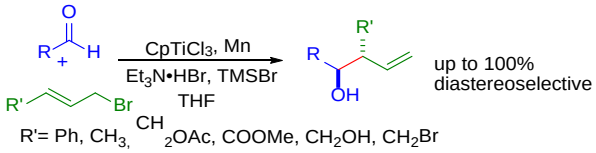
Stereoselective Barbier Type Allylations and Propargylations Mediated by $CpTiCl_3$

Josefa L. López-Martínez; Irene Torres-García; Ignacio Rodríguez-García; Manuel Muñoz-Dorado; Miriam Álvarez-Corral*

Dpto. Química Orgánica, Universidad de Almería, ceiA3, 04120 Almería, Spain.

ABSTRACT GRAPHIC



ABSTRACT: $CpTiCl_2$, prepared *in situ* by manganese reduction of $CpTiCl_3$, is an excellent new system for the Barbier-type allylation and propargylation of carbonyl compounds. It can be used in catalytic amounts when combined with Et_3N•HBr/TMSBr, which act as regenerating system. The high regio- and stereoselectivity shown by this system makes it useful for prenylation and crotylation processes in synthesis of natural products.

INTRODUCTION

The development of new synthetic methodologies and strategies is essential for the progress in the total synthesis of natural products.[1] The Ti(III) complex known as Nugent-Ranjanbabu[2] reagent (Cp_2TiCl) has been widely studied and many useful applications in organic synthesis have been reported. Its catalytic ability for radical and organometallic processes is in the line of new green reagents,[3] and remarkable efforts are being carried out to improve its efficiency in more sustainable reactions.[4] In this line, we have noticed that there is a structurally related analogue, with just one cyclopentadienyl ring and an extra chlorine atom, $CpTiCl_2$, which remains mostly unexplored. Due to its lower steric requirements, and its higher Lewis acid character, an enhanced coordination ability is expected for this complex, a fact that could increase its ability as stereoselective catalyst. In order to expand the knowledge on its chemical behavior, we have carried out several Barbier-type allylations and propargylations of carbonyl compounds.

The commercial parent compound $CpTiCl_3$, in addition to a lower steric hindrance than Cp_2TiCl_2, has a higher number of free coordination sites. Different applications have been reported for this reagent,

including monofluorination of β-keto esters,[5] defluorination of fluorine containing aromatic compounds,[6] cross-couplings of aryl fluorides with Grignard reagents,[6] and deprotection of amines blocked with allyl- or propargyl-carbamate groups.[7]

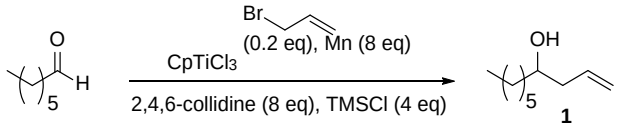
Allylation and propargylation reactions not only form a new C-C bond, but also incorporate a new double or triple bond to the product, which can easily be functionalized or transformed. Due to the great number of applications and versatility of these reactions in organic synthesis, different transition metals have been tested for the Barbier type strategy, including Zn, In, Sn, Pb, Cr (Nozaki-Hiyama-Kishi allylation),[8] SmI_2 (Samarium-Barbier reaction)[9] and Cp_2TiCl_2.[10]

RESULTS AND DISCUSSION

Barbier type allylation and propargylation of aliphatic aldehydes

We first attempted the allylation of heptanal with allylbromide under the catalytic conditions described by Oltra *et al*[11] for similar reactions catalyzed by Cp_2TiCl, which are, a mixture of 2,4,6-collidine and trimethylsilyl chloride (TMSCl) in THF at room temperature (Scheme 1).

Scheme 1. Allylation of heptanal with $CpTiCl_2$ generated in situ from $CpTiCl_3$ with Mn and 2,4,6-collidine and TMSCl



The homoallylic alcohol **1** was formed, but with a disappointing 15% yield. A fast change of color (from dark red to green) could be observed at the beginning of the reaction. This fact led us to think that, after the initial fast reduction of $CpTi^{IV}Cl_3$ into $CpTi^{III}Cl_2$ performed by the manganese present in the reaction medium, the regenerating mixture was failing to efficiently complete the catalytic cycle. Therefore, we tried other reagent combinations, similar to those reported in literature for the Cp_2TiCl system, like 2,4,6-collidine•HCl/TMSCl, Et_3N•HCl/TMSCl.[12] The best result was achieved by the use of a mixture of triethylamine hydrobromide (Et_3N•HBr) and trimethylsilylbromide (TMSBr). We were delighted to see that this system was able to perform the formation of **2** in a satisfying 82% yield (Table 1, entry 1). In addition, we carried out an optimization process of the amounts of reductant and regenerating mixture, finding a new optimal ratio with much lower values for each one of them (foot of Table 1) to those previously reported.[11] This result encouraged us to study the behavior of other aldehydes in allylation and propargylation processes (Scheme 2).

Scheme 2. Allylation and propargylation reactions of aliphatic aldehydes with $CpTi^{III}Cl_2$

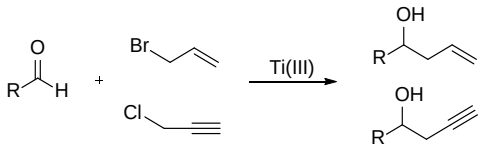
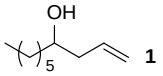
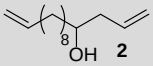
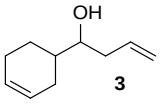
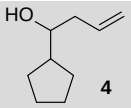
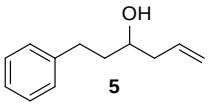
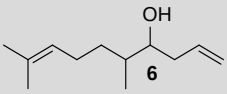
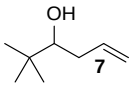
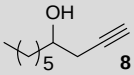
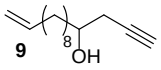
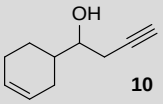
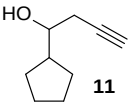
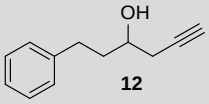
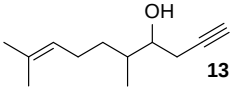

O
R
H
+
Br
Cl
Ti(III)
OH
R
OH
R

Table 1. $CpTi^{III}Cl_2$ mediated allylation and propargylation of aldehydes

entry	product	yield
1	 **1**	82%
2	 **2**	93%
3	 **3**	90%
4	 **4**	68%
5	 **5**	72%
6[a,b]	 **6**	88%
7[a]	 **7**	83%
8	 **8**	85%
9	 **9**	86%
10	 **10**	74%
11	 **11**	78%
12	 **12**	72%
13[a,b]	 **13**	60%

Reaction conditions: $CpTiCl_3$ (0.1 eq.), Mn (2 eq.), Et_3N•HBr (2 eq.), Me_3SiBr (3 eq.), THF; [a] $CpTiCl_3$ (1 eq.), Mn (2 eq.), THF; [b] an inseparable mixture of diastereomers in 1:1 ratio was formed.

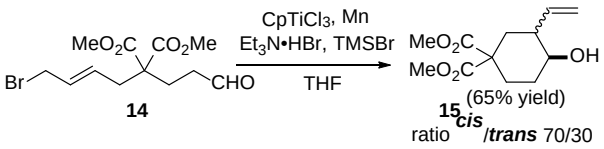
The reaction, successfully performed with a range of aldehydes, gave satisfactory yields under these reaction conditions (Table 1, entries 1-5). However, some aldehydes bearing a trisubstituted double

bond (Table 1, entry 6) led to the formation of the product in a very low yield.[13] Fortunately, when stoichiometric amounts of $CpTiCl_2$ were used, the homoallylic alcohol **6** was formed in a satisfactory yield (Table 1, entry 6). The special structural features of pivalaldehyde proved also to be a challenge for this reaction (Table 1, entry 7). Although **7** was formed in good yield under stoichiometric conditions, the catalytic system led to rearranged products.

A series of analogous Barbier-type propargylations were also tested. Similarly good results were also obtained (Table 1, entries 8-12). No allene products were detected, only alkynes, a fact that suggest a similar metallotropic equilibrium to that reported for the Cp_2TiCl mediated reaction.[14] Finally, propargylation of substrates bearing trisubstituted double bonds had the same special features than in the allylation process due to the structural characteristics of the parent aldehyde (Table 1, entry 13).

Intramolecular allylations are also very interesting processes, as cyclic polyfunctional systems are formed in a very straightforward way. Thus, we tried the intramolecular allylation of aldehyde **14** (Scheme 3) under the above mentioned optimized reaction conditions. The alcohol **15** was formed in good yield (65%), a similar result to that previously published, but with an improved diastereoselectivity, as the reaction catalyzed by $CpTiCl_2$ led to a *cis/trans* ratio of 70/30 while the Cp_2TiCl catalyzed reaction gave no diastereoselection.[15]

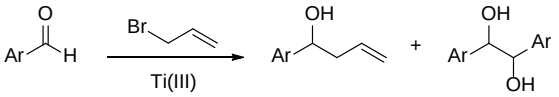
Scheme 3. Diastereoselective intramolecular allylation catalyzed by $CpTi^{III}Cl_2$



Barbier type allylation of aromatic aldehydes

Nucleophilic additions to aromatic aldehydes are highly conditioned by the electronic density of the aromatic ring, or, in other words, the nature of its substituents. In this sense, their behavior can be very different from that of aliphatic aldehydes. Aromatic or α,β-unsaturated carbonyl compounds treated with Nugent-Rajanbabu's reagent lead to pinacol coupling products.[11] The catalytic allylation of *m*-methoxybenzaldehyde under the above mentioned reaction conditions led to the formation of the pinacol dimer **17** as the major product (44%) together with a small amount of the homoallylic alcohol **16** (5%)[16] (Scheme 4, entry 1).

Scheme 4. Allylation reactions of aromatic aldehydes with $CpTi^{III}Cl_2$.



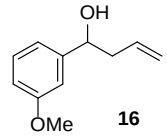
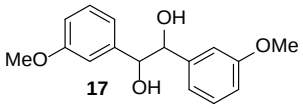
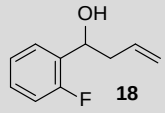
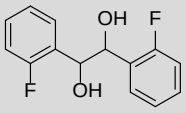
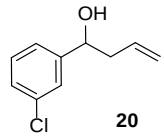
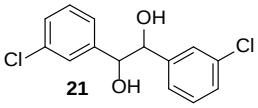
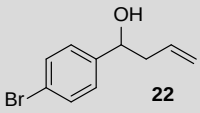
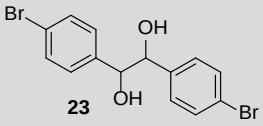
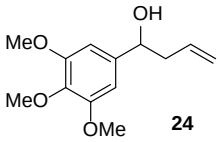
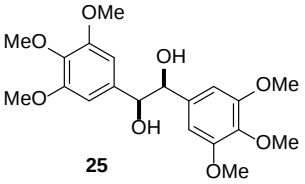
Ar= 3-MeOPh-

	$CpTiCl_3$	Mn	Me$_3$SiBr	Et_3NHBr	**16**	**17**
1	0.1	2	3	3	5%	44%
2	2.0	2	-	-	31%	67%
3*	2.0*	2	-	-	81%	19%

* dropwise addition of aldehyde

In an attempt to improve the results and to minimize the formation of by-products, the reaction was repeated using stoichiometric amounts of $CpTiCl_2$ (Scheme 4, entry 2). The pinacol coupling product **17** was still the major one (67% yield), although the yield of the homoallylic alcohol **16** had increased to 31% (98% of global reaction conversion). In all the above described reactions the experimental procedure was the addition of a solution of a mixture of aldehyde and allyl bromide to the Ti(III) system. In order to minimize the formation of **17**, the addition order was altered. We first added a solution of allylbromide to the Ti(III) system, and later, the aldehyde solution was dropwise added over a period of 2 hours. In this way, the product ratio for **16**:**17** was substantially increased to 81:19 (Scheme 4, entry 3), being now the major product the homoallylic alcohol. Therefore, the sequential addition of both substrates, together with longer addition times, decreases the pinacol coupling in favor of the allylation product, a trend which is also observed with other aromatic aldehydes (Table 2). Thus, with 3-chloro- and 4-bromobenzaldehyde, this procedure gives significant amounts of allylation products (Table 2 entries 3 and 4), opposite to the exclusive formation of the dimers with the initial protocol. Even better, the addition of allylbromide to 2-fluorobenzaldehyde or 3,4,5-trimethoxybenzaldehyde (Table 2, entries 2 and 5) leads to the formation of the homoallylic alcohol as the major reaction product. Interestingly, in the last example the homocoupling product is formed exclusively as *dl* adduct.

Table 2. $CpTi^{III}Cl_2$ in the allylation of aromatic aldehydes

entry	products	overall yield	ratio
1	 **16**  **17**	97%	**16**:**17** (81:19) **17** (*dl:meso* 6:4)
2	 **18**  **19**	87%	**18**:**19** (75:25) **19** (*meso:dl* 7:3)
3	 **20**  **21**	72%	**20**:**21** (33:67) **21** (*dl:meso* 7:3)
4	 **22**  **23**	75%	**22**:**23** (33:67) **23** (*dl:meso* 6:4)
5	 **24**  **25**	56%	**24**:**25*dl*** (71:29)

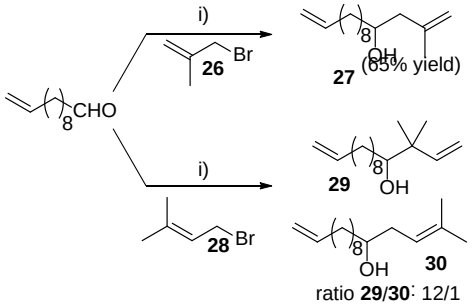
Reaction conditions: $CpTiCl_3$ (1 eq.), Mn (2 eq.), THF. Slow addition of aldehyde to the Ti(III)-allylbromide mixture.

Regio- and diastereoselective allylations

In order to study the regio- and stereoselectivity of the reaction, we have also explored the behavior of more complex allylic bromides. In this way, using undec-10-enal as substrate, we performed the addition of several allyl bromides in which the double bond was di- or tri-substituted or carried other functional groups, thus opening the door to more interesting synthetic applications.

We first tried the reaction between 1-bromo-3-methylprop-1-ene (**26**) and undec-10-enal (Scheme 5), which produced **27** in 65% yield as the only reaction product. On the other hand, the trisubstituted alkene 1-bromo-3-methylbut-2-ene (**28**) gave a regioselective addition through the more substituted end of the allyl system, leading mainly to the formation of **29** (the observed ratio for **29**:**30** was 12:1).

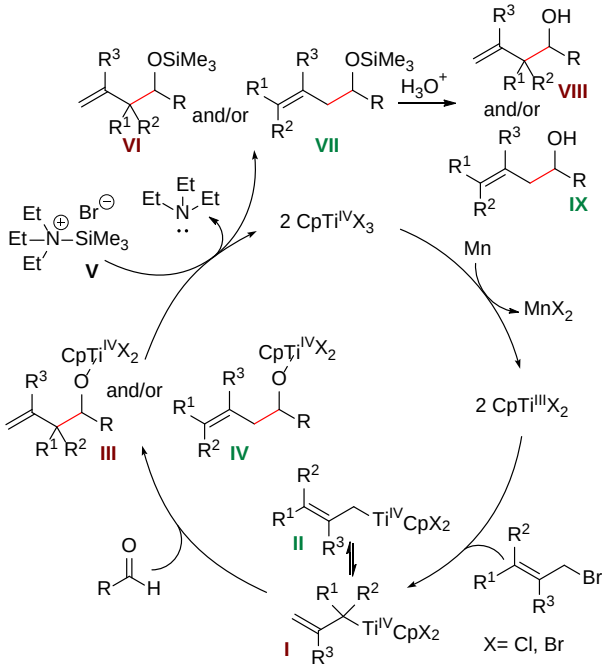
Scheme 5. Substituted allyl bromides in the allylation reaction with $CpTi^{III}Cl_2$



a) $CpTiCl_3$ (0.1 eq.), Mn (2 eq.), Et_3NHBr (2 eq.), Me_3SiBr (3 eq.), THF.

This is an interesting result with potential application in synthesis of terpenoid natural products in which the *tert*-prenyl motif is present. The formation of these compounds can be easily explained considering that the organometallic intermediates should be similar to those involved in the reaction reported for Cp_2TiCl in previous works.[17] In this way, a possible mechanism for this reaction could start by initial reduction of $CpTi^{IV}Cl_3$ by the manganese to form a Ti(III) complex (Scheme 6). This active species would react with the allylic bromide to yield a C-Ti(IV) complex in which the allyl group could experiment a metallotropic equilibrium[14] (species **I** and **II**, Scheme 6). Reaction of these C-Ti(IV) complexes with the carbonyl group would form the new C-C bond in the alkoxytitanocene products **III** and **IV**. Finally, the regenerating mixture transforms the O-Ti(IV) species into $CpTi^{IV}X_3$ liberating the homoallylic alcohols as a silyl derivatives **VI** and **VII**, which usually suffer hydrolysis during the reaction workup yielding **VIII** and **IX** respectively (Scheme 6).

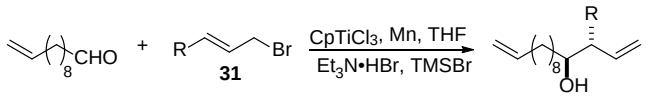
Scheme 6. Proposed catalytic cycle with substituted allylbromides

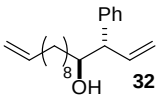
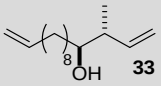
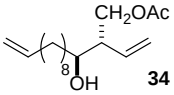
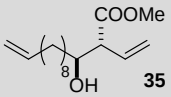
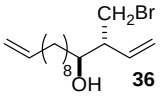
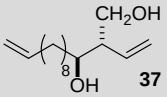
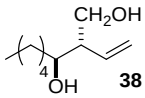


We have also explored the reaction with allyl bromides in which the double bond is 1,2-disubstituted (**31**, Table 3). Several functional groups were also included in order to study their behavior under the reaction conditions. The reaction proved to be completely regioselective in all the studied examples, as only products derived from intermediate **III** in the proposed catalytic cycle (Scheme 6) were detected. In addition, *anti* stereoisomers were mainly or even exclusively formed.

The results are summarized in Table 3. Entries 1-3 show complete regioselectivity, and good yields even in the presence of functional groups like the acetate in entry 3. Especially relevant is the result of entry 2, as the crotylation process is one of the most used methods in the construction of polypropionate natural products. The presence of a methyl ester (entry 4) was again totally regioselective, although in this case a mixture of diasteromers was formed in moderate yield (ratio **35*anti***:**35*syn*** 77:23). Performing the reaction under stoichiometric conditions led to a substantial increase in the yield with a slightly lower diastereoselectivity (ratio **35*anti***:**35*syn*** 67:33). A similar pattern was observed when 1,4-dibromobut-2 ene was used (Table 3, entry 5), showing again a good behavior under stoichiometric conditions. It is noteworthy the result obtained when a free hydroxy group is present (entry 6), proving the compatibility of this group with the process which affords **37** with complete regio and diastereoselection, although two equivalents of Ti(III) had to be used. A similar result was obtained with heptanal as aldehyde (entry 7). The hydroxymethyl 1,3-diol motif present in **37** and **38** appears in numerous natural products. Therefore, this method is a good and straightforward option for diastereoselective hydroxymethyl allylation.

Table 3. $CpTi^{III}Cl_2$ in the regio- and stereoselective addition of substituted allylbromides to aldehydes

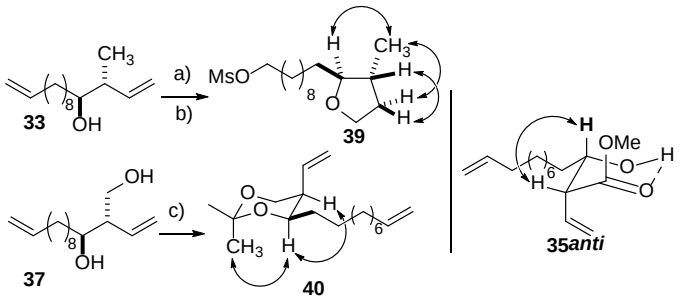


entry	**31**	product	*anti:syn*	yield
1	R= Ph	 **32**	100:0	76%
2	R= CH_3	 **33**	100	77%
3	R=CH_2OAc	 **34**	100	77%
4	R=COOMe	 **35**	77:23 67:33[a]	41% 81%[a]
5	R= CH_2Br	 **36**	100	60%[a]
6	R= CH_2OH	 **37**	100	57%[b]
7	R= CH_2OH	 **38**	100	56%[b,c]

Reaction conditions: $CpTiCl_3$ (0.1 eq.), Mn (2 eq.), Me_3SiBr (3 eq.), Et_3N•HBr (2 eq.), THF; [a] $CpTiCl_3$ (1 eq.), Mn (2 eq.); [b] $CpTiCl_3$ (3 eq.), Mn (6 eq.); [c] hexanal is the aldehyde used.

The relative stereochemistry proposed for **32-37** is based on NMR experiments, performed either on the reaction products or on some derivatives. Thus, while in **35*anti*** the intramolecular hydrogen bond between the OH and the CO_2Me groups fixes a particular conformation in which significant NOE effects can be observed (Scheme 7), compounds **33** and **37** had to be transformed into cyclic derivatives. In this way, **33** was transformed into the tetrahydrofuran **39** through a hydroboration + mesylation-cyclization process. On the other hand, acetonide protection of diol **37** gave the 1,3-dioxane derivative **40** (Scheme 7). NOE experiments confirmed the proposed relative stereochemistry (Scheme 7).

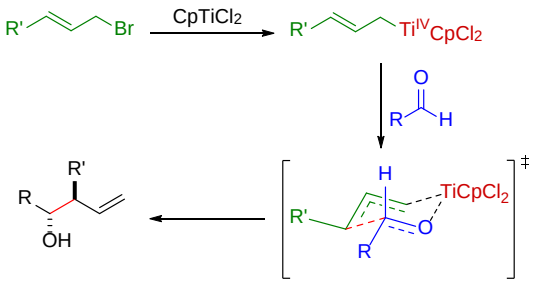
Scheme 7. Derivatization of **33** and **37** and diagnostic NOES for **35*anti*, 39 and 40**.



a) i) $BH_3.SMe_2$, THF; ii) H_2O_2, NaOH; b) MsCl, Et_3N, DMAP, CH_2Cl_2; c) $(CH_3)_2C(OMe)_2$, CSA, CH_2Cl_2.

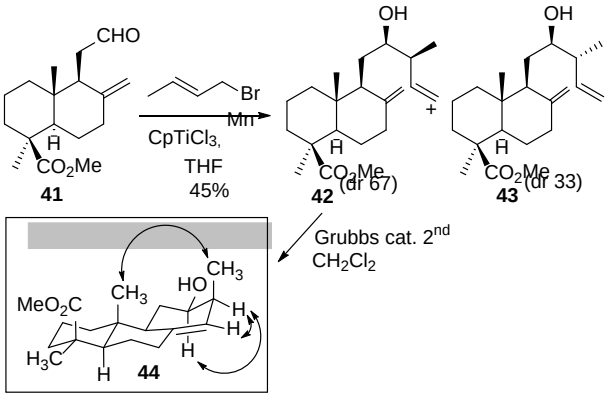
Scheme 8 shows a possible mechanistic interpretation for the formation of the *anti* isomer. Opposed to what happens with Cp_2TiCl, the higher number of vacant coordination sites in $CpTiCl_2$ allows the formation of a six member chair-like intermediate in which the oxygen of the aldehyde coordinates to the titanium core. The aldehyde R group adopts preferentially an equatorial disposition, leading to the formation of the *anti* isomer.

Scheme 8. Mechanistic interpretation for the $CpTiCl_2$ mediated allylation of aldehydes



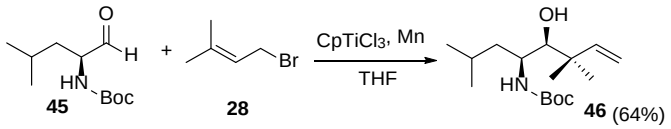
The good results obtained in the crotylation processes above mentioned encouraged us to test the reaction with other aldehydes of higher structural complexity. We chose aldehyde **41**, a communic acid derivative previously described.[18] The reaction led to the formation of both *anti* diastereomers **42** and **43** but in a relative ratio 2:1 (global yield 45%) (Scheme 9). Again, in order to establish the relative stereochemistry, a cyclic derivative was prepared, this time by olefin ring closing metathesis of **42,** which afforded the tricyclic system **44,** which was used to measure the NOEs (Scheme 9).

Scheme 9. Crotylation of 41 and diagnostic NOEs of 44



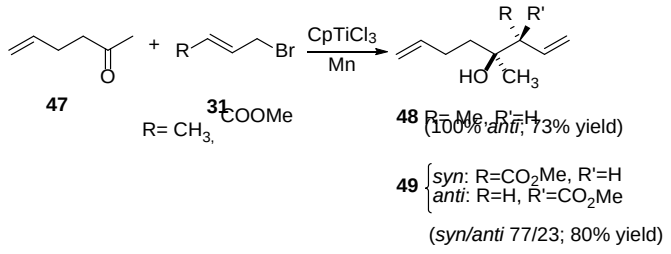
In 2014 Beveridge *et al* reported an outstanding synthesis of the depsipeptides kitastin and respirantin, highly cytotoxic neo-antimycin macrocyclic depsipeptide natural products[19] in which the key synthetic intermediate **46** requires several steps to be prepared. The $CpTiCl_3$ Barbier type allylation allows its straightforward preparation in a completely regio- and diastereoselective single step with a 64% yield (Scheme 10).

Scheme 10. Regio- and diastereoselective synthesis of 46



The method shows also stereoselectivity when the substrate is a ketone. For example, addition of crotylbromide to the ketone **47** under the previously optimized catalytic conditions yields **48** with complete regioselectivity in 73% yield (Scheme 11). The stereochemistry was temporarily assigned by analogy of ^{1}H NMR pattern with similar structures already described.[20] In the synthesis of **49**, which has a methyl ester, the reaction is not only regioselective, but also highly diastereoselective, as a mixture of *anti:syn* isomers is formed in a 77:33 ratio and with a 80% global yield under the stoichiometric conditions.

Scheme 11. Regio- and diastereoselective addition of substituted allylbromides to ketones



CONCLUSIONS

In summary, $CpTiCl_2$ generated in situ by reduction of $CpTiCl_3$ with Mn, promotes Barbier-type inter- and intramolecular allylation and propargylation reactions on different aldehydes. The regenerating mixture used, Et_3N•HBr and TMSBr, allowed the use of catalytic amounts of the $CpTiCl_2$ complex. In addition, homoallylic alcohols have been prepared regio- and diastereoselectively, by the intermolecular reaction between the undec-10-enal and various allylic bromides substituted with alkyl groups and other functional groups. Finally, we have proved that the system can be applied to the synthesis of natural products. When compared to Cp_2TiCl_2, although $CpTiCl_3$ might be more expensive, it offers the advantage of being more stereoselective, possibly due to its higher coordination ability, which makes it a highly promising reagent for new synthetic applications.

EXPERIMENTAL SECTION

General Remarks

In all experiments involving Ti(III), reactions were performed under argon atmosphere, using oven-dried glassware in all cases. THF was distilled from Na/benzophenone under argon, and was deoxygenated prior to use. NMR spectra were recorded on Bruker Nanobay Avance III HD 300 MHz, Avance III HD 500 MHz and Avance III HD 600 MHz spectrometers. Proton-decoupled $^{13}C\{1H\}$ NMR spectra and DEPT-135 were measured in all cases. When required, HSQC was used for signal assignation and disambiguation.and NOESY-2D for relative configuration determination. Chemical shifts (δ) are expressed in ppm and coupling constants (*J*) in hertzs (Hz). Chemical shifts are reported using $CDCl_3$ as internal reference. IR Spectra were recorded with a Bruker Alpha spectrometer. Mass spectra were recorded in a Waters Xevo by LC-QTof-MS by electrospray ionization. All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.2 mm DC-Fertigfolien Alugram® XtraSil G/UV254 silica gel plates. The TLC plates were visualized with UV light and 7% phosphomolybdic acid or $KMnO_4$ in water/heat. Flash chromatography was performed on silicagel 60 (0.04 - 0.06 mm).Commercially available chemicals were obtained from Aldrich Chemical Co., Acros, Alfa Aesar, TCI and used as received.

General procedure A for Ti-catalyzed allylation or propargylation of aldehydes

Under an Ar atmosphere, dry THF (8 mL/1.4 mmol of aldehyde) previously deoxygenated is added to a miscellany of $CpTiCl_3$ (0.1 eq.), Mn dust (2 eq.) and $Et_3N{\cdot}HBr$ (2 eq.) resulting a dark blue suspension. Then, Me_3SiBr (3 eq.) is added and the mixture turned turquoise. A solution of aldehyde (1 eq.) and propargyl chloride or allyl bromide (2 eq.) in THF (2mL/1.4 mmol of aldehyde) is dripped and the mixture is stirred (1-3h for allylation, and 3-5h for propargylation). The mixture filtered,

diluted with AcOEt, washed with HCl 3% and brine, dried (anhydrous $MgSO_4$) and the solvent removed. Products are purified by silica gel flash column chromatography (hexane/Et_2O mixtures).

Dec-1-en-4-ol (1). Reaction of heptanal (0.20 mL, 1.43 mmol) and allyl bromide (0.25 mL, 2.86 mmol), according to the general procedure **A**, afforded product **1** (183 mg, 82%), isolated as light yellow oil. Spectral data are in agreement with literature values.[21]

Tetradeca-1,13-dien-4-ol (2). Reaction of undec-10-enal (0.24 mL, 1.25 mmol) and allyl bromide (0.22 mL, 2.50 mmol), according to the general procedure **A**, afforded product **2** (245 mg, 93%) isolated as light yellow oil.Spectral data are in agreement with literature values.[22]

1-(Cyclohex-3-en-1-yl)but-3-en-1-ol (3). Reaction of cyclohex-3-ene-1-carbaldehyde (0.21 mL, 1.82 mmol) and allyl bromide (0.32 mL, 3.64 mmol), according to the general procedure **A**, afforded product **3** (249 mg, 90%), as an inseparable mixture of diastereoisomers (1:1), isolated as light yellow oil. IR (film) ν (cm^{-1}) 3387, 3022, 2911, 1640, 1435, 1100, 994, 910, 733, 650. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) both isomers: 5.93-5.79 (m, 1H, H3), 5.79 (m, 2H, H3', H4'), 5.18-5.13 (m, 2H, H4), 2.42-2.32 (m, 1H), 2.23-1.57 (m, 8H), 1.47-1.21 (m, 1H); isomer a: 3.54 (m, 1H, H1); isomer b: 3.44 (m, 1H, H1). ^{13}C{1H} NMR (75 MHz, $CDCl_3$, DEPT) δ (ppm) both isomers: 135.3, 135.2 (CH, C3), 127.3, 126.8 (CH, C3'), 126.4, 126.0 (CH, C4'), 118.2, 118.0 (CH_2, C4), 74.2, 74.1 (CH, C1), 39.1, 38.9 (CH, C1'), 39.0, 38.9 (CH_2, C2), 27.9 (CH_2), 26.5 (CH_2), 25.3 (CH_2), 25.3 (CH_2), 25.2 (CH_2), 24.3 (CH_2). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{10}H_{17}O$ 153.1279; Found: 153.1272.

1-Cyclopentylbut-3-en-1-ol (4). Reaction of cyclopentanecarbaldehyde (0.22 mL, 2.04 mmol) and allyl bromide (0.35 mL, 4.08 mmol), according to the general procedure **A**, afforded product **4** (194 mg, 68%) isolated as a colorless oil. Spectral data are in agreement with literature values.[23]

1-Phenylhex-5-en-3-ol (5). Reaction of 3-phenylpropanal (0.20 g, 1.49 mmol) and allyl bromide (0.26 mL, 2.98 mmol), according to the general procedure **A**, afforded product **5** (189 mg, 72%) isolated as light yellow oil.[22]

Dec-1-yn-4-ol (8). Reaction of heptanal (0.24 mL, 1.75 mmol) and propargyl chloride (0.25 mL, 3.50 mmol), according to the general procedure **A**, afforded product **8** (229mg, 85%) isolated as light yellow oil. Spectral data are in agreement with literature values.[24]

Tetradeca-13-en-1-yn-4-ol (9). Reaction of undec-10-enal (0.19 mL, 0.94 mmol) and propargyl chloride (0.14 mL, 1.96mmol), according to the general procedure **A**, afforded product **9** (168 mg, 86%), isolated as light orange oil. IR (film) ν (cm^{-1}) 3309, 2976, 2927, 2251, 1640, 1464, 906, 730, 648. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.83 (ddt, J = 17.1, 10.2, 6.9 Hz, 1H), 5.00 (ddt, J = 17.1, 2.2, 1.6 Hz, 1H), 4.94 (ddt, J = 10.1, 2.2, 1.2 Hz, 1H), 3.77 (m, 1H), 2.45 (ddd, J = 16.7, 4.8, 2.6 Hz, 1H), 2.33 (ddd, J = 16.7, 6.7, 2.6 Hz, 1H), 2.07 (t, J = 2.6 Hz, 1H), 2.03 (m, 2H), 1.54 (m, 2H), 1.33

(m, 12H). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$, DEPT) δ (ppm) 139.2 (CH), 114.1 (CH_2), 81.0 (C), 70.8 (CH), 69.9 (CH), 36.2 (CH_2), 33.8 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 27.3 (CH_2), 25.6 (CH_2). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{25}O$ 209.1905; Found 209.1924.

1-(Cyclohex-3-en-1-yl)but-3-yn-1-ol (10). Reaction of cyclohex-3-ene-1-carbaldehyde (0.21 mL, 1.82 mmol) and propargyl chloride (0.26 mL, 3.64 mmol), according to the general procedure **A**, afforded **10** (202 mg, 74%), as an inseparable mixture of diastereoisomers (1:1), isolated as light orange oil. IR (film) *v* (cm^{-1}) 3397, 3305, 3024, 2915, 2251, 1435, 1051, 905, 728, 648. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) both isomers: 5.70 (m, 2H), 2.57-2.35 (m, 2H), 2.17-1.91 (m, 5H), 1.86-1.63 (m, 2H), 1.46-1.28 (m, 1H); isomer a: 3.70 (m, 1H); isomer b: 3.51 (m, 1H). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$, DEPT) δ (ppm) both isomers: 127.4, 126.8 (CH), 126.1, 125.6 (CH), 81.1, 80.9 (C, C3), 73.4, 73.3 (CH, C1), 71.0, 70.8 (CH, C4), 38.6, 38.4 (CH, C1'), 27.9 (CH_2), 26. 6 (CH_2), 25.2 (CH_2), 25.0 (CH_2), 25.0 (CH_2), 24.8 (CH_2), 24.3 (CH_2). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{10}H_{15}O$ 151.1123; Found 151.1107.

1-Cyclopentylbut-3-yn-1-ol (11). Reaction of cyclopentanecarbaldehyde (0.22 mL, 2.04 mmol) and propargyl chloride (0.29 mL, 4.08 mmol), according to the general procedure **A**, afforded product **11** (220 mg, 78%), isolated as oil. IR (film) *v* (cm^{-1}) 3409, 3307, 2951, 2913, 2868, 2118, 1261, 1094, 1045, 732, 626. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.51 (m, 1H, H1), 2.45 (ddd, *J* = 6.8, 3.9, 2.7 Hz, 1H, H2a), 2.29 (ddd, *J* = 16.8, 6.9, 2.7 Hz, 1H, H2b), 2.27 (brs, 1H, OH), 2.03 (t, *J* = 2.7 Hz, 1H, H4), 1.96 (quint, *J* = 8.1 Hz, 1H, H1'), 1.79 (m, 1H), 1.57 (m, 5H), 1.40 (m, 1H), 1.17 (m, 1H). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$, DEPT) δ (ppm) 81.3 (C, C3), 73.9 (CH, C1), 70.6 (CH, C4), 45.2 (CH, C1'), 29.1 (CH_2), 28.8 (CH_2), 26.4 (CH_2, C2), 25.6 (CH_2), 25.5 (CH_2). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_9H_{15}O$ 139.1123; Found 139.1132.

1-Phenylhex-5-yn-3-ol (12). Reaction of 3-phenylpropanal (0.20 g, 1.49 mmol) and propargyl chloride (0.21mL, 2.98 mmol), according to the general procedure **A**, afforded product **12** (187 mg, 72%) isolated as light yellow oil.[24]

Dimethyl 4-hydroxy-3-vinylcyclohexane-1,1-dicarboxylate (15). Reaction of compound **14** (0.13 g, 0.40 mmol), according to the general procedure **A**, afforded products **15*cis*** (45 mg, 46%) and **15*trans*** (19 mg, 20%) isolated as yellow oils. Spectral data are in agreement with literature values.[15]

*Synthesis of aldehyde **14**.* To a suspension of NaH (60% dispersion in mineral oil) (0.14 g, 3.56 mmol) in THF (10 mL) at 0ºC under N_2 atmosphere, dimethyl malonate (0.35 g, 2.97 mmol) was added. The mixture was stirred for 1h. Then, a solution of 2-(2-bromoethyl)-1,3-dioxolane (0.56 g, 2.97 mmol) in THF (2 mL) was added dropwise. The mixture was stirred under reflux for 24 h. Aqueous NaCl saturated solution (30 mL) was added and extracted with Et_2O (3x20 mL). The ethereal solution was dried over anhydrous $MgSO_4$. The solvent was removed and the residue was submitted to flash

chromatography (hexane/Et_2O 1:2) to give dimethyl 2-(2-(1,3-dioxolan-2-yl)ethyl)malonate (531 mg, 77%) as a colorless oil. IR (film) *v* (cm^{-1}) 3057, 2955, 2888, 1732, 1437, 1265, 1142, 1029. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 4.87 (t, *J* = 4.5 Hz, 1H), 3.98-3.90 (m, 2H), 3.89-3.81 (m, 2H), 3.73 (s, 6H), 3.46 (t, *J* = 7.2 Hz, 1H), 2.03 (q, *J* =7.8 Hz, 2H), 1.73-1.66 (m, 2H). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$, DEPT) δ (ppm) 169.6 (C), 103.7 (CH), 64.9 (CH_2), 52.5 (CH_3), 51.2 (CH), 31.1 (CH_2), 23.1 (CH_2). To a solution of dimethyl 2-(2-(1,3-dioxolan-2-yl)ethyl)malonate (0.49 g, 2.14 mmol) in THF (12 mL) at 0ºC under N_2 atmosphere, NaH (60% dispersion in mineral oil) (0.09 g, 2.14 mmol) was added. The mixture was stirred for 1 h at room temperature. Then, a solution of (*E*)-1,4-dibromobut-2-ene (0.55 g, 2.56 mmol) in THF (12 mL) was added dropwise. The mixture was stirred under reflux overnight. Aqueous NaCl saturated solution (15 mL) was added and extracted with Et_2O (3x15 mL). The ethereal solution was dried over anhydrous $MgSO_4$. The solvent was removed and the residue was submitted to flash chromatography (hexane/Et_2O 1:2) to give product dimethyl (*E*)-2-(2-(1,3-dioxolan-2-yl)ethyl)-2-(4-bromobut-2-en-1-yl)malonate (460 mg, 59%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.78 (dt, *J* = 14.7, 7.2 Hz, 1H), 5.65 (dt, *J* = 14.7, 7.2 Hz, 1H), 4.87 (t, *J* = 4.5Hz, 1H), 4.00-3.96 (m, 2H), 3.92-3.83 (m, 4H), 3.74 (s, 6H), 2.66 (d, *J* = 7.2 Hz, 2H), 2.01 (dt, *J* = 4.6, 8.3Hz, 2H), 1.59 (m, 2H). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$, DEPT) δ (ppm) 171.2 (C), 130.7 (CH), 129.5 (CH), 103.8 (CH), 64.9 (CH_2), 57.2 (C), 52.5 (CH_3), 35.7 (CH_2), 32.3 (CH_2), 28.6 (CH_2), 26.8 (CH_2). To a solution of dimethyl (*E*)-2-(2-(1,3-dioxolan-2-yl)ethyl)-2-(4-bromobut-2-en-1-yl)malonate (0.09 g, 0.25 mmol) in $CHCl_3$ (8 mL) and water (4 mL) at 0ºC, CF_3COOH (4 mL) was added. The mixture was stirred for 48h at room temperature. Aqueous $NaHCO_3$ saturated solution (15 mL) was added and extracted with $CHCl_3$ (3x20 mL). The organic solution was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was submitted to flash chromatography (hexane/Et_2O 1:2) to give product **14** (53 mg, 66%) as a colorless oil. IR (film) *v* (cm^{-1}) 2955, 1724, 1437, 1201, 1099, 972, 907, 727. $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$, DEPT) δ (ppm) 200.5 (C), 170.9 (C), 131.1 (CH), 129.1 (CH), 56.8 (C), 52.7 (CH_3), 39.1 (CH_2), 36.5 (CH_2), 32.0 (CH_2), 25.3 (CH_2). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{12}H_{18}O_5Br$ 321.0338, 323.0319; Found: 321.0336, 323.0325. Although this compound had been once prepared[11], it was described as quite unstable to obtain $^{13}C\{1H\}$ NMR or HRMS data. However, we have had no problem.

2-Methyltetradeca-1,13-dien-4-ol (27). Reaction of undec-10-enal (0.24 mL, 1.25 mmol) and 3-bromo-2-methylprop-1-ene (**26**) (0.26 mL, 2.50 mmol), according to the general procedure **A**, afforded product **27** (182 mg, 65%) isolated as light yellow oil. IR (film) *v* (cm^{-1}) 3376, 3076, 2925, 1643, 1444, 1075, 994, 906, 890. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.81 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.03-4.90 (m, 2H), 4.88 (br s, 1H), 4.80 (br s, 1H), 3.72 (m, 1H), 2.20 (dd, *J* = 13.5, 3.6 Hz, 1H), 2.12-2.01 (m, 3H), 1.83 (br s, 1H), 1.76 (s, 3H), 1.46 (m, 3H), 1.30 (m, 11H). $^{13}C\{1H\}$ NMR

(75 MHz, $CDCl_3$, DEPT) δ (ppm) 142.9 (C), 139.2 (CH), 114.1 (CH_2), 113.4 (CH_2), 68.7 (CH), 46.2 (CH), 37.1 (CH_2), 33.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 25.7 (CH_2), 22.4 (CH_3). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{29}O$ 225.2218; found: 225.2205.

3,3-Dimethyltetradeca-1,13-dien-4-ol (29) and 2-methylpentadeca-2,14-dien-5-ol (30). Reaction of undec-10-enal (0.24 mL, 1.25 mmol) and **28** (0.30 mL, 2.50 mmol), according to the general procedure **A**, afforded products **29** (179 mg, 60%) and **30** (12 mg, 4%), isolated as light yellow oils. **29:** IR (film) *v* (cm^{-1}) 3415, 3080, 2926, 1640, 1464, 1074, 998, 911. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.90-5.76 (m, 2H), 5.12-4.92 (m, 4H), 3.25 (d, *J* = 9.9 Hz, 1H), 2.05 (q, *J* = 6.6 Hz, 2H), 1.51 (m, 3H), 1.30 (m, 12H), 1.02 (s, 6H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$, DEPT) δ (ppm) 145.6 (CH), 139.2 (CH), 114.1 (CH_2), 113.3 (CH_2), 78.3 (CH), 41.7 (C), 33.8 (CH_2), 31.4 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 27.1 (CH_2), 23.1 (CH_3), 22.0 (CH_3). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{31}O$ 239.2375; found: 239.2380. **30**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.90-5.76 (m, 1H), 5.19 (t, *J* = 7.5 Hz, 1H), 5.19-4.93 (m, 2H), 3.61 (m, 1H), 2.17 (m, 2H), 2.05 (m, 2H), 1.76 (s, 3H), 1.66 (s, 3H), 1.30 (m, 12H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$, DEPT) δ (ppm) 139.2 (CH), 135.2 (C), 120.2 (CH), 114.1 (CH_2), 71.7 (CH), 36.8 (CH_2), 36.2 (CH_2), 33.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 27.1 (CH_3), 26.0 (CH_2), 18.0 (CH_3).

(3*S, 4*S**)-3-Phenyltetradeca-1,13-dien-4-ol (32).** Reaction of undec-10-enal (0.12 mL, 0.63 mmol) and (*E*)-(3-bromoprop-1-en-1-yl)benzene (**31** R=Ph) (0.19 mL, 1.25 mmol), according to the general procedure **A**, afforded product **32** (137 mg, 76%) isolated as light yellow oil. IR (film) *v* (cm^{-1}) 3460, 2925, 1639, 1394, 1070, 994, 911, 700. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.40-7.25 (m, 5H), 6.20 (ddd, *J* = 19.5, 10.2, 9.0 Hz, 1H, H2), 5.86 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1H, H13), 5.29-5.22 (m, 2H, H1), 5.08-4.98 (m, 2H, H14), 3.84 (m, 1H, H4), 3.30 (dd, *J* = 9.3, 7.0 Hz, 1H, H3), 2.13-2.03 (m, 3H), 1.43-1.30 (m, 14H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$, DEPT) δ (ppm) 141.9 (C, C1'), 139.2 (CH, C13), 138.5 (CH, C2), 128.7 (CH), 128.1 (CH), 126.7 (CH), 117.8 (CH_2, C1), 114.2 (CH_2, C14), 74.0 (CH, C4), 57.4 (CH, C3), 34.5 (CH_2), 33.9 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 25.8 (CH_2). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{31}O$ 287.2375; Found: 287.2370.

(3*R, 4*S**)-3-Methyltetradeca-1,13-dien-4-ol (33).** Reaction of undec-10-enal (0.24 mL, 1.25 mmol) and (*E*)-1-bromobut-2-ene (**31** R=CH_3) (0.30 mL, 2.50 mmol), according to the general procedure **A**, afforded product **33** (216 mg, 77%) isolated as light yellow oil. IR (film) *v* (cm^{-1}) 3369, 3077, 2926, 1640, 1460, 996, 910. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.83 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1H), 5.77 (m, 1H), 5.13 (ddd, *J* = 9.3, 2.1, 0.9 Hz, 1H), 5.22 (ddd, *J* = 16.2, 2.1, 1.2 Hz, 1H), 5.01 (ddt, *J* = 17.1, 2.1, 1.5 Hz, 1H), 4.94 (ddt, *J* = 10.2, 2.1, 1.2 Hz, 1H), 3.40 (m, 1H), 2.22 (m, 1H), 2.05 (m, 2H), 1.60 (br s, 1H), 1.51 (m, 1H), 1.39 (m, 4H), 1.30 (br s, 9H), 1.05 (d, *J* = 6.9 Hz, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$, DEPT) δ (ppm) 140.4 (CH), 139.2 (CH), 116.2 (CH_2), 114.1 (CH_2), 74.7

(CH), 44.1 (CH), 34.3 (CH_2), 33.8 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 25.7 (CH_2), 16.3 (CH_3). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{29}O$ 225.2218; Found: 225.2210.

(2*S, 3*S**)-3-Hydroxy-2-vinyltridec-12-en-1-yl acetate (34).** Reaction of undec-10-enal (0.08 mL, 0.38 mmol) and (*E*)-4-bromobut-2-en-1-yl acetate (**31** R=CH_2OAc) (0.14 g, 0.76 mmol), according to the general procedure **A**, afforded product **34** (83 mg, 77%) isolated as light yellow oil. IR (film) *v* (cm^{-1}) 3456, 2926, 2854, 1740, 1640, 1383, 1264, 1235, 913, 734. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.87-5.70 (m, 2H), 5.23 (dd, *J* = 10.5, 1.8 Hz, 1H), 5.16 (br d, *J* = 17.4 Hz, 1H), 5.02-4.90 (m, 2H), 4.27 (dd, *J* = 11.1, 7.8 Hz, 1H), 4.06 (dd, *J* = 11.1, 6.6 Hz, 1H), 3.63 (m,1H), 2.41 (m, 1H), 2.06 (s, 3H), 2.02 (m, 3H), 1.44-1.28 (m, 14H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$, DEPT) δ (ppm) 171.4 (C), 139.2 (CH), 133.9 (CH), 119.2 (CH_2), 114.1 (CH_2), 70.3 (CH), 64.8 (CH_2), 48.6 (CH), 34.9 (CH_2), 33.8 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 25.8 (CH_2), 20.9 (CH_3). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{31}O_3$ 283.2273; Found: 283.2267.

Methyl (2*R, 3*S**)-3-hydroxy-2-vinyltridec-12-enoate (35*anti*) and methyl (2*R**, 3*R**)-3-hydroxy-2-vinyltridec-12-enoate (35*syn*).** Reaction of undec-10-enal (0.24 mL, 1.25 mmol) and methyl (*E*)-4-bromobut-2-enoate (**31** R=COOMe) (0.35 mL, 2.50 mmol), according to the general procedure **A**, afforded product **35*anti*** (104 mg, 31%) and **35*syn*** (34 mg, 10%) isolated as light yellow oils. **35*anti:*** IR (film) *v* (cm^{-1}) 3483, 3078, 2927, 1731, 1642, 1438, 1320, 1199, 1082, 916. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.93 (ddd, *J* = 17.1, 10.1, 9.4 Hz, 1H, H1'), 5.79 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1H, H12), 5.29 (dd, *J* = 10.2, 1.5 Hz, 1H, H2'*cis*), 5.22 (br d, *J* = 16.9 Hz, 1H, H2'*trans*), 5.01-4.89 (m, 2H, H13), 3.91 (m, 1H, H3), 3.71 (s, 3H, OMe), 3.06 (dd, *J* = 9.3, 4.5 Hz, 1H, H2), 2.72 (d, *J* = 3.3 Hz, 1H, OH, exchanged with D_2O), 2.02 (dt, *J* = 6.6, 7.5 Hz, 2H, H11), 1.40 (m, 5H), 1.27 (br s, 9H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$, DEPT) δ (ppm) 173.8 (C, C1), 139.2 (CH, C12), 131.7 (CH, C1'), 120.3 (CH_2, C2'), 114.1 (CH_2, C13), 71.4 (CH, C3), 55.7 (CH_3, OMe), 52.0 (CH, C2), 34.1 (CH_2), 33.8 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 25.6 (CH_2). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{29}O_3$ 269.2117; Found: 269.2136. **35*syn***: IR (film) *v* (cm^{-1}) 3469, 2926, 2855, 1729, 1640, 1437, 1265, 1166, 734. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.81 (m, 2H), 5.26 (dd, *J* = 10.2, 1.5 Hz, 1H), 5.20 (br d, *J* = 16.9 Hz, 1H), 5.02-4.91 (m, 2H), 3.84 (m, 1H), 3.73 (s, 3H), 3.06 (t, *J* = 8.4 Hz, 1H), 2.54 (br s, 1H), 2.02 (m, 2H), 1.40 (m, 2H), 1.27 (br s, 12H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$, DEPT) δ (ppm) 173.6 (C), 139.2 (CH), 132.9 (CH), 119.4 (CH_2), 114.1 (CH_2), 72.3 (CH), 57.0 (CH_3), 52.0 (CH), 34.5 (CH_2), 33.8 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 25.4 (CH_2). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{29}O_3$ 269.2117; found: 269.2125.

(3*R,4*S**)-3,4-Dimethylocta-1,7-dien-4-ol (48).** Reaction of **47** (0.12 mL, 1.02 mmol) and **31** (R=CH_3) (0.25 mL, 2.04 mmol), according to the general procedure **A**, afforded product **48** (115 mg,

73%) isolated as light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.86 (m, 2H), 5.15-4.95 (m, 4H), 2.28 (m, 1H), 2.19 (m, 2H), 1.61-1.56 (m, 3H), 1.13 (s, 3H), 1.03 (d, *J* = 6.9 Hz, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$, DEPT) δ (ppm) 140.2 (CH), 139.1 (CH), 116.4 (CH_2), 114.3 (CH_2), 73.6 (C), 47.4 (CH), 38.9 (CH_2), 27.8 (CH_2), 23.5 (CH_3), 14.9 (CH_3). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{10}H_{19}O$ 155.1436; found: 155.1412.

General procedure B for Ti-induced allylation or propargylation

Under an Ar atmosphere, dry THF (8 mL/1.4 mmol of aldehyde) previously deoxygenated is added to a mixture of $CpTiCl_3$ (1 eq.), Mn dust (2 eq.) resulting a green suspension. Then, a solution of aldehyde (1 eq.) and propargyl chloride or allyl bromide (2 eq.) in THF (2mL/1.4 mmol of aldehyde) is dripped and the mixture is stirred (1-3h for allylation, and 3-5h for propargylation). The mix is filtered, diluted with AcOEt, washed with HCl 3% and brine, dried (anhydrous $MgSO_4$) and the solvent removed. Products are purified by silica gel flash column chromatography (hexane/Et_2O mixtures).

5,9-Dimethyldeca-1,8-dien-4-ol (6). Reaction of 2,6-dimethylhept-5-enal (0.23 mL, 1.43 mmol) and allyl bromide (0.25 mL, 2.86 mmol), according to the general procedure **B**, afforded product **6** (229 mg, 88%), as an inseparable mixture of diastereoisomers (1:1), isolated as light yellow oil. IR (film) *v* (cm^{-1}) 3411, 3077, 2919, 1641, 1440, 1378, 1266, 987, 737. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) both isomers: 5.93-5.78 (m, 1H, H2), 5.20-5.09 (m, 3H, H1, H8), 2.37-1.92 (m, 4H), 1.57 (m, 2H), 1.21 (m, 1H); isomer a: 3.57 (dt, *J* = 8.7, 4.2 Hz, 1H, H4), 1.71 (s, 3H), 1.63 (s, 3H), 0.94 (d, *J* = 5.7 Hz, 3H, H12); isomer b: 3.50 (ddd, *J* = 9.0, 5.4, 3.3 Hz, 1H, H4), 1.70 (s, 3H), 1.62 (s, 3H), 0.93 (d, *J* = 6.6 Hz, 3H, H12). ^{13}C{1H} NMR (75 MHz, $CDCl_3$, DEPT) δ (ppm) both isomers: 135.6, 135.5 (CH, C2), 131.5 (C, C9), 124.6, 124.6 (CH, C8), 118.0, 117.8 (CH_2, C1), 74.5, 73.9 (CH, C4), 39.1, 38.2 (CH_2, C3), 37.8, 37.4 (CH, C5), 33.2 (CH_2), 32.3 (CH_2), 25.7 (CH_3), 25.7 (CH_2), 25.6 (CH_2), 17.7 (CH_3), 15.0 (CH_3), 13.8 (CH_3). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{12}H_{23}O$ 183.1749; found: 183.1719.

2,2-Dimethylhex-5-en-3-ol (7). Reaction of pivalaldehyde (0.26 mL, 2.21 mmol) and allyl bromide (0.38 mL, 4.42 mmol), according to the general procedure **B**, afforded product **7** (235 mg, 83%) isolated as light yellow oil. Spectral data are in agreement with literature values.[25]

5,9-Dimethyldec-8-en-1-yn-4-ol (13). Reaction of 2,6-dimethylhept-5-enal (0.23 mL, 1.43 mmol) and propargyl chloride (0.25 mL, 2.86 mmol), according to the general procedure **B**, afforded product **13** (155 mg, 60%), as an inseparable mixture of diastereoisomers (1:1), isolated as light yellow oil. IR (film) *v* (cm^{-1}) 3446, 3306, 2918, 2118, 1453, 1265, 1049, 735, 635. ^{1}H NMR (300 MHz, $CDCl_3$)

δ (ppm) both isomers 5.16-5.08 (m, 1H), 2.49-2.30 (m, 2H), 2.06 (dt, *J* = 2.7, 0.9 Hz, 1H), 2.04-1.76 (m, 3H), 1.59-1.43 (m, 1H), 1.30-1.14 (m, 1H); isomer a: 3.69 (dt, *J* = 6.3, 4.5 Hz, 1H), 1.71 (s, 3H), 1.63 (s, 3H), 0.95 (d, *J* = 6.3 Hz, 3H); isomer b: 3.60 (ddd, *J* = 7.8, 6.0, 4.2 Hz, 1H), 1.70 (s, 3H), 1.62 (s, 3H), 0.92 (d, *J* = 6.0 Hz, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$, DEPT) δ (ppm) both isomers: 131.6, 131.6 (C), 124.4, 124.3 (CH), 81.5, 81.4 (C), 73.8, 73.2 (CH), 70.7, 70.5 (CH), 37.4, 37.0 (CH), 33.1 (CH_2), 32.2 (CH_2), 25.7 (CH_3), 25.5 (CH_2), 25.4 (CH_2), 24.8 (CH_2), 24.2 (CH_2), 17.7 (CH_3), 15.0 (CH_3), 13.7 (CH_3). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{12}H_{21}O$ 181.1592; Found: 181.1582.

Methyl (2*R, 3*S**)-3-hydroxy-2-vinyltridec-12-enoate (35*anti*) and methyl (2*R**, 3*R**)-3-hydroxy-2-vinyltridec-12-enoate (35*syn*).** Reaction of undec-10-enal (0.12 mL, 0.62 mmol) and **31** (R=COOMe) (0.35 mL, 2.50 mmol), according to the general procedure **B**, afforded product **35*anti*** (90 mg, 54%) and **35*syn*** (45 mg, 27%) isolated as light yellow oils.

(3*R, 4*S**)-3-(Bromomethyl)tetradeca-1,13-dien-4-ol (36).** Reaction of undec-10-enal (0.06 mL, 0.3 mmol) and 1,4-dibromobut-2-ene (**31** R=CH_2Br) (0.14 mL, 0.6 mmol), according to the general procedure **B**, afforded product **36** (55 mg, 60%) isolated as light yellow oil. IR (film) *ν* (cm^{-1}) 3384, 3077, 2925, 2854, 1640, 1462, 1058, 911. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.89-5.71 (m, 2H), 5.27 (d, *J* = 10.2 Hz, 1H), 5.20 (d, *J* = 17.1 Hz, 1H), 5.00 (d, *J* = 17.1 Hz, 1H), 4.94 (d, *J* = 10.5 Hz, 1H), 3.86 (m, 1H), 3.60 (dd, *J* = 9.6, 7.5 Hz, 1H), 3.43 (dd, *J* = 9.6, 6.0 Hz, 1H), 2.43 (m, 1H), 2.05 (q, *J* = 6.9 Hz, 2H), 1.70 (br s, 1H), 1.45 (m, 4H), 1.30 (br s, 10H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$, DEPT) δ (ppm) 139.2 (CH, C13), 134.9 (CH, C2), 119.6 (CH_2, C1), 114.2 (CH_2, C14), 71.3 (CH, C4), 51.2 (CH, C3), 35.1 (CH_2), 34.7 (CH_2), 33.8 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 25.8 (CH_2). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{32}BrO$ 331.1637; found: 331.1658; $[M+H+2]^+$ Calcd 333.1616; found: 333.1630.

(2*S, 3*S**)-2-Vinyltridec-12-ene-1,3-diol (37).** Reaction of undec-10-enal (0.24 mL, 1.25 mmol) and 4-bromobut-2-en-1-ol (**31** R=CH_2OH) (185 mg, 1.23 mmol), according to the general procedure **B** (but with $CpTiCl_3$ (2 eq.) and Mn dust (3 eq.)), afforded product **37** (171 mg, 57%) isolated as light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.98 (m, 2H), 5.40 (bd, *J* = 10.5 Hz, 1H), 5.33 (bd, *J* = 17.4 Hz, 1H), 5.18-5.07 (m, 2H), 3.93 (m, 3H), 2.78 (br s, 2H), 2.47 (m, 1H), 2.18 (m, 2H), 1.61-1.44 (m, 14H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$, DEPT) δ (ppm) 139.3 (CH), 134.9 (CH), 119.0 (CH_2), 114.3 (CH_2), 72.9 (CH), 64.8 (CH_2), 50.8 (CH), 35.0 (CH_2), 33.9 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 26.0 (CH_2). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{29}O_2$ 241.2168; found: 241.2179.

(2*S,3*S**)-2-Vinyloctane-1,3-diol (38).** Reaction of hexanal (0.19 mL, 1.55 mmol) and 4-bromobut-2-en-1-ol (**31** R=CH_2OH) (466 mg, 3.11 mmol), according to the general procedure **B** (but with

$CpTiCl_3$ (2 eq.) and Mn dust (3 eq.)), afforded product **38** (152 mg, 57%) isolated as light yellow oil. ^{1}H NMR and IR spectra data of **38** are in agreement with literature value.[26] ^{13}C{1H} NMR (75 MHz, $CDCl_3$, DEPT) δ (ppm) 134.8 (CH), 118.9 (CH_2), 72.9 (CH), 64.8 (CH_2), 50.7 (CH), 34.9 (CH_2), 31.8 (CH_2), 25.5 (CH_2), 22.6 (CH_2), 14.0 (CH_3). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{10}H_{21}O_2$ 173.1542; found: 173.1524.

Synthesis of compounds 42 and 43. Reaction of compound **41**[18] (61 mg, 0.28 mmol) and (*E*)-bromobut-2-ene (68 µL, 0.56 mmol) according to the general procedure **B**, afforded products **42** (28 mg, 30%) and **43** (14 mg, 15%) as colorless oils. Compound **42**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.78 (m, 1H), 5.15-5.09 (m, 2H), 4.86 (br s, 1H), 4.44 (br s, 1H), 3.63 (s, 3H), 3.46 (ddd, *J* = 12, 6, 0.9 Hz, 1H), 2.43 (m, 1H), 2.19 (m, 2H), 2.05 (m, 3H), 1.84 (m, 3H), 1.60 (m, 3H), 1.49-1.30 (m, 3H), 1.20 (s, 3H), 1.08 (d, *J* = 6.6 Hz, 3H), 0.52 (s, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$, DEPT) δ (ppm) 177.8 (C), 148.7 (C), 140.4 (CH), 116.3 (CH_2), 106.4 (CH_2), 72.6 (CH), 56.3 (CH), 51.6 (CH), 51.1 (CH_3), 45.3 (CH), 44.3 (C), 39.9 (CH_2), 38.7 (CH_2), 38.2 (CH_2), 28.8 (CH_2), 28.8 (CH_3), 26.2 (CH_2), 19.9 (CH_2), 16.1 (CH_3), 12.7 (CH_3). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{35}O_3$ 335.2586; found: 335.2558. Compound **43**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.85 (ddd, *J* = 18.6, 10.5, 8.1 Hz, 1H), 5.17-5.08 (m, 2H), 4.92 (d, *J* = 1.5 Hz, 1H), 4.74 (br s, 1H), 3.64 (s, 3H), 3.52 (m, 1H), 2.43 (m, 1H), 2.22 (m, 2H), 2.06-1.64 (m, 9H), 1.35 (dd, *J* = 12.3, 3 Hz, 1H), 1.21 (s, 3H), 1.09 (d, *J* = 6.9 Hz, 3H), 1.03 (m, 2H), 0.52 (s, 3H). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{35}O_3$ 335.2586; found: 335.2564.

***Tert*-butyl ((4*S*,5*S*)-5-hydroxy-2,6,6-trimethyloct-7-en-4-yl)carbamate (46).** Reaction of compound **45**[27] (0.17 g, 0.80 mmol) and **28** (0.19 mL, 1.60 mmol) according to the general procedure **B** (during 1h 45 min), afforded product **46** (146 mg, 64%). Spectral data are in agreement with literature values.[19]

Methyl 3-hydroxy-3-methyl-2-vinylhept-6-enoate (49). Reaction of **47** (0.24 mL, 2.04 mmol) and **31** (R=COOMe) (0.57 mL, 4.08 mmol), according to the general procedure **B**, afforded product **49** (324 mg, 80%) isolated as light yellow oil as an inseparable mixture of two diastereomers tentatively assigned as (*anti*:*syn*) 77:33). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) signals common to both isomers: 6.05-5.76 (m, 2H), 5.31-5.21 (m, 2H), 5.04 (dd, *J* = 17.1, 1.8 Hz, 1H), 4.96 (d, *J* = 10.2 Hz, 1H), 3.75 (s, 3H), 2.18 (m, 2H), 1.57 (m, 2H); signals due to isomer (*anti*): 3.13 (d, *J* = 9.6 Hz, 1H), 1.18 (s, 3H); signals due to isomer (*syn*): 3.12 (d, *J* = 9.6 Hz, 1H), 1.23 (s, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$, DEPT) δ (ppm) signals common to both isomers: 138.5 (CH), 114.4 (CH_2), 51.9 (CH); signals due to isomer (*anti*) 174.0 (C), 132.5 (CH), 119.8 (CH_2), 73.0 (C), 59.2 (CH), 40.3 (CH_2), 27.9 (CH_2), 23.3 (CH_3); signals due to isomer (*syn*) 173.9 (C), 132.3 (CH), 119.9 (CH_2), 72.7 (C), 59.3 (CH), 38.1 (CH_2), 27.6 (CH_2), 25.2 (CH_3).

General procedure C for Ti-induced allylation of aromatic aldehydes

Under an Ar atmosphere, dry THF (8 mL/1.4 mmol of aldehyde) previously deoxygenated is added to a mixture of $CpTiCl_3$ (1 eq.), Mn dust (2 eq.) resulting a green suspension. A solution of allyl bromide (2 eq.) in THF (1mL/1.4 mmol of aldehyde) is added. Then the aldehyde (1 eq) in THF (1mL/1.4 mmol), is slowly dripped over a period of 40 min and the mixture was stirred for 1-3h. The mix is filtered, diluted in AcOEt, washed with HCl 3% and brine, dried (anhydrous $MgSO_4$) and the solvent removed. Products are purified by silica gel flash column chromatography (hexane/Et_2O mixtures).

1-(3-Methoxyphenyl)but-3-en-1-ol (16) and 1,2-bis(3-methoxyphenyl)ethane-1,2-diol (17) (*dl* and *meso*). Reaction of 3-methoxybenzaldehyde (0.17 mL, 1.43 mmol) and allyl bromide (0.25 mL, 2.86 mmol), according to the general procedure **C**, afforded product **16** (199 mg, 78%) isolated as light yellow oil; and compound **17** as a pale yellow solid (*dl:meso* 6:4 mixture) (75 mg, 19%). Spectral data are in agreement with literature values.[25, 28]

1-(2-Fluorophenyl)but-3-en-1-ol (18) and 1,2-bis(2-fluorophenyl)ethane-1,2-diol (19) (*dl* and *meso*). Reaction of 2-fluorobenzaldehyde (0.17 mL, 1.61 mmol) and allyl bromide (0.28 mL, 3.22 mmol), according to the general procedure **C**, afforded product **18** (174 mg, 65%), compound **19** *meso* (64 mg, 16%) and compound **19** (*dl*) (24 mg, 6%). Compound **18** was isolated as a light yellow oil. Spectral data are in agreement with literature values.[29] ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm) -119.63 (s). Compound **19** *meso* was isolated as a pale yellow solid. m.p.: 176.2 ºC. IR (film) *v* (cm^{-1}) 3399, 3047, 2925, 1587, 1488, 1456, 1224, 1102, 1030, 820, 752, 680. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.31-7.21 (m, 2H), 7.06 (dt, *J* = 7.5, 1.1 Hz, 1H), 6.95 (ddd, *J* = 10.4, 8.2, 1.1 Hz, 1H), 5.39 (s, 1H), 2.67 (brs, 1H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$, DEPT) δ (ppm) 160.1 (d, *J* = 243.8 Hz, C), 129.3 (d, *J* = 8.3 Hz, CH), 128.2 (d, *J* = 4.5 Hz, CH), 126.4 (d, *J* = 12.8 Hz, C), 123.8 (d, *J* = 3.0 Hz, CH), 114.8 (d, *J* = 21.8 Hz, CH), 70.6 (CH). ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm) – 118.80 (s). HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_{14}H_{12}F_2O_2Na$ 273.0703; Found: 273.0672. Compound **19** *dl*. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.43 (dt, *J* = 7.5, 1.7 Hz, 1H), 7.22 (m, 1H), 7.11 (dt, *J* = 7.5, 1.2 Hz, 1H), 6.91 (m, 1H), 5.13 (s, 1H), 3.40 (brs, 1H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$, DEPT) δ (ppm) 159.9 (d, *J* = 245.3 Hz, C), 129.5 (d, *J* = 9 Hz, CH), 128.5 (d, *J* = 4.5 Hz, CH), 126.4 (d, *J* = 13.5 Hz, C), 124.1 (d, *J* = 3.0 Hz, CH), 115.1 (d, *J* = 21.8 Hz, CH), 71.8 (CH).

1-(3-Chlorophenyl)but-3-en-1-ol (20) and 1,2-bis(3-chlorophenyl)ethane-1,2-diol (21) (*dl* and *meso*). Reaction of 3-chlorobenzaldehyde (0.16 mL, 1.42 mmol) and allyl bromide (0.24 mL, 2.84 mmol), according to the general procedure **C**, afforded product **20** (62 mg, 24%) isolated as colorless oil, and compound **21** as a colorless solid (*dl:meso* 7:3 mixture) (193 mg, 48%). Spectral data of **20** are in agreement with literature values.[30] ^{1}H NMR and IR spectra data of **21** are in agreement with

literature values.[31] $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$, DEPT) δ (ppm) 141.6 (C), 141.4 (C), 134.2 (C), 134.2 (C), 129.4 (CH), 129.4 (CH), 128.3 (CH), 127.2 (CH), 127.0 (CH), 125.2 (CH), 125.2 (CH), 78.3 (CH), 77.2 (CH).

1-(4-Bromophenyl)but-3-en-1-ol (22) and 1,2-bis(4-bromophenyl)ethane-1,2-diol (23) (*dl* and *meso*). Reaction of 4-bromobenzaldehyde (0.2 g, 1.08 mmol) and allyl bromide (1.39 mL, 2.16 mmol), according to the general procedure **C**, afforded product **22** (61 mg, 25%) isolated as yellow oil. Spectral data are in agreement with literature values.[21] Compound **23** was also isolated as a colorless oil (*dl:meso* 6:4 mixture) (201 mg, 50%). ^1H NMR spectral data are in agreement with literature values.[32] $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$, DEPT) δ (ppm) 138.4 (C), 138.3 (C), 131.3 (CH), 131.3 (CH), 128.71 (CH), 128.67 (CH), 122.0 (CH), 78.5 (CH), 77.1 (CH).

1-(3,4,5-Trimethoxyphenyl)but-3-en-1-ol (24) and 1,2-bis(3,4,5-trimethoxyphenyl)ethane-1,2-diol (25*dl*). Reaction of 3,4,5-trimethoxybenzaldehyde (0.20 g, 1.02 mmol) and allyl bromide (0.18 mL, 2.04 mmol), according to the general procedure **C**, afforded product **24** (97 mg, 40%) isolated as yellow oil. Spectral data are in agreement with literature values.[21] Compound **25** (*dl*) was also isolated as a solid (64 mg, 16%). m.p.: 177.5ºC. IR (film) *v* (cm^{-1}) 3481, 2989, 2941, 1594, 1508, 1464, 1450, 1229, 1127, 961, 765. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.29 (s, 2H), 4.52 (s, 1H), 3.78 (s, 3H), 3.72 (s, 6H). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$, DEPT) δ (ppm) 152.8 (C), 137.3 (C), 135.6 (C), 103.8 (CH), 71.2 (CH), 60.8 (CH_3), 56.0 (CH_3). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{27}O_8$ 395.1706; found: 395.1729; $[M-H_2O+H]^+$ Calcd for $C_{20}H_{25}O_7$ 377.1595; found 377.1601.

Synthesis of tetrahydrofuran derivative 39. a) $BH_3.Me_2S$ (0.19 mL, 1.86 mmol) was added to a solution of **33** (138 mg, 0.62 mmol) in dry THF (3 mL). The mixture was stirred under N_2 at room temperature for 4 hours. Then, H_2O_2 30% w/w (0.57 mL) and NaOH (230 mg, 5.58 mmol) were subsequently added at 0ºC. Then, the reaction was heated to 40ºC for 4h. The two phases were separated, and the aqueous one was extracted with Et_2O (x2). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (CH_2Cl_2: acetone 7:3) provided (3*R*,4*S*)-3-methyltetradecane-1,4,14-triol (54 mg, 33%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.76 (dt, *J* = 10.8, 5.2 Hz, 1H), 3.64 (t, *J* = 6.6 Hz, 2H), 3.64 (m, 1H), 3.42 (m, 1H), 2.48 (br s, 3H), 1.68-1.65 (m, 2H), 1.60-1.55 (m, 2H), 1.48 (m, 3H), 1.30 (br s, 14H), 0.95 (d, *J* = 6.7 Hz, 3H). b) Mesyl chloride (50 µL, 0.64mmol) was added to a solution of (3*R*,4*S*)-3-methyltetradecane-1,4,14-triol (54 mg, 0.21 mmol), Et_3N (120 µL, 0.84mmol), DMAP (2 mg, 0.012 mmol) in CH_2Cl_2 (5 mL) at 0ºC. After 3h, water (5 mL) was added and the mixture was extracted with CH_2Cl_2(x3). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (hexane:Et_2O 3:7) provided **39** (42 mg, 63%) as a colorless oil. IR (film) *v* (cm^{-1}) 2928, 2855, 1461, 1355, 1175, 904, 726, 648. ^1H NMR (600

MHz, $CDCl_3$) δ (ppm) 4.24 (t, *J* = 6.6 Hz, 2H, H1), 3.82 (m, 2H, H5'), 3.29 (td, *J* = 7.8, 3.6 Hz, 1H, H2'), 3.02 (s, 3H, CH_3OSO_2), 2.08 (dtd, *J* = 19.2, 7.8, 5.4 Hz, 1H, H4a'), 1.81 (m, 1H, H3'), 1.76 (m, 2H, H2), 1.57-1.51 (m, 3H, H10, H4b'), 1.50-1.38 (m, 3H), 1.30 (br s, 11H), 1.04 (d, *J* = 6.7 Hz, 3H, CH_3). $^{13}C\{1H\}$ NMR (150 MHz, $CDCl_3$, DEPT) δ (ppm) 86.0 (CH, C2'), 70.2 (CH_2, C1), 66.7 (CH_2, C5'), 39.0 (CH, C3'), 37.4 (CH_3, CH_3OSO_2), 34.8 (CH_2, C10), 34.4 (CH_2, C4'), 29.8 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.1 (CH_2), 29.0 (CH_2, C2), 26.5 (CH_2), 25.4 (CH_2), 17.3 (CH_3).

Synthesis of ketal derivative 40. 2,2-Dimethoxypropane (54μL, 0.44 mmol) was added to a solution of **37** (53 mg, 0.22 mmol) in anhydrous CH_2Cl_2 (5 mL) under N_2 atmosphere at room temperature. Then, the mixture was cooled at 0ºC and camphor-10-sulfonic acid (10 mg, 0.044 mmol) was added. After 4h at rt, Et_3N (two drops) is added and the solvent removed. Purification by flash chromatography (hexane:ACOEt1:1) provided **40** as an oil (43 mg, 70%). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.24 (dt, 1H, *J* = 17.5, 10.0 Hz, H1'), 5.82 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, H12), 5.16 (dd, *J* = 10.5, 2.0 Hz, 1H, H2'*cis*), 5.10 (d, *J* = 17.0 Hz, 1H, H2'*trans*), 5.00 (d, *J* = 17.5 Hz, 1H, H13*trans*), 4.94 (d, *J* = 10.0 Hz, 1H, H13*cis*), 4.16 (dd, *J* = 11.5, 3 Hz, 1H, H1ax), 3.92 (m, 1H, H3), 3.72 (dd, *J* = 11.5, 1.5 Hz, H1ec), 2.05 (m, 2H, H11), 1.97 (d, *J* = 9.5 Hz, 1H, H2), 1.48 (s, 3H), 1.42 (s, 3H), 1.38 (m, 2H), 1.28 (br s, 12H). $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$, DEPT) δ (ppm) 139.2 (CH, C2), 136.0 (CH, C1'), 116.7 (CH_2, C2'), 114.1 (CH_2, C13), 98.7 (C, C1''), 71.1 (CH, C3), 65.9 (CH_2, C1), 43.1 (CH, C2), 33.8 (CH_2), 33.4 (CH_2), 29.7 (CH_3), 29.5 (CH_2), 29.4 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 24.9 (CH_2), 19.1 (CH_3). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{33}O_2$ 281.2481; found: 281.2502.

Synthesis of derivative 44. Grubbs catalyst 2nd generation (10 mg, 0.012 mmol) was added to a solution of **42** (15 mg, 0.045 mmol) in anhydrous CH_2Cl_2 (10 mL) under N_2 atmosphere. The mixture was heated under reflux overnight, and concentrated *in vacuo*. Purification by flash chromatography (hexane:diethyl ether 7:3) provided **44** as an oil (5 mg, 36%). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.43 (d, *J* = 6.3Hz, 1H), 3.88 (dt, *J* = 12.3, 4.9 Hz, 1H), 3.65 (s, 3H), 2.32 (m, 2H), 2.20 (br d, *J* = 12.9 Hz, 1H), 2.03-1.63 (m, 8H), 1.53-1.45 (m, 2H), 1.21 (s, 3H), 1.07 (m, 2H), 0.96 (d, *J* = 7.2 Hz, 3H), 0.62 (s, 3H). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{31}O_3$ 307.2273; found: 307.2290.

ASSOCIATED CONTENT

Supporting Information. Copies of IR and NMR spectra (PDF)

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