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Convergent Synthesis of Deoxypropionates**

Peter S. Diez and **Glenn C. Micalizio***

Keywords

convergent coupling; polyketide synthesis; total synthesis; deoxypropionates; metallacycles; titanium

Over the last thirty years, substantial advances in stereoselective synthesis have enabled the preparation of exquisitely complex and therapeutically valuable polyketide-derived natural products.[1] While impressive, these accomplishments are typically composed of multistep sequences that are required to manage the reactivity of synthetic intermediates in the course of iterative chain growth (i.e. protecting/functional group manipulations and carbonyl redox chemistry). This is particularly evident in synthesis strategies for deoxypropionate-containing natural products (Figure 1). Reduced polypropionate architecture is found in natural products that possess a broad range of biological properties and, as such, has been the target of numerous studies in stereoselective synthesis.[2] A variety of iterative synthetic strategies to deoxypropionates have been described that can be characterized in one of two ways: (1) Those that forge single C–C bonds in the iterative chain elongation process (i.e. methods based on sequential enolate alkylation,[3] SN2' chemistry,[4] and carbonyl olefination/asymmetric hydrogenation),[5] and (2) those that proceed by constructing 2 C–C bonds in the course of chain elongation (i.e. methods based on asymmetric carbometalation/oxidation/carbonyl olefination,[6] and stereoselective 1,4-addition/carbonyl olefination[7]).[8, 9] While these iterative synthesis strategies to deoxypropionates are powerful and stereochemically flexible, they uniformly suffer from the requirement of long sequences of chemical transformations to construct a complex deoxypropionate chain and, as such, suffer from poor step-economy (3–4 steps required for 2-carbon chain elongation).[10]

Accepting the value of convergent strategies in chemical synthesis, and the impact that such processes have on synthesis efficiency, it is surprising that the general approaches to deoxypropionate synthesis remain largely dependent on synthetic methods that target iterative chain growth.[11] Here, we describe a chemical solution for the convergent synthesis of deoxypropionates that is enabled by metallacycle-mediated allylic alcohol–alkyne cross-coupling and stereoselective hydrogenation (Figure 2). Based on the stereoselective course of metallacycle-mediated coupling, and the established selectivity of hydroxyl-directed hydrogenation, a range of stereoisomeric deoxypropionate tetrads can be accessed with high step economy and stereoselectivity – albeit, only a subset of the stereoisomers possible can be prepared with this strategy. In addition to establishing the convergent method, we demonstrate the utility of this process in natural product synthesis by

*Prof. Glenn C. Micalizio, Department of Chemistry, The Scripps Research Institute, 130 Scripps Way #3A2, Jupiter, FL 33458 (USA), micalizio@scripps.edu.

**The authors dedicate this manuscript to their colleague and mentor Professor William R. Roush on the occassion of his 60th birthday.

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achieving an efficient synthesis of the C1–C11 subunit of borrelidin and completing a concise total synthesis of (–)-vittatalactone.

Recently, we described a stereoselective metallacycle-mediated reductive cross-coupling reaction between allylic alcohols and alkynes that proceeds with regio- and stereochemical control.[12, 13] With our sights set on securing the convergent approach to deoxypropionates illustrated in Figure 2, we initiated efforts to accomplish the allylic alcohol–alkyne coupling reaction depicted in Figure 3. While initial attempts with the homopropargylic alcohol substrate **1** were met with failure, when the free hydroxy group was masked as its corresponding methyl ether (**4**), Ti-mediated reductive cross-coupling with allylic alcohol **2** (1.5 equiv) delivered the stereodefined 1,4-diene product **5** in 73% yield as a single regio- and stereoisomer (ds ≥ 20:1).[14] Regio-and stereochemical control for this process is consistent with our previous studies and the empirical model depicted. In short, regioselective alkoxide directed carbometalation proceeds proximal to the Me-group and distal to the branched substitution of the Ti–alkyne complex, and stereochemical control derives from minimization of A-1,2 strain in a boat-like transition state. Subsequent *syn*-elimination of the fleeting stereodefined oxametallacyclobutane intermediate then delivers the (*Z*,*E*)-1,4-diene product **5**. In this manner, stereoselective reductive cross-coupling ensues independent of the relative stereochemistry of the allylic alcohol (as depicted in the bottom portion of Figure 3).

With what appeared to be a robust coupling reaction en route to polyunsaturated substrates bearing the appropriate Me-substitution pattern for the synthetic goal in mind, effort was focused on exploring the substrate scope of this process. Specifically, attention was focused on exploring substrates that contained varying stereochemistry and substitution patterns of relevance in natural product synthesis. As depicted in entries 1–3 of Table 1, substrates derived from propargylation (**6** and **9**)[15] and Grignard addition to a readily available chiral aldehyde (3-benzyl- or 3-silyloxy-2-methylpropanal; **2** and **10**) were competent reaction partners for reductive cross-coupling. In each case the crude reaction mixture was advanced by subsequent deprotection (TBAF, HMPA, 35 °C) to deliver the stereodefined diols **7**, **11**, and **13** with similarly high levels of stereoselection (yields reported are for the combined two-step process).

Moving on to stereoselective functionalization of the 1,4-diene products, we directed our attention to the use of hydroxyl-directed Rh-catalyzed hydrogenation.[5a, 16] As anticipated from the early reports of Evans, these hydroxyl-directed hydrogenation reactions [Rh[nbd(dppb)] BF_4, CH_2Cl_2, H_2 (500–700 psi] were uniformly successful and resulted in the formation of the stereodefined deoxypropionates **8**, **12**, and **14**.[17]

As illustrated in entries 4 and 5, internal alkyne substrates bearing less branching were also viable substrates in this coupling process. Here the 1,4-diene-containing diol products **16** and **18** were produced in 56 and 62% yield over the two-step process, and subsequent hydroxyl-directed hydrogenation delivered the stereodefined deoxypropionates **17** and **19** in 80 and 79% yield, respectively. In the case of entry 5, this three-step process, consisting of Ti-mediated coupling, desilylation and directed hydrogenation, delivers the C1–C11 deoxypropionate core of the natural product borrelidin (**19**).[11a, 18]

Finally, selective deprotection of 1,4-diene products derived from the reductive cross-coupling reaction leads to intermediates that can be functionalized in a site-selective manner. As depicted in entry 6, coupling of alkyne **6** with allylic alcohol **10**, followed by selective removal of the primary TBS ether delivers the stereodefined 1,4-diene **20** in 72% overall yield. Such substrates are ideal for chemoselective hydroxyl-directed hydrogenation, in this case delivering the unsaturated deoxypropionate product **21** in 87% yield. While not

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investigated in the context of this study, the remaining alkene of **21** can be functionalized by a variety of well-established reactions to deliver more highly oxygenated products than those depicted in entries 1–5.

While our stereochemical assignments of the deoxypropionate products depicted in Table 1 were supported by application of Breit's empirical model,[17] we selected to secure an alternative stereochemical proof by applying this process in natural product synthesis. Vittatalactone is a deoxypropionate natural product that was isolated in a search for sex pheromones specific to the cucumber beetle (*Acylymma vittatum)* – an insect that causes major damage to the cucurbit crops in North America (Figure 4A). Despite its relative structural simplicity, reported laboratory syntheses of this natural product proceed in up to 27 linear steps – a fact that supports the great difficulty/inefficiency associated with the synthesis of deoxypropionate targets.[19] While our convergent coupling chemistry is ideally suited for convergent union of larger/more complex coupling partners than would be required to prepare vittatalactone, our focus on this target was solely based on our desire to confirm the stereochemical assignments made previously in Table 1.

As depicted in Figure 4B, our synthesis begins with titanium-mediated reductive cross-coupling of the stereodefined homopropargylic ether **9** (available from propargylation of 3-benzyloxy-2-methylpropanal) with allylic alcohol **2**. Desilylation, and directed hydrogenation then delivers the deoxypropionate product **22** in 55% yield (over three steps). Site-selective tosylation and reduction furnishes **23** in 84% yield, and benzyl deprotection, site-selective oxidation to the acid, and lactonization delivers (–)-vittatalactone (57% yield over three steps).

In summary, a convergent route to deoxypropionates is described that proceeds by metallacycle-mediated cross-coupling and stereoselective hydrogenation. Overall, this approach has been demonstrated to be useful for a considerable subset of deoxypropionate stereoisomers, providing a solution to the assembly of such targets that is no longer limited to iterative C–C bond formation. While the stereochemical scope of the current study is constrained by the use of hydroxyl-directed hydrogenation, we anticipate that the identification of other methods for substrate- or catalyst-controlled hydrogenation of the complex stereodefined 1,4-diene intermediates will further increase the utility of this approach. From a broader perspective, the chemical pathway described lays a foundation to polyketide synthesis where alkene–alkyne coupling chemistry plays a central role.[20, 21] In addition to reporting the general aspects of this synthesis pathway, convergent and stereoselective syntheses of (–)-vittatalactone and the C1–C11 subunit of borrelidin are described. We look forward to future developments that emerge from these initial findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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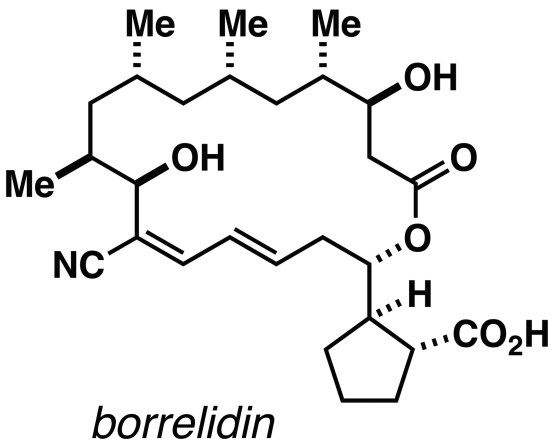
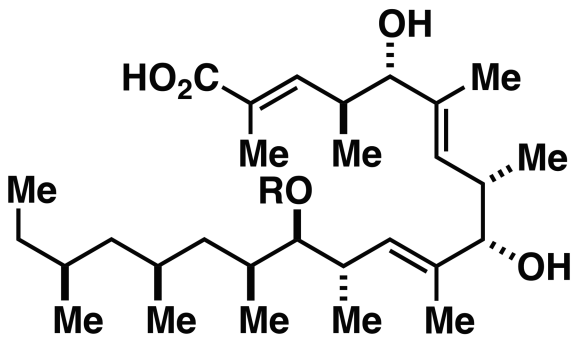


borrelidin



TMC-151A
(R = β-mannosyl)

Figure 1.
Representative deoxypropionate-containing natural products.

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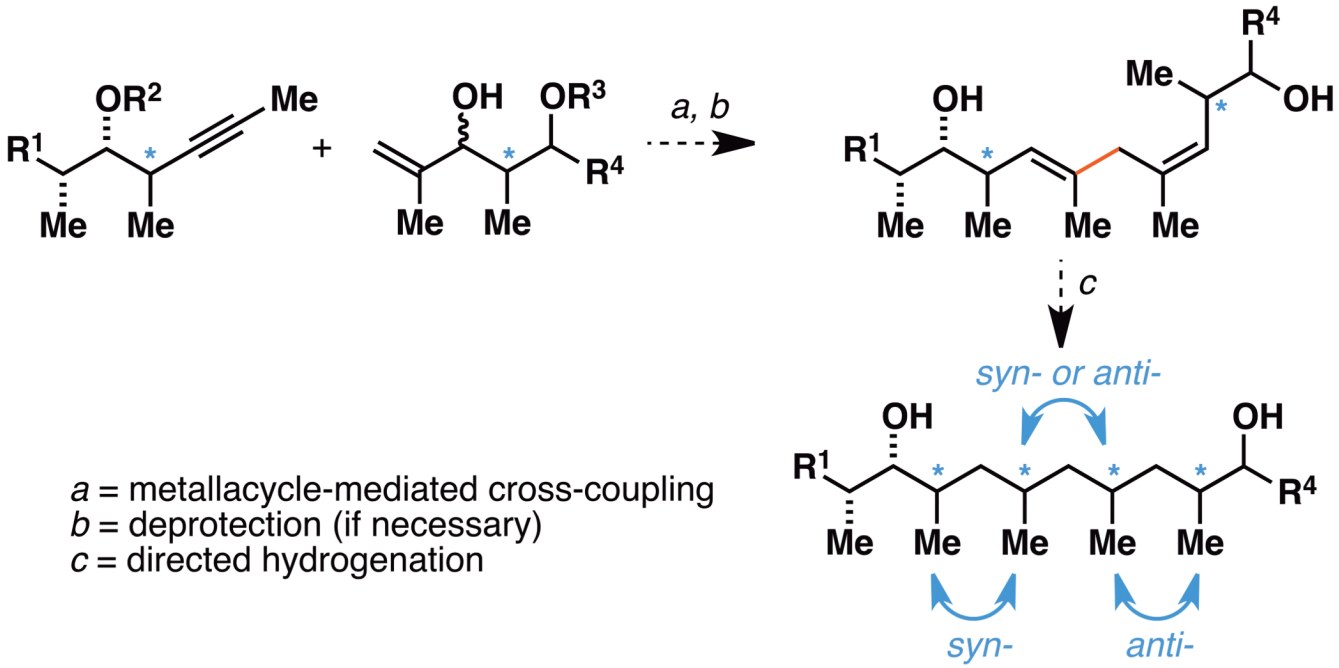

Figure 2.
A convergent strategy for deoxypropionate synthesis.

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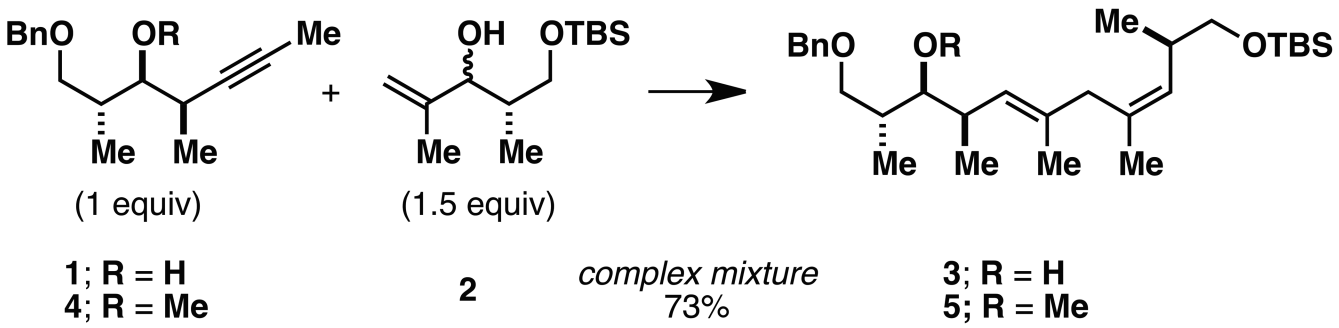

1; **R** = **H**
4; **R** = **Me**

2

complex mixture
73%

3; **R** = **H**
5; R = **Me**

Reaction conditions: alkyne (1 equiv), $ClTi(O\textit{i}\text{-}Pr)_3$ (1.5 equiv), *c*-C_5H_9MgCl (3 equiv), PhMe, then add Li-alkoxide of allylic alcohol in Et_2O.

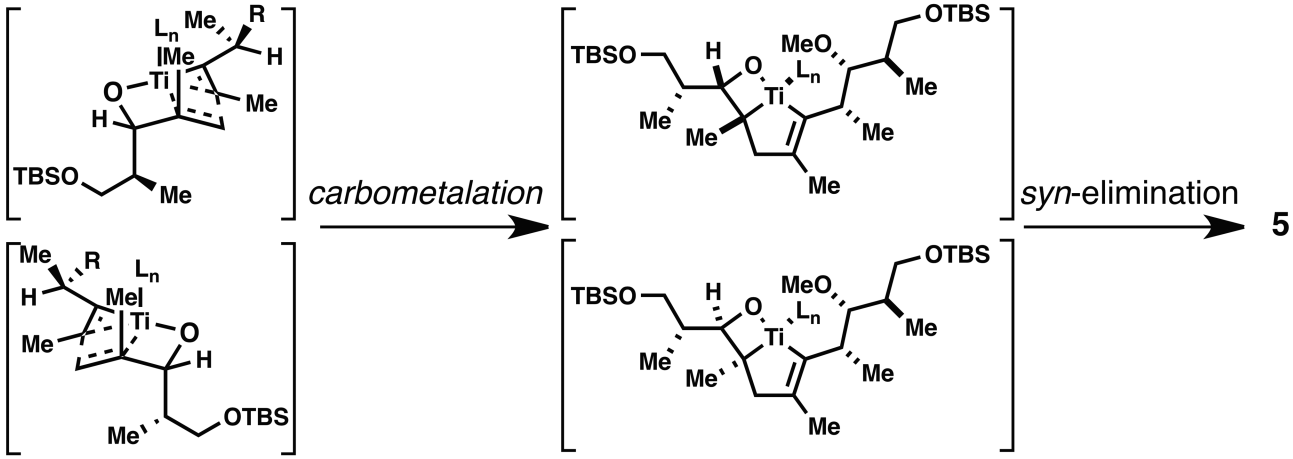

Figure 3.
Reductive cross-coupling process.

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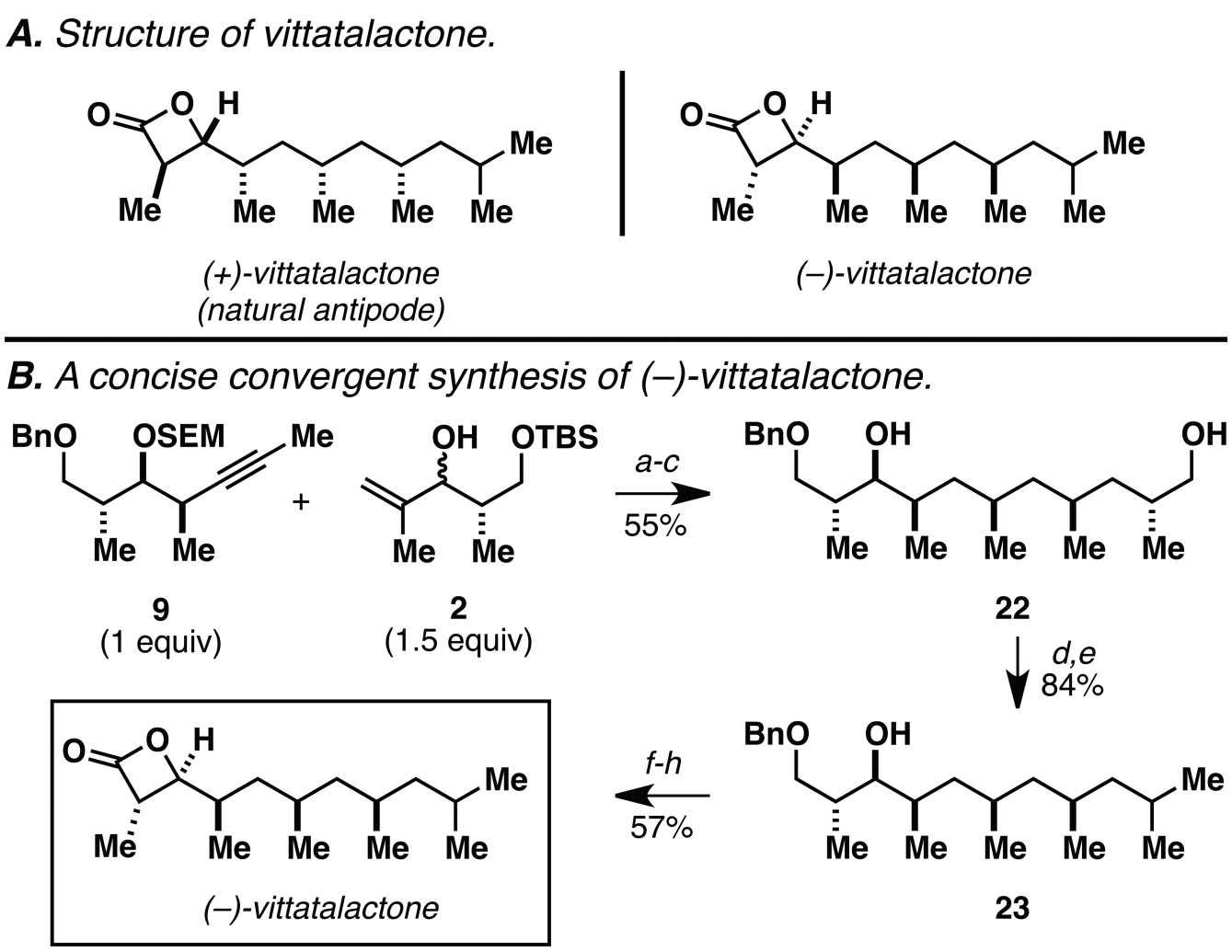

Figure 4.

Structure and laboratory synthesis of vittatalactone.

Reaction conditions: (a) $ClTi(O\textit{i}\text{-}Pr)_3$, $\textit{c}\text{-}C_5H_9MgCl$, PhMe, Et_2O (−78 to 0 °C); (b) TBAF, HMPA; (c) $Rh[nbd(dppb)]BF_4$, H_2 (500 psi), CH_2Cl_2; (d) TsCl, pyridine, CH_2Cl_2; (e) $LiEt_3BH$, THF; (f) $Pd(OH)_2$, EtOH; (g) 4-methoxy-TEMPO, NaClO, CH_2Cl_2/H_2O, then $NaClO_2$, $\textit{t}$-BuOH/H_2O; (h) TsCl, pyridine.

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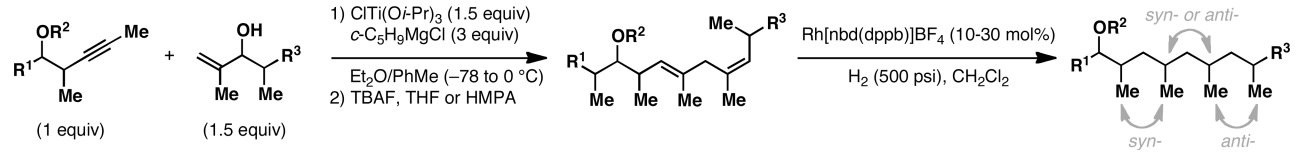
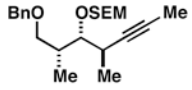
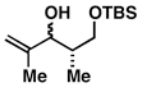
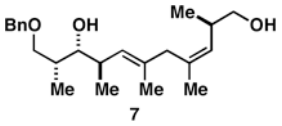
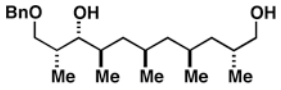
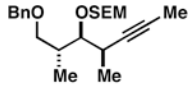
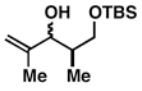
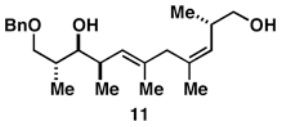
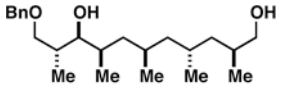
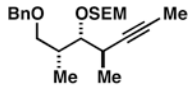
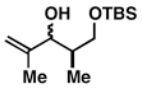
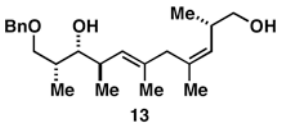
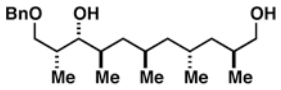
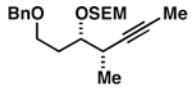
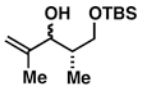
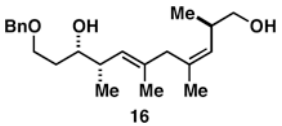
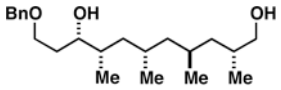
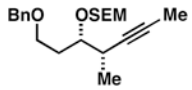
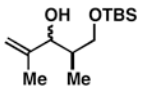
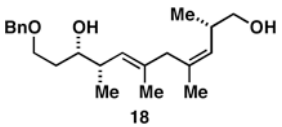
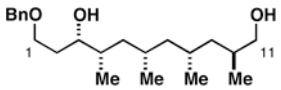
Table 1

Deoxypropionates by metallacycle-mediated alkyne–allylic alcohol cross-coupling and directed hydrogenation.



entry	alkyne	allylic alcohol	combined yield for coupling/deprotection (%)	1,4-diene	yield for conversion to deoxypropionate (%)	deoxypropionate
1	 **6**	 **2**	50[a]	 **7**	80[c]	 **8** (*syn,syn,anti*)
2	 **9**	 **10**	60[a]	 **11**	82[c]	 **12** (*syn,anti,anti*)
3	 **6**	 **10**	50[a]	 **13**	82[c]	 **14** (*syn,anti,anti*)
4	 **15**	 **2**	56[a]	 **16**	80[c]	 **17** (*syn,anti,anti*)
5	 **15**	 **10**	62[a]	 **18**	79[c]	 **19** (*syn,syn,anti*) *C1-C11 of borrelidin*

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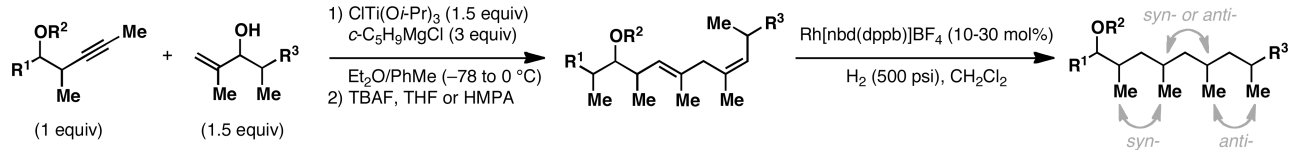
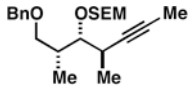
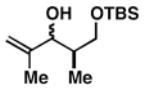
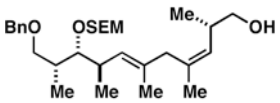
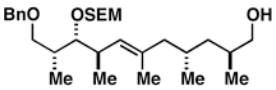


entry	alkyne	allylic alcohol	combined yield for coupling/deprotection (%)	1,4-diene	yield for conversion to deoxypropionate (%)	deoxypropionate
6	 6	 10	72[b]	 20	87[c]	 21

Reaction conditions:

[a] For Ti-mediated reductive cross-coupling: $ClTi(O\textit{i}\text{-}Pr)_3$, *c*-$C_5H_9MgCl$, PhMe, Et_2O; For global desilylation: TBAF, HMPA, 35 °C.

[b] Mono desilylation: TBAF, THF.

[c] $Rh[nbd(dppb)]BF_4$, CH_2Cl_2, H_2 (500 psi) – reactions were typically run using 30 mol% of the Rh-catalyst; similar yields were observed when catalyst loading was reduced to 10 mol%. See Supporting Information for experimental details.

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