Chiral α-substituted allylboronates in a one-pot three-component asymmetric allylic alkylation/carbonyl allylation reaction sequence — Applications to the syntheses of (+)-(3*R*,5*R*)-3-hydroxy-5-decanolide and (–)-massoialactone

Lisa Carosi and Dennis G. Hall

Abstract: The use of different organomagnesium reagents in the copper-catalyzed allylic alkylation of 3-chloropropenyl boronates with chiral phosphoramidite ligands produces the desired α-substituted allylic boronate reagents in high regioselectivity and with modest to high enantioselectivities (up to 96% ee). The size of the incoming alkyl substituent from the organomagnesium reagent was found to impact the yield and selectivity of the allylic alkylation. A one-pot procedure for the preparation of these chiral allylic boronates followed by a Lewis acid (BF_3) catalyzed addition to aldehydes delivers the desired allylboration products, homoallylic secondary alcohols, in good yields and very high diastereoselectivity. This three-component reaction methodology was applied to the syntheses of two lactone-containing natural products, (–)-massoialactone and (+)-(3*R*,5*R*)-3-hydroxy-5-decanolide. The key step of these syntheses involved the one-pot enantioselective copper-catalyzed allylic alkylation/allylboration reaction with a benzylic aldehyde, and afforded the desired product in 87% yield, 92% ee, and high *E*/*Z* selectivity in a ratio of 22:1. Remarkably, the allylic alkylation step of this sequential reaction was performed with a low catalyst loading of 2 mol% on a scale of >15 mmol that can provide multiple grams of the three-component product.

Key words: allylboration, allylic alkylation, boronic esters, carbonyl allylation, copper catalysis.

Résumé : L'utilisation de divers réactifs organomagnésiens dans une réaction d'alkylation allylique des boronates 3-chloropropénylés catalysée par le cuivre et un ligand chiral de type phosphoramidite produit les réactifs boronates allyliques α-substitués avec une haute régiosélectivité et une enantiosélectivité variant de modeste à élevée (jusqu'à 96 % ee). Il fut observé que la grosseur du substituant alkyle sur le réactif organomagnésien joue un rôle déterminant sur le rendement chimique et la sélectivité de l'alkylation allylique. Une procédure réactionnelle de type « one-pot » pour la préparation des boronates allyliques chiraux est suivie d'une addition sur les aldéhydes catalysée par un acide de Lewis (BF_3) qui mena aux produits désirés d'allylboration, les alcools secondaires homoallyliques, avec un bon rendement chimique et une diastereoselectivité très élevée. Cette réaction à trois-composants fut par la suite appliquée à une synthèse de deux produits naturels, la (–)-massoialactone and la (+)-(3*R*,5*R*)-3-hydroxy-5-decanolide. L'étape-clé de ces synthèses impliqua la réaction « one-pot » catalytique énantioselective d'alkylation allylique/allylboration avec un aldehyde benzylique, produisant le produit désiré dans un rendement chimique de 87 %, avec un ee de 92 % et une sélectivité *E*/*Z* élevée dans un ratio de 22 :1. Il est remarquable de constater que l'étape d'alkylation allylique de cette réaction séquentielle fut réalisée avec une faible charge catalytique de 2 mol% sur une échelle supérieure a 15 mmol qui permet d'isoler plusieurs grammes du produit de réaction à trois-composants.

Mots-clés : alkylation allylique, allylation de composés carbonylés, allylboration, catalyse du cuivre, esters boroniques.

Introduction

Over the past three decades, additions of allylic boron reagents have undergone tremendous developments and have emerged as one of the most powerful methods for stereoselective C–C bond formation.[1] In additions of allylic boron reagents to achiral aldehydes, three strategies were set forth to provide control of the enantiofacial selectivity of the reaction: (1) the use of "B-chiral" allylic boranes and boronates where the two nonallylic substituents on the boron are chiral directors such as terpene units,[2] a chiral diol,[3] or a chiral diamine;[4] (2) the use of a chiral Lewis or Brønsted acid catalyst with achiral reagents;[5] and (3) the use of optically pure α-substituted allylboronates of type **1**,[6] also called "C-chiral" or "α-chiral" allylboronates. Amongst these methods, the use of B-chiral allylic boron reagents has been in use for a long time and is still the method of choice even though it is far from ideal, as it uses a stoichiometric amount of chiral directors. Nevertheless, this class of reagents has been widely

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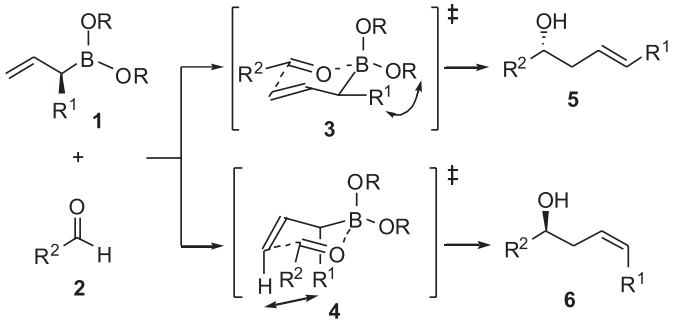
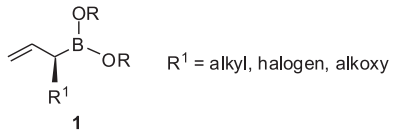
L. Carosi and D.G. Hall.[1] Department of Chemistry, University of Alberta, Edmonton, AB T6G 2G2, Canada.

[1]Corresponding author (e-mail: dennis.hall@ualberta.ca).

Fig. 1. Possible transition structures in additions of α-substituted allylboronates **1** to aldehydes.



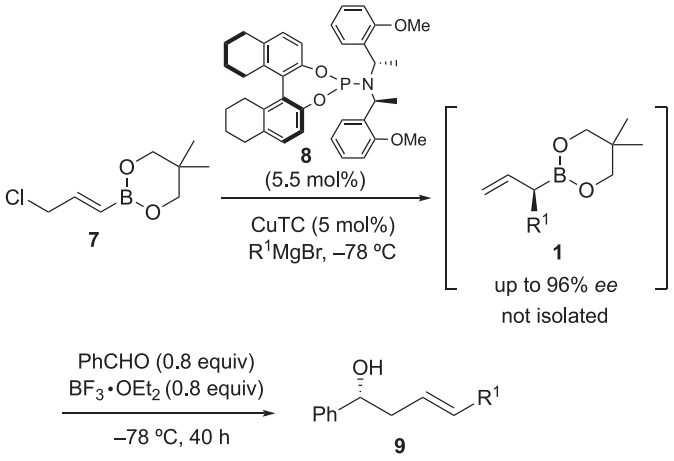
used in the synthesis of acetate and propionate units found in numerous polyketide natural products.[1b] In contrast, chiral α-substituted allylboronate reagents of type **1** have undergone modest development and applications, which is likely due to their stepwise preparation and the difficulty to control the enantiofacial selectivity of their additions to carbonyl compounds.



Selectivity with α-substituted allylboronates

Hoffmann and co-workers[6] have demonstrated that the reagent-controlled additions of optically enriched α-substituted allylboronates (**1**) to achiral aldehydes (**2**) proceed with near perfect transfer of chirality from the chiral reagent to the allylic alcohol product. As seen in Fig. 1, the two possible transition states lead to diastereomeric homoallylic alcohol products, **5** and **6**, which have opposite stereochemistry at the alcohol center and opposite alkene geometry. Hence, the *E*/*Z* proportion in the reaction products mirrors the enantioselectivity of the reaction process.[6] The proportion of *E* and *Z* diastereomers is dependent on the nature of the α-substituent and on the structure of the boronic ester. The selectivity between transition states **3** and **4** can be explained in terms of dipolar effects and steric effects. With a nonpolar α-substituent (R^1) such as an alkyl group, steric effects are dominant. It is known that the use of a nonpolar α-substituent leads to mixtures of products **5** and **6** with a modest selectivity for product **5**. In fact, there are unfavorable interactions in both transition states. In the chairlike transition structure, **3**, the unfavorable nonbonding interactions between the boronic ester and the pseudo-equatorial α-substituent (R^1) can be aggravated by the use of a large boronic ester or a bulky α-substituent.[7] In contrast, transition structure **4**, with the α-substituent at the pseudo-axial position, suffers from 1,3-allylic strain between the α-substituent and the pseudo-axial olefinic hydrogen. One transition state can be favored over the other by changing the size of the boronic ester.[7] Hence, the use of the bulky pinacol boronic ester will provide a modest selectivity for transition state **4** leading to the *Z* isomer **6**. On the other hand, the use of the smaller 2,2-dimethyl-1,3-propanediol boronic ester provides selectivity for transition state **3** leading to the *E* isomer **5**.[7] Furthermore, the use of Lewis or Brønsted acid catalysis can provide improved selectivity for the *E* isomer.[8] Recent density functional theory (DFT) calculations by Sakata and Fujimoto[9] have shown that under Lewis acid activation, the transition state displays a shorter B–O bond and a longer B–C bond with the aldehyde. Compared to the uncatalyzed reaction, this longer B–C bond alleviates the unfavorable steric interactions between the boronic ester and the α-substituent in transition state **3**. As a result, the use of Lewis acid catalysis can afford high selectivity for the *E* isomer even with the bulky pinacol boronic ester.[8]

Scheme 1. Optimal conditions for the one-pot three-component allylic alkylation/aldehyde allylation with substrate **7** and exemplified with benzaldehyde.



Enantioselective approaches to α-substituted allylboronates

The preparation of α-substituted allylboron reagents is limited to the more stable allylic boronic esters because allylic dialkyl boranes undergo a rapid 1,3-borotropic shift at and below ambient temperatures.[1e,10] Hoffmann and co-workers[6] pioneered the preparation and applications of acyclic optically enriched α-substituted allylboronates. Equations [1]–[4] show examples of preparative methods for chiral α-substituted allylic boronates (pin = $OCMe_2CMe_2O$). Until the mid-1990s, methods to access these reagents were limited to the asymmetric Matteson homologation reaction using a stoichiometric chiral directing group,[11] which may subsequently be exchanged through a transesterification reaction (eq. [1]). Recently, additional methods to access chiral α-substituted allylboronates were reported. For example, a [3,3] sigmatropic rearrangement reaction of chiral 3-hydroxy propenyl boronates was developed (eq. [2]).[12] The ideal approach would be catalytic and would avoid the use of stoichiometric chiral directors. Such methods were also reported and include the use of a palladium-catalyzed enantioselective diboration of allenes (eq. [3]),[13] and the use of a copper-catalyzed enantioselective allylic substitution of allylic carbonates with diboron reagents (eq. [4]),[14a,14b] or an iridium-catalyzed variant.[14c]

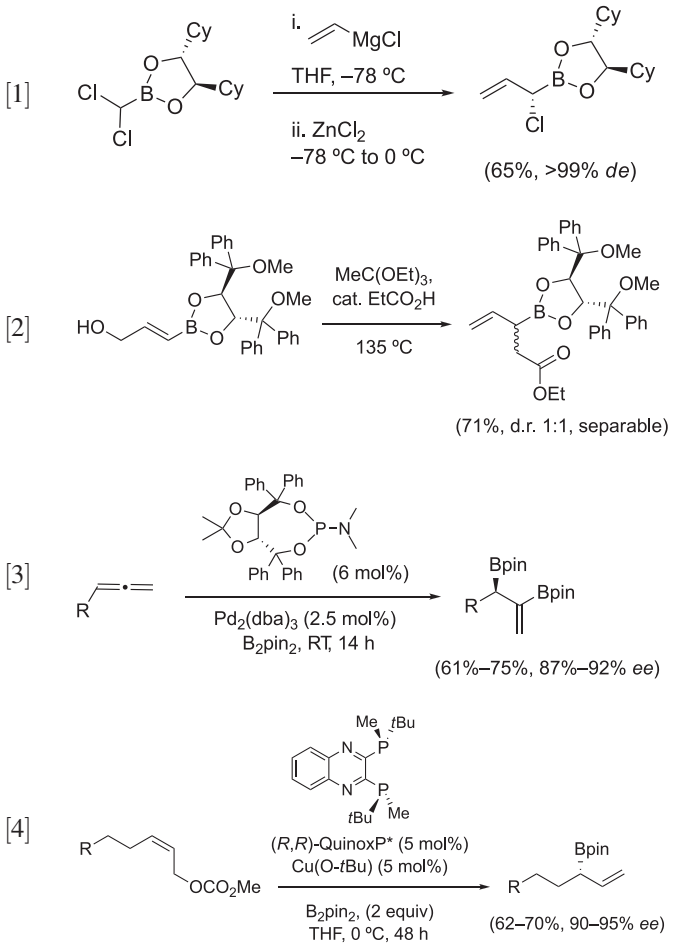
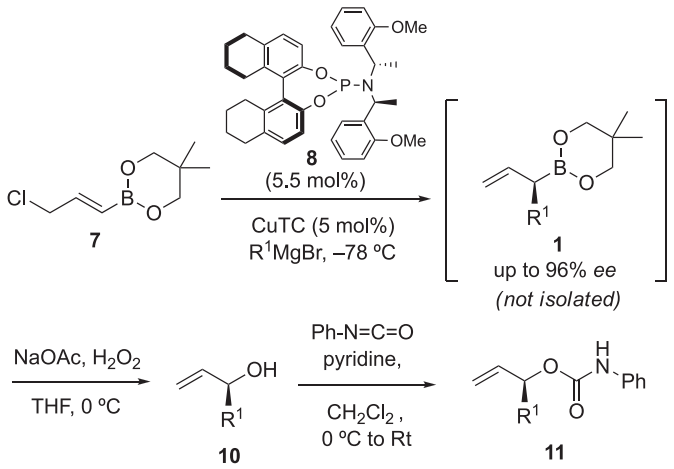


Table 1. Exploration of the scope of the Grignard reagent with **7** under the optimal conditions of Scheme 1.



Entry	R^1MgX^a	Product	S_N2'/S_N2 ratio[b]	ee (%)[c]
1	EtMgBr	**1a**	7:1	96
2	*n*-BuMgBr	**1b**	11:1	86
3	(4-Pentenyl)MgBr	**1c**	17:1	88
4	(Cyclohexyl)MgBr	**1d**	12:1	69

Note: Reaction conditions: ligand **8** and CuTC were premixed at RT, then **7** was added, followed by R^1MgX at –78 °C. Typical reaction scale: 1.0 mmol at 0.3 mol/L concentration.

[a]From halide-free 3 mol/L solutions in Et_2O.

[b]Measured by ^1H NMR spectroscopy of an aliquot of the crude reaction mixtures.

[c]Measured by chiral HPLC of isocyanate derivatives (**11**) of oxidation products (**10**) of boronates (**1**) as shown in the above scheme.

In 2007, we reported a new preparative method based on a copper-catalyzed enantioselective allylic substitution reaction (Scheme 1).[15] We were able to employ the resulting chiral α-substituted allylboronates (**1**) in a one-pot sequential protocol initiated by the enantioselective copper-catalyzed allylic alkylation and followed by an aldehyde allylation. The optimal combination of alkenylboronate (**7**) and chiral phosphoramidite (**8**)[16] led to reagent **1** with up to 96% ee.

This protocol resulted in a new enantioselective multicomponent route to homoallylic alcohols. Even though the preliminary communication included the scope and limitations of the three-component reaction sequence with regards to the aldehyde, it provided little information on the scope of the alkyl α-substituent (i.e., the organomagnesium reagent). Herein we report on the scope of the reaction with regards to the alkyl α-substituent, and on the application of this methodology to the synthesis of two small α-lactone natural products.

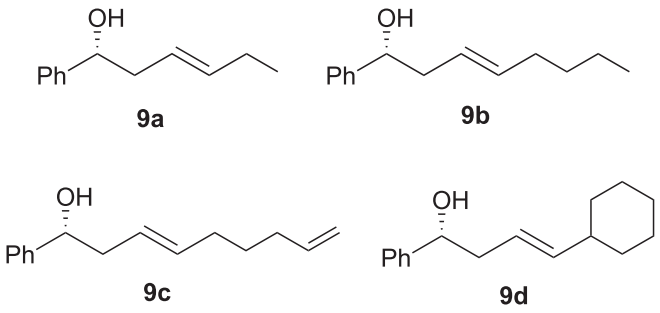
Results and discussion

Reaction scope

Our preliminary results on the nature of the Grignard reagent had indicated that the size of the organomagnesium alkyl group had an important effect on the enantioselectivity of the allylic substitution reaction.[15] To further investigate this trend, we prepared aliphatic Grignard reagents with various size and length. We then used these reagents in the allylic substitution reaction with the 3-chloropropenyl boronate (**7**) using our previously optimized reaction conditions. The outcome of this study is summarized in Table 1. In this initial study, the enantioselectivity was measured on carbamate derivatives (**11**), which were obtained from the boronate oxidation products (**10**). It is well-established that this oxidation process occurs with near perfect retention of stereochemistry.[17] Because of the volatility of alcohols **10**, no yields were compiled for this derivatization process.

We found that the use of linear organomagnesium reagents allow for a higher level of enantioselectivity. The length of the alkyl chain also affects the S_N2'/S_N2 regioselectivity and the level of enantioselectivity. The short ethylmagnesium bromide reagent afforded the best enantioselectivity, giving **1a** with 96% ee (Table 1, entry 1), whereas the longer butylmagnesium or pentenylmagnesium bromide provided very good, albeit lower enantioselectivity (Table 1, entries 2–3). On the other hand, the bulkier cyclohexylmagnesium bromide gave a much lower level of enantioselectivity (Table 1, entry 4). With this data in hand, we set out to gain information on the behavior of the chiral α-substituted allylboronates in their additions to aldehydes. Performing the one-pot allylic alkylation/aldehyde allylation protocol with our previously optimized reaction conditions allowed us to verify the efficiency of the chirality transfer

Table 2. Exploration of the scope of α-substituted allylboronates **1a**–**1d** in the one-pot three-component reaction from **7** under the optimal conditions of Scheme 1.



Entry	R^1MgX^a	Product	*E*/*Z* ratio[b]	Yield (%)[c]	ee (%)[d]
1	EtMgBr	**9a**	18:1	75	92
2	*n*-BuMgBr	**9b**	99:1	52	85
3	(4-Pentenyl)MgBr	**9c**	98:2	40	83
4	(Cyclohexyl)MgBr	**9d**	99:1	41	68

Note: Reaction conditions: ligand **8** and CuTC were premixed at RT, then **7** was added, followed by R^1MgX at –78 °C. Typical reaction scale: 1.0 mmol at 0.3 mol/L concentration.

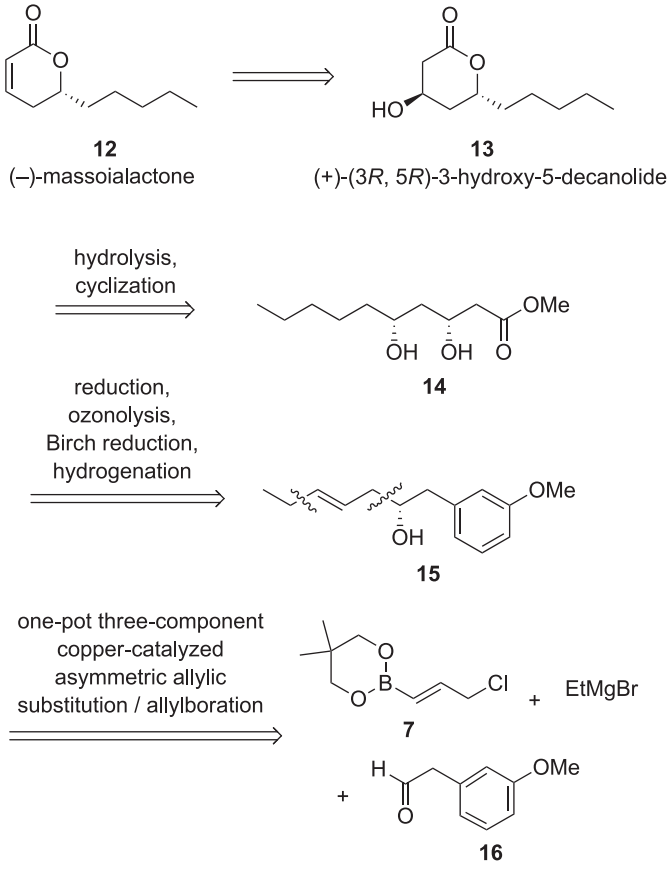
[a]From halide-free 3 mol/L solutions in Et_2O.
[b]Measured by HPLC-MS of crude reaction mixtures.
[c]Isolated yields.
[d]Measured by chiral HPLC of pure products (**9**).

from reagents **1a**–**1d** to the homoallylic alcohol products **9a**–**9d**. Indeed, the enantioselectivity level found in the chiral α-substituted allylboronates (Table 1) was representative of that found in the benzaldehyde allylation products (Table 2). Larger α-substituents proved to be favorable in providing high selectivity for the *E* isomer. Unfortunately, the overall efficiency of the transformation was negatively affected by the use of larger α-substituents as lower yields were obtained with the butylmagnesium, pentenylmagnesium, and cyclohexylmagnesium bromides (respective products are **9b**–**9d** in Table 2, entries 2–4). Small amounts of the undesired allylic alcohol products resulting from the 1,3-borotropic shift of the allylboronates, followed by aldehyde allylboration, were found in these cases. Trombini and co-workers[18] had found that with α-substituted allylboronates, the nature of the boronic ester has a big influence on the propensity of the 1,3-borotropic shift to take place. For instance, the 2,2-dimethyl-1,3-propanediol boronic ester is known to undergo this shift more easily than the corresponding pinacol ester. Nevertheless, as demonstrated with the preparation of **9a** from reagent **1a** (Table 2, entry 1), our approach to homoallylic alcohols via a one-pot enantioselective copper-catalyzed allylic alkylation/aldehyde allylation reaction sequence allows for high selectivity of the desired products (**9**) in good yield from two steps.

Application to the synthesis of lactone natural products

Our next objective was to demonstrate the versatility of this methodology with an application in target-oriented synthesis. As targets, we selected two naturally occurring δ-lactones: (+)-(3*R*,5*R*)-3-hydroxy-5-decanolide and (–)-massoialactone (**13** and **12** in Scheme 2). (+)-(3*R*,5*R*)-3-Hydroxy-5-decanolide was isolated in 1971 from the culture liquor of the fungus *Cephalosporium recifei* NRRL 5161.[19] This metabolite is part of the *trans*-β-hydroxy-δ-lactone family, which is known to inhibit the enzyme HMG-CoA reductase, thus it is potentially a cholesterol-lowering agent.[20] (–)-Massoialactone's structure is related to (+)-(3*R*,5*R*)-3-hydroxy-5-decanolide's structure as it lacks the 3-hydroxy group, which is replaced by the α,β-unsaturation. (–)-Massoialactone has antibacterial and antifungal activity,[21] it is a skin irritant, and can be isolated from many different natural sources. Abe[22] first isolated (–)-massoialactone in 1937 from the bark oil of *Cryptocarya massoia*, an oil used for centuries in native medicine. It was found to be the defense secretion of two species of formicin ants of the genus *Camponotus* found in western Australia.[23] Numerous syntheses of both (+)-(3*R*,5*R*)-3-hydroxy-5-decanolide and (–)-massoialactone have been reported.[24] As well, separate syntheses for (+)-(3*R*,5*R*)-3-hydroxy-5-decanolide[25] or for (–)-massoialactone[26] have been published. Various strategies were used to introduce chirality, including stereoselective reduction with Baker's yeast,[24a,24b,25a] enzymatic lactonization,[24d] dynamic kinetic resolution of starting material,[26c] metal-catalyzed enantioselective reduction,[26e] allylboration with a chiral auxiliary,[26a] and simply using the chiral pool.[24c, 24e, 24f, 26b, 26d, 26f] Amongst all those strategies, the most efficient synthesis

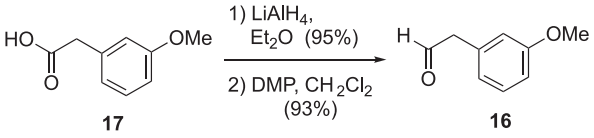
Scheme 2. Retrosynthesis of (–)-massoialactone from (+)-(3*R*,5*R*)-3-hydroxy-5-decanolide using the one-pot three component allylic alkylation/aldehyde allylation.



of (–)-massoialactone to date features the chiral auxiliary directed allylboration reaction as the key initial step followed by esterification and ring closing metathesis providing (–)-massoialactone with an overall yield of 49%.[26a]

Retrosynthetically, we first planned to access (–)-massoialactone, **12**, from (+)-(3*R*,5*R*)-3-hydroxy-5-decanolide (**13**) through a dehydration reaction (Scheme 2). Our strategy to access (+)-(3*R*,5*R*)-3-hydroxy-5-decanolide was to perform the lactonization reaction from the open chain intermediate **14**. This intermediate could be accessed through a Birch reduction followed by ozonolysis of the aromatic precursor **15**, which in turn could be synthesized from our key enantioselective copper-catalyzed allylic alkylation/aldehyde allylation one-pot reaction sequence with benzylic aldehyde **16**. The use of reagent **1a**, assembled from **7** and EtMgBr, will provide the requisite pentyl side chain of **12** and **13** following hydrogenation of the disubstituted alkene of **15**.

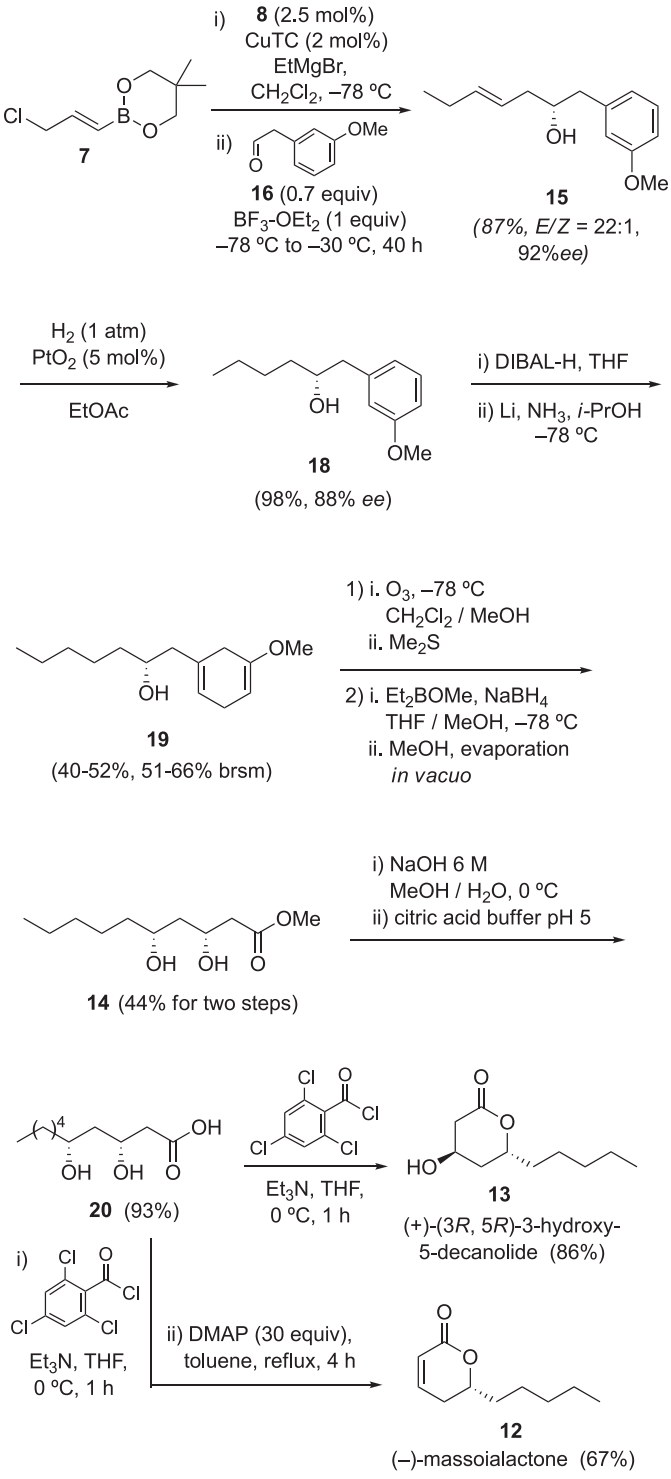
Even though aldehyde **16** is commercially available, its prohibitive price prompted us to find a more affordable source. Therefore, it was synthesized in two steps: reduction of the inexpensive (3-methoxyphenyl)acetic acid, **17**, followed by Dess–Martin periodinane oxidation. This sequence provided aldehyde **16** in high yield (eq. [5]).[27]

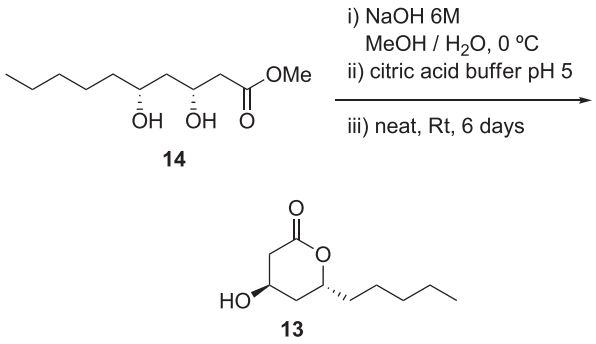
[5] 

From **16**, the key step of one-pot enantioselective copper-catalyzed allylic substitution/allylboration reaction afforded the desired product **15** in 87% yield, 92% ee, and high *E*/*Z* selectivity with a ratio of 22:1 (Scheme 3). Furthermore, scale-up of this key step was straightforward: the catalyst loading had to be lowered to 2 mol% to provide a constantly high *E* selectivity and the allylboration reaction had to be performed at –30 °C to ensure reaction completion. Additionally, the reaction was performed on up to 16 mmol of starting material **7** resulting in over 2 g of pure product **15**.

Hydrogenation of **15** was first attempted with palladium on charcoal but when this reaction was performed on a larger scale, isomerization of the alcohol's stereogenic center was observed, providing product **18** with only 76% ee. In this event, hydrogenation of the double bond was performed with Adams catalyst to afford the desired product **18** in 98% yield with 88% ee. The decrease in enantiomeric excess observed under these conditions, from 92% ee for the starting material **15** to 88% ee for the product **18**, is expected. This decrease is due to the diastereomeric nature of the inseparable *E* and *Z* mixture of **15** obtained after the allylboration step. From **18**, the carbonyl and the 1,3-diol moieties of **14** were introduced in a three-step sequence. First, a Birch reduction with in situ protection of the alcohol with DIBAL-H provided diene **19** in moderate yield with recoverable unreacted starting material. A longer reaction time, a higher reaction temperature, or the addition of more lithium did not provide a better conversion. On the other hand, Birch reduction without in situ protection of the alcohol afforded a full, but messy conversion of the starting material with a lower yield. Therefore, we chose to use the Birch reduction with in situ protection of the alcohol. Following this sequence, ozonolysis of diene **19** and immediate stereoselective 1,3-syn reduction of the ketone afforded compound **14** in 44% yield for the two steps. Hydrolysis of the methyl ester was performed with sodium hydroxide in methanol and water. Letting acid **20** stand at room temperature for 6 d formed the desired natural product in 71% yield (eq. [6]).

Scheme 3. Synthesis of (–)-massoialactone and (+)-(3*R*,5*R*)-3-hydroxy-5-decanolide.





[6]

(+)-(3*R*, 5*R*)-3-hydroxy-5-decanolide (71%)

Alternatively, (+)-(3*R*,5*R*)-3-hydroxy-5-decanolide (**13**) could be accessed from **20** by forming the mixed anhydride, which self-cyclized immediately in 86% yield.[28] Thus, the synthesis of (+)-(3*R*,5*R*)-3-hydroxy-5-decanolide was completed in five or six steps with an overall yield of 15%. Optical rotation for pure (+)-(3*R*,5*R*)-3-hydroxy-5-decanolide (**13**) ($[\alpha]_D^{20}$: +25.5° (*c* 1.2, $CHCl_3$)) matched that from its natural source (lit.[20] $[\alpha]_D^{25}$: +27.4° (*c* 11.7, $CHCl_3$)).

On the other hand, (–)-massoialactone (**12**) was also formed from intermediate **20** by performing the cyclization, which was immediately followed by dehydration with DMAP in refluxing toluene. This sequence provided (–)-massoialactone in six steps with an overall yield of 13%. The optical rotation of synthetic (–)-massoialactone ($[\alpha]_D^{20}$: –74.2° (*c* 1.0, $CHCl_3$)) was lower than that of its natural source (lit.[23] $[\alpha]_D^{25}$: –91° (*c* 1.0, $CHCl_3$)), but all other analytical data for the sample of synthetic (–)-massoialactone agreed to that reported in the literature. It is interesting to note that the high-dilution Yamaguchi lactonization of **20** has been alleged to provide the macrocyclic dimeric lactone verbalactone,[29] which is also a natural substance.[30] However, under several conditions and after numerous attempts, in our hands verbalactone was never isolated, and the only products observed were **12** and **13**.

Conclusion

In summary, the one-pot three-component enantioselective copper-catalyzed allylic substitution/allylation reaction sequence proved to be efficient with regards to various chiral α-alkyl allylboronate reagents. The α-substituent was used in a productive way for the short syntheses of two natural products: (+)-(3*R*,5*R*)-3-hydroxy-5-decanolide and (–)-massoialactone.

Experimental

Unless otherwise noted, all reactions were performed under an argon atmosphere using flame-dried glassware. Toluene, hexanes, and dichloromethane were distilled over CaH_2. THF and Et_2O were distilled over sodium/benzophenone ketyl. Ethylmagnesium bromide was purchased from Sigma-Aldrich as a 3.0 mol/L solution in Et_2O and titrated using a literature procedure.[31] Other Grignard reagents were prepared[32] and titrated using literature procedures. Alkenylboronate **7** was prepared according to refs. 15 and 17. Ligand **8** was prepared according to refs. 15 and 16a. Thin layer chromatography (TLC) was performed on Merck Silica Gel 60 F_{254} plates and was visualized with UV light and 5% phosphomolybdic acid in EtOH (PMA); or 1% potassium permanganate in water ($KMnO_4$); or 5% vanillin, 4% concentrated sulfuric acid in ethanol (vanillin); or 4% ammonium molybdate, 0.08% cerium (IV) sulfate in 10% aqueous sulfuric acid. Flash chromatography was performed on Silicycle SiliaFlash® F60 ultra pure silica gel 230–400 mesh or on a Teledyne Isco Combiflash® Companion® automated flash instrument. NMR spectra were recorded on Varian INOVA-300, INOVA-400, or INOVA-500 MHz instruments. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal standards. ^1H NMR data are presented as follows: chemical shift in ppm downfield from tetramethylsilane (multiplicity, integration, coupling constant). The accuracy of coupling constants is deemed to be ±0.4 Hz. High-resolution mass spectra were recorded by the University of Alberta Mass Spectrometry Services Laboratory using either electron impact (EI) or electrospray (ES). Infrared spectra were obtained on a Nicolet Magna-IR 760 instrument equipped with a Nic-Plan microscope. Elemental analyses were performed on a Carlo Erba EA1108 system. Optical rotations were obtained with a PerkinElmer 241 polarimeter. Infrared spectra, elemental analyses, and optical rotations were recorded by the University of Alberta Analytical and Instrumentation Laboratory.

General procedure for the synthesis and characterization of chiral α-substituted allylboronates (1a–1d)

Copper thiophene carboxylate (CuTC) (9.5 mg, 0.050 mmol) and ligand **8** (0.054 mmol) were charged in a 25 mL round-bottom flask equipped with a magnetic stirrer. The flask was purged three times with a light vacuum and argon sequence. Dichloromethane (1.5 mL) was added and the mixture was stirred for 30 min at room temperature. In the meantime, a solution of boronic ester **7** (0.19 g, 1.0 mmol) in dichloromethane (0.5 mL) was prepared. The solution of **7** was added dropwise and the reaction mixture was stirred another 5 min at room temperature before cooling to –78 °C (the reaction turned to a blue-green color). The Grignard reagent (3.0 mol/L in Et_2O, 1.2 mmol) diluted with dichloromethane (0.6 mL) was added at –78 °C over 4 h using a syringe pump, keeping the needle immersed in the reaction mixture. The reaction mixture turned to a bright yellow color after about 3.5 h of addition. Once the addition was complete, the mixture was stirred for another 1.5–2 h at –78 °C. At that point a small aliquot was taken to verify for completion of reaction and for S_N2/S_N2' ratio measurement by ^1H NMR of chiral α-substituted allylboronates (**1a**–**1d**). In situ oxidation to alcohols **10a**–**10d** was performed using the following sequence: water (0.5 mL) and tetrahydrofuran (2 mL) were added and the reaction mixture was brought to 0 °C. An aqueous 3 mol/L solution of sodium acetate (1 mL, 3 mmol) was added followed by 30% aqueous hydrogen peroxide (0.6 mL, 5 mmol). The mixture was stirred overnight while being allowed to reach room temperature. After this time, an aqueous saturated solution of sodium sulfite (1.5 mL) was added and the mixture was stirred for 15 min at room temperature. The mixture was then extracted three times with Et_2O. The combined organic phases were washed once with a saturated aqueous solution of ammonium chloride and once with brine. It was dried over anhydrous sodium sulfate, filtered, and partially con-

centrated in vacuo due to high volatility of the allylic alcohol product. The isocyanate derivative was synthesized as follows: the allylic alcohol solution was cooled to 0 °C, dichloromethane (1 mL) was added followed by pyridine (0.17 mL, 2.0 mmol) and phenylisocyanate (0.17 mL, 1.5 mmol). The mixture was stirred overnight while being allowed to reach room temperature. It was quenched with water and the water layer was extracted three times with dichloromethane. The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford the crude isocyanate derivatives **11a**–**11d**. Although yields for these products were not compiled due to the high volatility of alcohols (**10a**–**10d**), analytical samples were characterized as follows.

(3S)-3-[Phenylcarbamic ester] 1-pentene (11a) for chiral α-substituted allylboronate (1a)

Flash chromatography (5% Et_2O–pentane) yielded a colorless oil (52 mg, 25% yield), which had satisfactory analytical data (NMR, MS) as reported in the literature.[15] TLC (30% Et_2O–pentane, UV, PMA): 0.53. HPLC followed a literature procedure: Chiralcel OD, 25 °C, 20% *i*-PrOH hexanes, 0.60 mL/min, UV detection at 280 nm, major peak at 9.8 min, minor peak at 11.6 min, 96% ee.

(3S)-3-[Phenylcarbamic ester] hept-1-ene (11b) for chiral α-substituted allylboronate (1b)

Flash chromatography (100% hexane to 2% EtOAc–hexane) yielded a colorless oil (82 mg, 34% yield). TLC (25% EtOAc–hexane, UV, PMA): 0.53. $[\alpha]_D^{20}$: +5.7° (*c* 1.2, $CHCl_3$). IR (neat, cm^{-1}): 3322, 3061, 2957, 2872, 1700, 1601, 1539, 1444, 1313, 1228, 1120, 752, 692. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.39–7.29 (m, 4H), 7.06 (dd, 1H, *J* = 7.4, 7.4 Hz), 6.58 (br s, 1H), 5.83 (ddd, 1H, *J* = 17.3, 10.7, 6.6 Hz), 5.31 (ddd, 1H, *J* = 17.3, 1.3, 1.3 Hz), 5.23 (ddd, 1H, *J* = 6.6, 6.6, 6.6 Hz), 5.20 (ddd, 1H, *J* = 10.6, 1.3, 1.3 Hz), 1.75–1.68 (m, 1H), 1.67–1.60 (m, 1H), 1.40–1.32 (m, 4H), 0.91 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.06, 138.00, 136.81, 129.01, 123.30, 118.56, 116.64, 75.82, 34.11, 27.23, 22.50, 14.0. HRMS (EI, *m*/*z*) calcd. for $C_{14}H_{19}O_2N$: 233.1416; found: 233.1414. HPLC: Chiralcel OD, 25 °C, 5% *i*-PrOH hexanes, 0.60 mL/min, UV detection at 280 nm, major peak at 16.3 min, minor peak at 19.8 min, 86% ee.

(3S)-3-[Phenylcarbamic ester] 1,7-octadiene (11c) for chiral α-substituted allylboronate (1c)

Flash chromatography (100% hexane to 2% EtOAc–hexane) yielded a colorless oil (62 mg, 25% yield). TLC (25% EtOAc–hexane, UV, PMA): 0.52. $[\alpha]_D^{20}$: +9.6° (*c* 1.0, $CHCl_3$). IR ($CHCl_3$ cast film, cm^{-1}): 3322, 3078, 2940, 1705, 1602, 1537, 1445, 1313, 1226, 1052, 915, 753. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.37–7.35 (m, 2H), 7.30–7.26 (m, 2H), 7.03 (dd, 1H, *J* = 7.3, 7.3, Hz), 6.58 (br s, 1H), 5.84–5.74 (m, 2H), 5.29 (ddd, 1H, *J* = 17.2, 1.3, 1.3 Hz), 5.24 (ddd, 1H, *J* = 6.2, 6.2, 6.2 Hz), 5.18 (ddd, 1H, *J* = 10.5, 1.3, 1.3 Hz), 5.03–4.98 (m, 1H), 4.97–4.94 (m, 1H), 2.12–2.07 (m, 2H), 1.75–1.61 (m, 2H), 1.52–1.44 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.9, 138.3, 137.9, 136.6, 129.0, 123.3, 118.6, 116.8, 114.9, 75.6, 33.8, 33.4, 24.3. HRMS (EI, *m*/*z*) calcd. for $C_{15}H_{19}O_2N$: 245.1416; found: 245.1414. HPLC: Chiralcel OD, 25 °C, 5% *i*-PrOH hexanes, 0.60 mL/min, UV detection at 280 nm, major peak at 18.4 min, minor peak at 26.7 min, 88% ee.

(3S)-3-[Phenylcarbamic ester]-3-cyclohexyl-1-propene (11d) for chiral α-substituted allylboronate (1d)

Flash chromatography (100% hexane to 2% EtOAc–hexane) yielded a white solid (136 mg, 53% yield). TLC (25% EtOAc–hexane, UV, PMA): 0.56. $[\alpha]_D^{20}$: +18.7° (*c* 1.0, $CHCl_3$). IR ($CHCl_3$ cast film, cm^{-1}): 3319, 3061, 2928, 2854, 1704, 1602, 1542, 1444, 1230, 1050, 751. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.39–7.36 (m, 2H), 7.30–7.26 (m, 2H), 7.03 (dd, 1H, *J* = 7.4, 7.4 Hz), 6.58 (br s, 1H), 5.79 (ddd, 1H, *J* = 17.4, 10.5, 7.0 Hz), 5.27 (ddd, 1H, *J* = 17.2, 1.5, 1.5 Hz), 5.21 (ddd, 1H, *J* = 10.5, 1.5, 1.5 Hz), 5.03 (dd, 1H, *J* = 6.8, 6.8 Hz), 1.83–1.57 (m, 6H), 1.28–1.01 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.03, 137.96, 135.17, 128.93, 123.20, 118.53, 117.45, 79.82, 41.66, 28.53, 28.34, 26.30, 25.90, 25.88. HRMS (EI, *m*/*z*) calcd. for $C_{16}H_{21}O_2N$: 259.1572; found: 259.1575. HPLC: Chiralcel OD, 25 °C, 5% *i*-PrOH hexanes, 0.60 mL/min, UV detection at 280 nm, major peak at 14.9 min, minor peak at 16.4 min, 69% ee.

General procedure for the one-pot protocol of enantioselective copper-catalyzed allylic substitution/aldehyde allylation — Preparation of homoallylic alcohols (9a–9d)

Copper thiophene carboxylate (CuTC) (9.5 mg, 0.050 mmol) and ligand **8** (33 mg, 0.054 mmol) were charged in a flame-dried 25 mL round-bottom flask equipped with a magnetic stirrer. The flask was purged three times with a light vacuum and argon sequence. Dichloromethane (1.5 mL) was added and the mixture was stirred for 30 min at room temperature. In the meantime, a solution of boronic ester **7** (188 mg, 1.0 mmol) in dichloromethane (0.5 mL) was prepared. The solution of **7** was added dropwise to the reaction mixture and stirred for 5 min at room temperature (the reaction mixture turned to a blue-green color) before cooling to –78 °C. The Grignard reagent (3.0 mol/L in Et_2O, 1.2 mmol) diluted with dichloromethane (0.6 mL) was added at –78 °C over 4 h using a syringe pump, keeping the needle immersed in the reaction mixture. The reaction mixture turned to a bright yellow color after about 3.5 h of addition. Once the addition was complete, the mixture was stirred another 1.5–2 h at –78 °C. The aldehyde (0.7–0.8 mmol) was added at –78 °C immediately followed by boron trifluoride diethyl etherate (BF_3-OEt_2) (0.10 mL, 0.80 mmol). The reaction mixture was stirred approximately 24 h at –78 °C and 16 h at –30 °C. The reaction was cooled back to –78 °C and was quenched with the addition of a saturated aqueous solution of sodium bicarbonate (1.5 mL). The mixture was then warmed up to room temperature over 3 h and stirred for an additional 30 min at room temperature. The phases were separated and the aqueous phase was extracted three times using dichloromethane. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo.

(3E,1R)-1-Phenyl-3-hexen-1-ol (9a)

Flash chromatography (100% hexanes to 5% EtOAc–

hexanes) yielded a colorless oil (108 mg, 75%), which gave satisfactory analytical data (NMR, MS) as reported in the literature.[15,33] TLC: (20% EtOAc–hexanes, UV, PMA) 0.34. $[\alpha]_D^{20}$: +57.4° (*c* 1.0, $CHCl_3$). HPLC for *E*/*Z* ratio measurement on the crude product: Zorbax SB-C18 4.6 mm × 150 mm, 5 μm, 40 °C, mobile phase A: 0.05% formic acid – H_2O, mobile phase B: 0.05% formic acid – MeOH, program: 70:30 at 0 min, 64.5% of B at 55 min, 80% of B at 58 min, 30% of B at 58.01 min, 1 mL/min, UV detection at 220 nm, retention times: (3*Z*)-1-phenyl-3-hexen-1-ol, 44.5 min; (3*E*)-1-phenyl-3-hexen-1-ol, 45.8 min. HPLC for enantiomeric excess measurement on purified product is based on a literature procedure:[15] Chiralcel OD, 10 °C, 5% *i*-PrOH hexane, 0.3 mL/min, UV detection at 220 nm, retention times: (3*E*,1*R*)-1-phenyl-3-hexen-1-ol, 25.8 min; (3*Z*,1*R* or 1*S*)-1-phenyl-3-hexen-1-ol, 29.4 min; (3*E*,1*S*)-1-phenyl-3-hexen-1-ol, 32.0 min; (3*Z*,1*R* or 1*S*)-1-phenyl-3-hexen-1-ol, 35.2 min; 92% ee.

*(3*E*,1*R*)-1-Phenyl-3-octen-1-ol (9b)*

Flash chromatography using an automated flash system (4 g SiO_2 column, 10 column volumes (CV) 100% petroleum ether, 20 CV 100% petroleum ether to 5% EtOAc, 30 CV 5% EtOAc, 10 CV 5% EtOAc to 50% EtOAc) yielded a colorless oil (84 mg, 52%), which gave satisfactory analytical data (NMR, MS) as reported in the literature.[34] Note: 34 mg (21%) of the borotropic shift/allylation product was also isolated. TLC (10% EtOAc–petroleum ether, PMA): 0.28. $[\alpha]_D^{20}$: +32.2° (*c* 1.0, $CHCl_3$). HPLC for *E*/*Z* ratio measurement on crude product: Zorbax SB-C18 4.6 mm × 150 mm, 5 μm, 40 °C, mobile phase A: 0.05% formic acid – H_2O, mobile phase B: 0.05% formic acid – MeOH, program: 70:30 at 0 min, 64.5% of B at 110 min, 30% of B at 110.01 min, 1 mL/min, UV detection at 210 nm, retention times: (3*Z*)-1-phenyl-3-octen-1-ol, 104.4 min; (3*E*)-1-phenyl-3-octen-3-ol, 106.9 min. HPLC for enantiomeric excess measurement on purified product: Chiralcel OD, 10 °C, 2% *i*-PrOH hexane, 0.5 mL/min, UV detection at 254 nm, retention times: (3*E*,1*R*)-1-phenyl-3-octen-1-ol, 22.7 min; (3*E*,1*S*)-1-phenyl-3-octen-1-ol, 26.5 min; 85% ee.

*(3*E*,1*R*)-1-Phenyl-3,8-nonadien-1-ol (9c)*

Flash chromatography using an automated flash system (4 g SiO_2 column, 10 column volumes (CV) 100% petroleum ether, 20 CV 100% petroleum ether to 5% EtOAc, 30 CV 5% EtOAc, 10 CV 5% EtOAc to 50% EtOAc) yielded a colorless oil (68 mg, 40%). Note: 41 mg (24%) of the borotropic shift/allylation product was also isolated. TLC (10% EtOAc–petroleum ether, PMA): 0.24. $[\alpha]_D^{20}$: +30.9° (*c* 1.0, $CHCl_3$). IR ($CHCl_3$ cast film, cm^{-1}): 3378, 3030, 2927, 2855, 1640, 1454, 970, 911. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.36–7.35 (m, 4H), 7.29–7.27 (m, 1H), 5.78 (dddd, 1H, *J* = 17.0, 10.3, 6.7, 6.7 Hz), 5.55 (dm, 1H, *J* = 15.1 Hz), 5.39 (dm, 1H, *J* = 15.5 Hz), 4.98 (dm, 1H, *J* = 17.1 Hz), 4.93 (dm, 1H, *J* = 10.2 Hz), 4.67 (ddd, 1H, *J* = 8.0, 4.9, 3.2 Hz), 2.50–2.38 (m, 2H), 2.06–2.00 (m, 5H), 1.48–1.42 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.0, 138.7, 134.6, 128.3, 127.4, 125.8 (2C), 114.5, 73.5, 42.8, 33.2, 32.0, 28.5. HRMS (EI, *m*/*z*) calcd. for $C_{15}H_{20}O$: 216.1514; found: 216.1520. HPLC for *E*/*Z* ratio measurement on crude product: Zorbax SB-C18 4.6 mm × 150 mm, 5 μm, 40 °C, mobile phase A: 0.05% formic acid – H_2O, mobile phase B: 0.05% formic acid – MeOH, program: 70:30 at 0 min, 64.5% of B at 110 min, 30% of B at 110.01 min, 1 mL/min, UV detection at 210 nm, retention times: (3*Z*)-1-phenyl-3,8-nonadien-1-ol, 104.4 min; (3*E*)-1-phenyl-3,8-nonadien-1-ol, 106.7 min. HPLC for enantiomeric excess measurement on purified product: Chiralcel OD, 10 °C, 2% *i*-PrOH hexane, 0.5 mL/min, UV detection at 270 nm, retention times: (3*E*,1*R*)-1-phenyl-3,8-nonadien-1-ol, 25.6 min; (3*E*,1*S*)-1-phenyl-3,8-nonadien-1-ol, 33.2 min; 83% ee.

*(3*E*,1*R*)-4-Cyclohexyl-1-phenyl-3-buten-1-ol (9d)*

Flash chromatography using an automated flash system (4 g SiO_2 column, 10 column volumes (CV) 100% petroleum ether, 20 CV 100% petroleum ether to 5% EtOAc, 30 CV 5% EtOAc, 10 CV 5% EtOAc to 50% EtOAc) yielded a colorless oil (74 mg, 41%), which gave satisfactory analytical data (NMR, MS) as reported in the literature.[35] Note: 46 mg (23%) of the borotropic shift/allylation product was also isolated. TLC (10% EtOAc–petroleum ether, PMA): 0.28. $[\alpha]_D^{20}$: +23.2° (*c* 1.0 $CHCl_3$). HPLC for *E*/*Z* ratio measurement on crude product: Zorbax SB-C18 4.6 mm × 150 mm, 5 μm, 40 °C, mobile phase A: 0.05% formic acid – H_2O, mobile phase B: 0.05% formic acid – acetonitrile, program: 50:50 at 0 min, 95% of B at 25 min, 50% of B at 25.01 min, 1 mL/min, UV detection at 210 nm, retention times: (3*Z*)-4-cyclohexyl-1-phenyl-3-buten-1-ol, 12.6 min; (3*E*)-4-cyclohexyl-1-phenyl-3-buten-1-ol, 13.2 min. HPLC for enantiomeric excess measurement on purified product: Chiralcel OD, 10 °C, 2% *i*-PrOH hexane, 0.5 mL/min, UV detection at 220 nm, retention times: (3*E*,1*R*)-4-cyclohexyl-1-phenyl-3-buten-1-ol, 23.4 min; (3*E*,1*S*)-4-cyclohexyl-1-phenyl-3-buten-1-ol, 33.4 min; 68% ee.

Experimental procedures in the syntheses of (+)-(3*R*,5*R*)-3-hydroxy-5-decanolide (13) and (–)-massoialactone (12)

2-(3-Methoxyphenyl) ethanol

This compound was synthesized following a literature procedure[27a] and yielded a colorless oil (4.33 g, 95%), which gave satisfactory analytical data (NMR, MS), as reported in the literature,[27b] and was used without further purification.

(3-Methoxyphenyl) acetaldehyde (16)

This compound was synthesized following a published procedure.[27c] Flash chromatography (5% Et_2O–dichloromethane) yielded a light yellow oil (1.74 g, 93%). TLC (50% Et_2O–dichloromethane, UV, $KMnO_4$): 0.38. IR (CH_2Cl_2 cast film, cm^{-1}): 3004, 2941, 2837, 2728, 1723, 1602, 1492, 1258, 1152, 1042, 782, 697. ^1H NMR (400 MHz, $CDCl_3$) δ: 9.74 (t, 1H, *J* = 2.4 Hz), 7.30 (dd, 1H, *J* = 7.9, 7.9 Hz), 6.88–6.76 (m, 3H), 3.82 (s, 3H), 3.66 (d, 2H, *J* = 2.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 199.3, 160.1, 133.2, 130.0, 121.9, 115.3, 112.8, 55.2, 50.6. HRMS (EI, *m*/*z*) calcd. for $C_9H_{10}O_2$: 150.0681; found: 150.0683. Anal. calcd. for $C_9H_{10}O_2$: C 71.98, H 6.71; found: C 71.78, H 6.71.

*(4*E*,2*R*)-1-(3-Methoxyphenyl)-4-heptene-2-ol (15)*

Copper thiophene carboxylate (CuTC) (61 mg, 0.32 mmol) and ligand **8** (240 mg, 0.39 mmol) were charged in a flame-dried 100 mL round-bottom flask equipped with a

magnetic stirrer. The flask was purged three times with a light vacuum and argon sequence. Dichloromethane (24 mL) was added and the mixture was stirred for 30 min at room temperature. In the meantime, a solution of boronic ester **7** (3.01 g, 16.0 mmol) in dichloromethane (8 mL) was prepared. The solution of **7** was added dropwise to the reaction mixture and stirred for 5 min at room temperature (the reaction mixture turned to a blue-green color) before cooling to –78 °C. Ethylmagnesium bromide (3.0 mol/L in Et_2O, 19 mmol) diluted with dichloromethane (10 mL) was added at –78 °C over 4 h using a syringe pump, keeping the needle immersed in the reaction mixture. The reaction mixture turned to a bright yellow color after about 3.5 h of addition. Once the addition was complete, the mixture was stirred for another 2 h at –78 °C. Boron trifluoride diethyl etherate (BF_3-OEt_2) (2.0 mL, 16 mmol) was added immediately followed by (3-methoxyphenyl) acetaldehyde (**16**) (1.65 g, 11.0 mmol) at –78 °C. The reaction mixture was stirred for approximately 24 h at –78 °C and 16 h at –30 °C. The reaction was quenched at –78 °C via the addition of a saturated aqueous solution of sodium bicarbonate (20 mL). The mixture was then warmed up to room temperature over 3 h and stirred for an additional 30 min at room temperature. The phases were separated and the aqueous phase was extracted three times using dichloromethane. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo.

Flash chromatography (100% hexanes to 20% Et_2O–hexanes) yielded a colorless oil as an inseparable mixture of *E*/*Z* isomers **15** in a 22:1 ratio (2.12 g, 87%). TLC (50% Et_2O–hexanes, UV, PMA): 0.27. $[\alpha]_D^{20}$: –2.9° (*c* 1.0, $CHCl_3$). IR ($CHCl_3$ cast film, cm^{-1}): 3421, 2961, 2934, 1602, 1585, 1489, 1261, 1046. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.23, (dd, 1H, *J* = 8.9, 7.5 Hz), 6.79–6.76 (m, 3H), 5.62 (dm, 1H, *J* = 15.1 Hz), 5.45 (dm, 1H, *J* = 15.5 Hz), 3.88–3.81 (m, 1H), 3.81 (s, 3H), 2.79 (dd, 1H, *J* = 13.6, 5.1 Hz), 2.70 (dd, 1H, *J* = 13.6, 7.9 Hz), 2.29–2.27 (m, 1H), 2.17–2.15 (m, 1H), 2.10–2.02 (m, 2H), 1.71 (d, 1H, *J* = 3.2 Hz), 1.00 (t, 3H, *J* = 7.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.6, 140.1, 136.1, 129.3, 124.5, 121.7, 115.0, 111.7, 71.8, 55.0, 43.2, 39.9, 25.6, 13.7. HRMS (EI, *m*/*z*) calcd. for $C_{14}H_{20}O_2$: 220.1463; found: 220.1461. HPLC for enantiomeric excess: Chiralcel OD, 10 °C, 2% *i*-PrOH hexane, 0.7 mL/min, UV detection at 280 nm, retention times: (4*E*,2*S*)-1-(3-methoxyphenyl)-4-heptene-2-ol, 20.8 min; (4*Z*,2*R* or 2*S*)-1-(3-methoxyphenyl)-4-heptene-2-ol, 22.7 min; (4*E*,2*R*)-1-(3-methoxyphenyl)-4-heptene-2-ol, 28.2 min; (4*Z*,2*R* or 2*S*)-1-(3-methoxyphenyl)-4-heptene-2-ol, 30.2 min; 92% ee.

*(2**R**)-1-(3-Methoxyphenyl)-2-heptanol (18)*

(4*E*,2*R*)-1-(3-Methoxyphenyl)-4-heptene-2-ol (**15**) (2.12 g, 9.6 mmol) was charged in a flame-dried flask under argon. Ethyl acetate (100 mL) and Adams's catalyst (PtO_2) (108 mg, 0.48 mmol) were added and the flask was purged three times with a light vacuum and argon sequence and three times with a light vacuum and H_2 sequence. The reaction mixture was stirred for 1.5 h at room temperature under an atmospheric pressure of H_2 (using a H_2 balloon). The reaction mixture was then purged with a light vacuum and argon sequence before being filtered on celite and rinsed with EtOAc. The filtrate was concentrated in vacuo. Flash chromatography on a short column (30% Et_2O–hexanes) yielded a yellow oil (2.10 g, 98%). TLC: (50% Et_2O–hexanes, UV, $KMnO_4$, vanillin (blue stain)) 0.33. Note: even though the product and the starting material have the same R_f, the product took longer to stain with $KMnO_4$. $[\alpha]_D^{20}$: –10.4° (*c* 1.0, $CHCl_3$). IR ($CHCl_3$ cast film, cm^{-1}): 3407, 2931, 2858, 1602, 1489, 1465, 1259, 1154, 1046. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.24 (ddd, 1H, *J* = 7.4, 7.4, 1.2 Hz), 6.83–6.78 (m, 3H), 3.82–3.81 (m, 1H), 3.81 (s, 3H), 2.82 (dd, 1H, *J* = 13.5, 4.2 Hz), 2.63 (dd, 1H, *J* = 13.6, 8.5 Hz), 1.57–1.51 (m, 4H), 1.34–1.31 (m, 5H), 0.91 (t, 3H, *J* = 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.7, 140.2, 129.4, 121.6, 115.0, 111.7, 72.5, 55.0, 44.0, 36.7, 31.8, 25.3, 22.6, 13.9. HRMS (EI, *m*/*z*) calcd. for $C_{14}H_{22}O_2$: 222.1620; found: 222.1621. Anal. calcd. for $C_9H_{10}O_2$: C 71.98, H 6.71; found: C 71.78, H 6.71. HPLC for enantiomeric excess: Chiralcel OD, 10 °C, 2% *i*-PrOH hexane, 0.7 mL/min, UV detection at 280 nm, retention times: (2*S*)-1-(3-methoxyphenyl)-2-heptanol, 21.0 min; (2*R*)-1-(3-methoxyphenyl)-2-heptanol, 28.8 min; 88% ee.

*(2**R**)-1-(5-Methoxy cyclohexadienyl)-2-heptanol (19)*

This compound was synthesized following a literature procedure performed on a different substrate.[36] Flash chromatography (100% petroleum ether to 6% EtOAc–petroleum ether) yielded a colorless oil (239 mg, 46%) along with starting material (152 mg, 65% yield brsm). TLC: (20% EtOAc–petroleum ether, vanillin (red stain)): 0.38. $[\alpha]_D^{20}$: –8.1° (*c* 1.0, $CHCl_3$). IR (microscope, cm^{-1}): 3418, 2930, 1695, 1665, 1467, 1390, 1222, 1136, 1024, 776. ^1H NMR (400 MHz, $CDCl_3$) δ: 5.56 (brs, 1H), 4.64 (dd, 1H, *J* = 3.6, 3.6 Hz), 3.80–3.69 (m, 1H), 3.56 (s, 3H), 2.87–2.81 (m, 2H), 2.78–2.68 (m, 1H), 2.66–2.56 (m, 1H), 2.19 (br d, 1H, *J* =13.8 Hz), 2.09 (dd, 1H, *J* = 13.8, 9.1 Hz), 1.63 (br s, 1H), 1.49–1.43 (m, 3H), 1.37–1.27 (m, 5H), 0.90 (t, 3H, *J* = 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.7, 131.3, 122.1, 90.2, 68.5, 53.9, 45.3, 37.0, 31.9, 31.6, 26.8, 25.4, 22.6, 14.0. HRMS (EI, *m*/*z*) calcd. for $C_{14}H_{24}O_2$: 224.1776; found: 224.1781. Anal. calcd. for $C_{14}H_{24}O_2$: C 74.95, H 10.78; found: C 74.94, H 10.81.

*(3**R**,5**R**)-Methyl 3,5-dihydroxydecanoate (14)*

Ozonolysis was performed following modified literature procedures performed on different substrates.[36,37] In a three-neck flask equipped with a $CaCl_2$ drying tube, a solution of (2*R*)-1-(5-methoxy cyclohexadienyl)-2-heptanol (**19**) (0.22 g, 1.0 mmol) in dichloromethane (4.2 mL) and methanol (1.8 mL) was prepared and pyridine (90 mL, 1.1 mmol) was added. The solution was cooled to –78 °C and a light stream of ozone was bubbled through until the reaction was saturated at which point the reaction mixture turned blue and the color persisted. Ozone was removed with oxygen until the blue color disappeared. Dimethyl sulfide (3 mL) was added at –78 °C and the reaction mixture was stirred for 1 h at room temperature. A saturated sodium chloride solution was added, the layers were separated, and the aqueous layer was extracted four times with dichloromethane. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The unstable crude material was immediately used in the following step.

The ketone reduction was performed following a modification of a literature procedure.[37,38] Crude (5*R*)-methyl-5-hydroxy-3-oxodecanoate was charged in a flame-dried flask under argon. It was diluted with THF (12 mL) and methanol (3 mL) and cooled to –78 °C for dropwise addition of diethylmethoxyborane (1.1 mL, 1.1 mmol) as a 1.0 mol/L solution in THF. The reaction mixture was stirred for 15 min at –78 °C and sodium borohydride (0.19 g, 5.1 mmol) was added in one portion. The reaction mixture was stirred for 3 h at –78 °C and was quenched with the addition of a saturated aqueous solution of ammonium chloride. The reaction flask was brought carefully to room temperature as gas evolution occurred. The reaction was stirred at room temperature until no more gas evolution was observed. The phases were separated and the aqueous phase was extracted three times with Et_2O. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The resulting boronate was purified on a short pad of silica (1% MeOH, 50% Et_2O–hexanes) and the diol was freed by performing the following cycle four times: addition of MeOH and evaporation in vacuo. The resulting oil (96 mg, 44% for two steps) was used without further purification as flash chromatography on the free diol resulted in decomposition. TLC (80% EtOAc–hexanes, 0.08% cerium (IV) sulfate in 10% aqueous sulfuric acid): 0.40. $[\alpha]_D^{20}$: –17.7° (*c* 1.1, $CHCl_3$). IR (neat, cm^{-1}): 3406, 2932, 1738, 1439, 1164. ^1H NMR (400 MHz, $CDCl_3$) δ: 4.30–4.23 (m, 1H), 3.86 (br s, 1H), 3.70 (s, 3H), 3.30 (br s, 1H), 2.49–2.48 (m, 2H), 1.61–1.53 (m, 2H), 1.50–1.37 (m, 3H), 1.34–1.24 (m, 6H), 0.87 (t, 3H, *J* = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.8, 72.2, 69.0, 51.8, 42.2, 41.6, 37.8, 31.8, 25.0, 22.6, 14.0. HRMS (ES, *m/z*) calcd. for $C_{11}H_{22}O_4$ (M + Na): 241.1410; found: 241.1410.

(3R,5R)- 3,5-Dihydroxydecanoic acid (20)

(3*R*,5*R*)-Methyl 3,5-dihydroxydecanoate (**14**) (0.20 g, 0.92 mmol) was diluted with MeOH (20 mL) and water (3 mL). The reaction flask was cooled to 0 °C and sodium hydroxide (3 mL, 18 mmol) as a 6 mol/L aqueous solution was added. The reaction was stirred at 0 °C for 1 h, and a sodium hydroxide/citric acid pH 5 buffer was added followed by a 1 mol/L aqueous citric acid solution until pH 5 was reached (measured with a pH meter). The aqueous phase was extracted three times with EtOAc. The combined organic extracts were washed once with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford a colorless oil (175 mg, 93%) containing 13% of cyclized product. This compound was used immediately, without purification, in subsequent reactions since it rapidly cyclized upon standing.

(–)-Massoialactone (12)

This compound was prepared following a modification of a literature procedure.[28b,29] In a flame-dried flask under argon, (3*R*,5*R*)-3,5-dihydroxydecanoic acid (**20**) (56 mg, 0.27 mmol) was added, then diluted with THF (27 mL) and cooled to 0 °C. Freshly distilled triethylamine (0.23 mL, 1.6 mmol) was added followed by freshly distilled 2,4,6-trichlorobenzoyl chloride (65 μL, 0.41 mmol). The reaction was stirred at 0 °C for 1 h. In the meantime, a three-neck flask equipped with a condenser in one neck, a 25 cm Vigreux column in the other, and a rubber septum in the third neck, was charged with DMAP (0.99 g, 8.1 mmol) and toluene (27 mL) and was heated at reflux so that 15 cm of the Vigreux column (isolated with cotton) would be heated with the refluxing toluene. The first reaction mixture, containing the mixed anhydride, was transferred to a syringe and added over 2 h using a syringe pump, at the top of the Vigreux column to the DMAP solution in refluxing toluene. Once the addition was complete the reaction mixture was refluxed for another 2 h. The reaction mixture was cooled to room temperature and the solvents were evaporated in vacuo. Flash chromatography (30% EtOAc–hexanes to 80% EtOAc–hexanes) afforded (–)-massoialactone (**12**) (30 mg, 67%) as a light yellow oil with a strong coconut fragrance. TLC (40% EtOAc–hexanes, 0.08% cerium (IV) sulfate in 10% aqueous sulfuric acid): 0.44. $[\alpha]_D^{20}$: –74.2° (*c* 1.0, $CHCl_3$) (lit.[23] $[\alpha]_D^{25}$: –91° (*c* 1.0, $CHCl_3$)). IR (neat, cm^{-1}): 3056, 2955, 2862, 1725, 1389, 1251, 1040, 816. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.88 (ddd, 1H, *J* = 9.7, 3.6, 3.6 Hz), 6.03 (ddd, 1H, *J* = 9.7, 1.5, 1.5 Hz), 4.47–4.38 (m, 1H), 2.36–2.31 (m, 2H), 1.87–1.27 (m, 8H), 0.90 (t, 3H, *J* = 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.6, 145.0, 121.5, 78.1, 34.9, 31.6, 29.4, 24.5, 22.5, 14.0. HRMS (EI, *m/z*) calcd. for $C_{10}H_{16}O_2$: 168.1150; found: 168.1150.

(+)-(3R,5R)-3-Hydroxy-5-decanolide (13)

In a flame-dried flask under argon, (3*R*,5*R*)-3,5-dihydroxydecanoic acid (**20**) (25 mg, 0.12 mmol) was charged, diluted with THF (1 mL), and cooled to 0 °C. Freshly distilled triethylamine (0.10 mL, 0.72 mmol) was added followed by freshly distilled 2,4,6-trichlorobenzoyl chloride (30 μL, 0.18 mmol). The reaction was stirred at 0 °C for 1 h and solvents were removed in vacuo. Flash chromatography (30% EtOAc-hexanes to 50% EtOAc-hexanes) afforded (+)-(3*R*,5*R*)-3-Hydroxy-5-decanolide **13** (19 mg, 86%) as a colorless oil. TLC (80% EtOAc–hexanes, 0.08% cerium (IV) sulfate in 10% aqueous sulfuric acid): 0.31. $[\alpha]_D^{20}$: +25.48° (*c* 1.2, $CHCl_3$) (lit.[19] $[\alpha]_D^{20}$: +27.4° (*c* 11.7, $CHCl_3$)). IR ($CHCl_3$ cast film, cm^{-1}): 3415, 2932, 2861, 1713, 1256, 1069. ^1H NMR (500 MHz, $CDCl_3$) δ: 4.69 (dm, 1H, *J* = 11.0 Hz), 4.41–4.40 (m, 1H), 2.75 (1H, dd, *J* = 17.6, 5.1 Hz), 2.62 (ddd, 1H, *J* = 17.6, 3.7, 1.7 Hz), 1.96 (dm, 1H, *J* = 14.5 Hz), 1.75 (ddd, 1H, *J* = 14.6, 11.4, 3.4 Hz), 1.73–1.69 (m, 1H), 1.63–1.49 (m, 2H), 1.45–1.38 (m, 2H), 1.34–1.29 (m, 4H), 0.90 (t, 3H, *J* = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.8, 76.0, 62.7, 38.6, 35.9, 31.5, 24.5, 22.5, 13.9. HRMS (ES, *m/z*) calcd. for $C_{10}H_{18}O_3$ (M + Na): 209.1148, found: 209.1150.

Supplementary data

Supplementary data for this article are available on the journal Web site (canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 3915. For more information on obtaining material refer to cisti-icist.nrc-cnrc.gc.ca/cms/unpub_e.shtml.

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