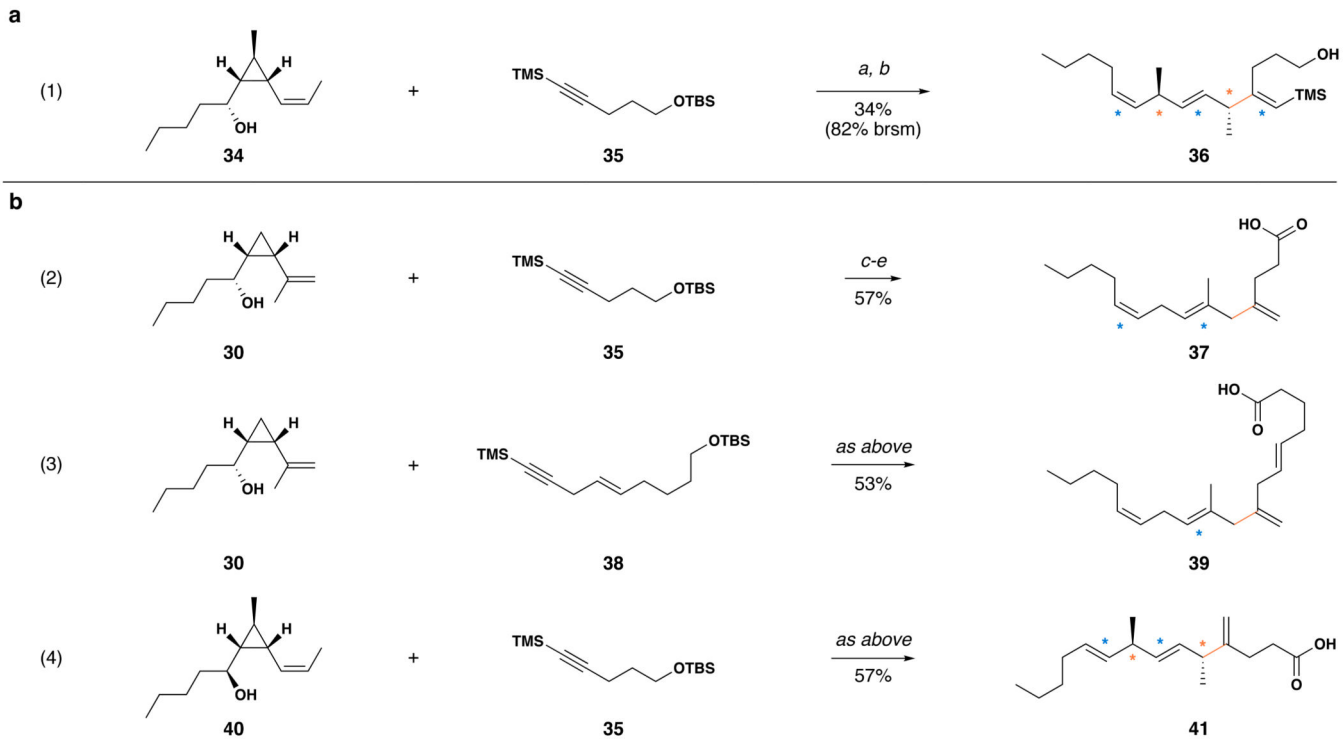

Figure 4. Synthesis of skipped polyenes by the coupling of vinylcyclopropanes with TMS-alkynes

a, Direct synthesis of complex skipped trienes by reductive cross-coupling of vinylcyclopropanes with alkynes. **b**, Stereoselective preparation of complex synthetic polyunsaturated fatty acids (PUFAs). Reaction conditions employed: (a) $ClTi(O\textit{i}\text{-}Pr)_3$, *c*-$C_5H_9MgCl$, **35** (−78 to −30 °C), PhMe, then lithium alkoxide of **34** in Et_2O (−70 °C to rt over 3 h). (b) TBAF, THF. (c) $ClTi(O\textit{i}\text{-}Pr)_3$, *c*-$C_5H_9MgCl$, alkyne (−78 to −30 °C), PhMe, then lithium alkoxide of the vinylcyclopropane in Et_2O (−70 °C to rt over 3 h). (d) HF•pyr, CH_3CN, CH_2Cl_2, (e) PDC, DMF, H_2O. Yields reported are over the three-step sequence (c–e) and adjusted based on the quantity of recovered starting material (vinylcyclopropane). Isolated yields for each reaction sequence are 38% (eq 2), 36% (eq 3) and 23% (eq 4) over the three-step process (corresponding to average yields of 60–70% per step). * = up to three stereodefined alkenes are generated in concert with C–C bond formation; * = 1,4-dienes are generated that house central C3-stereochemistry; / = carbon–carbon bond formed in Ti-mediated cross-coupling.

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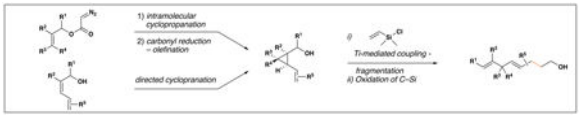
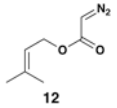
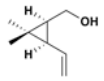
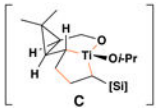
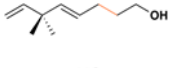
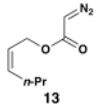
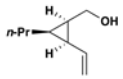
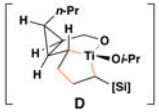
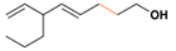
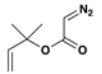
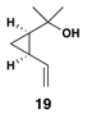
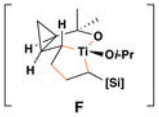
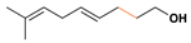
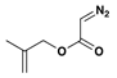
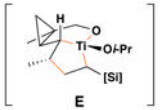
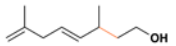
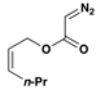
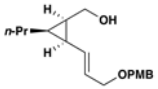
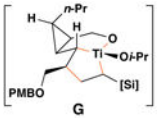
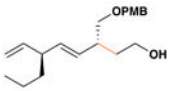
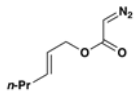
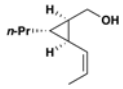
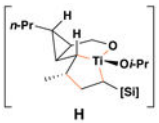
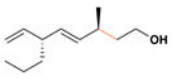
Table 1



entry	allylic alcohol or diazoacetate starting material	vinylcyclopropane	Presumed metallacyclic intermediate[a]	Yield (%)[b]	(E:Z)[c]	dr[c]	product[d]
1	 12	 17	 C	58 (82% brsm)	20:1	–	 23[e]
2	 13	 18	 D	54	20:1	–	 24[e]
3	 14	 19	 F	50	20:1	–	 25[f]
4	 15	 20	 E	61	10:1	–	 26[e]
5	 13	 21	 G	55	20:1	20:1	 27[e]
6	 16	 22	 H	52	20:1	20:1	 28[e]

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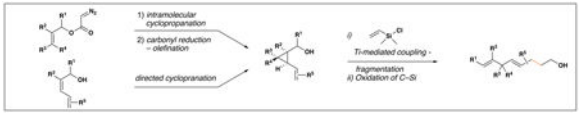
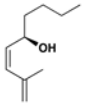
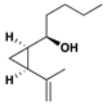
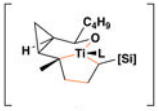
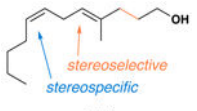
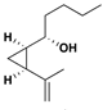
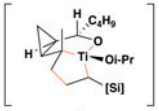
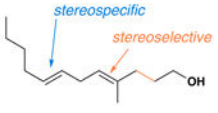


entry	allylic alcohol or diazoacetate starting material	vinylcyclopropane	Presumed metallacyclic intermediate[a]	Yield (%)[b]	(E:Z)[c]	dr[c]	product[d]
7	 **29**	 **30**[g]	 **I**	52	20:1	20:1	 **31**[e]
8	**29**	 **32**[g,h]	 **J**	42	20:1	20:1	 **33**[f]

[a] _ = bonds formed in the coupling process.

[b] While not computed for examples 2–8, as seen in entry 1, these reactions did not consume all of the vinylcyclopropane starting material.

[c] No evidence was found for the production of stereoisomeric products.

[d] Reaction conditions for cross-coupling: vinylsilane, $ClTi(O\textit{i}\text{-}Pr)_3$, *c*-$C_5H_9MgCl$, Et_2O (−78 to −50 °C), then add Li-alkoxide of vinylcyclopropane (−70 °C to rt over 3 h).

[e] Oxidation conditions: TBHP, H_2O, $CsOH{\bullet}H_2O$, TBAF, DMF, 70 °C.

[f] Oxidation conditions: KF, $KHCO_3$, H_2O_2, MeOH, THF.

[g] ICH_2Cl, Sm[Hg], THF, (85%, dr ≥ 20:1).

[h] PDC, 4 Å sieves, CH_2Cl_2 (91%), then L-Selectride, THF (76% of desired isomer, dr = 6:1).