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Pd-catalyzed cross-coupling of allylsilane-vinylcopper species with aryl and vinyl halides: the first total synthesis of (−)-nomadone

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ABSTRACT

The reaction of allene with a lower order silylcuprate **3** leads to an allylsilane-vinylcopper intermediate **4**, which undergoes palladium-catalyzed cross-coupling reaction with both vinyl and aryl halides. The influence of several factors such as the nature of the transition metal used as catalyst, the temperature of the reaction, and the order of addition are studied. This simple methodology allows the synthesis in one step of isoprenylsilanes, which can be conveniently coupled with different isoprenic aldehydes to give several acyclic natural terpenes. Thus, we were able to synthesize, in two steps from allene, the natural monoterpenes (±)-ipsdienol and (±)-ipsenol, which are the principal components of the aggregation pheromone of the bark beetle *Ips paraconfusus*. On the other hand, the allyl-terminated reaction of isoprenylsilane **7** with the natural monoterpene (*S*)-citronellal leads to an intermediate, which is readily converted into the natural sesquiterpene (−)-Nomadone in two almost quantitative steps. The nomadone sesquiterpene is a component of the cephalic gland's secretion of *Nomada* bees. As far as we know this is the first reported total synthesis of (−)-nomadone.

1. Introduction

The search and development of efficient and highly selective methods for the synthesis of complex molecules of both natural and unnatural origin continue to be a challenge in organic synthesis and much effort has been directed toward this goal. Thus, the stereospecific synthesis of conjugated dienes is of considerable importance since a great variety of aliphatic natural products contain the 1,3-diene unit or even higher degrees of conjugation.[1–3] In this sense, metal-catalyzed cross-coupling reactions have shown to be the most reliable strategy for the synthesis of such conjugated alkenes since the method allows the reaction to proceed under very mild conditions and with very high stereoselectivities.[4–6] In particular, palladium-catalyzed cross-coupling reactions of vinyl halides with vinylic metals are now powerful tools for the stereospecific synthesis of polyunsaturated molecules.[7,8] The rate, yield, and scope of the palladium-catalyzed cross-coupling reactions are influenced by both the reaction partners and the choice of ligands of the metal.[9] Historically, palladium-catalyzed cross-coupling reactions used iodides and bromides as the organic acceptors, though the reaction has now being extended to aryl chlorides. The organometallic donors in palladium-catalyzed cross-coupling reactions can be a variety of main group metals (Fig. 1), including both the so-called 'first-generation' Pd-catalyzed cross-couplings [Zn (Negishi reaction),[10] Al,[11] Zr or Mg (Kumada–Tamao–Corriu reaction)[12]] and the 'second-generation' cross-couplings with more electronegative metals such as B (Suzuki–Miyaura reaction),[13] Sn (Stille reaction),[14] and Si (Hiyama reaction).[15]

However, less well developed is the Pd-catalyzed cross-coupling of organocuprates. In fact, whereas alkyl copper or cuprate reagents couple easily with alkyl, alkenyl, aryl or alkynyl halides, the corresponding alkenylcopper or cuprate reagents only react with alkyl and alkynyl halides. Normant et al. reported that lithium alkenylcuprates as well as alkenylcopper reagents showed very little reactivity toward vinyl halides, under Pd catalysis, unless they are transmetallated with zinc halides or activated with magnesium salts, respectively (Scheme 1).[16–18]

On the other hand, allylsilanes display a multitude of functions in organic synthesis as valuable intermediates for the construction of natural occurring products.[19] The usefulness of these versatile building blocks in stereoselective reactions can be attributed both to their ability to react with electrophiles via selective formation of a carbocation β to the silyl group (the so-called β-effect) and to their stability toward a large number of functional groups and reaction conditions. For many years, our research group has been involved in the study of the metallocupration of allenes as a simple and useful methodology for the synthesis of vinyl- and allylsilanes or stannanes.[20] Silylcupration of allene occurs *syn*-stereospecifically

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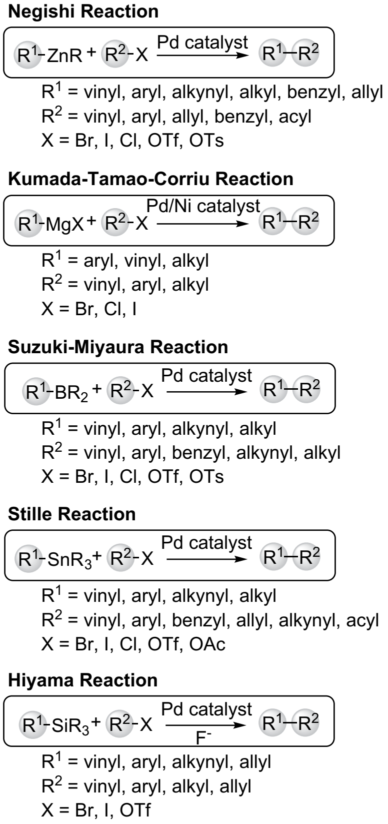
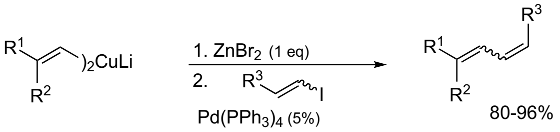
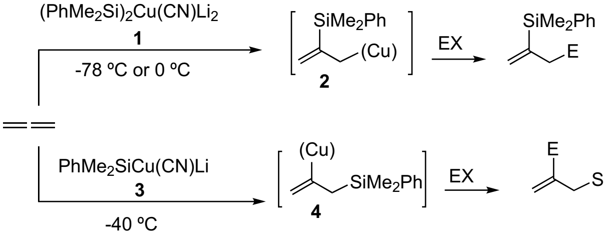


Figure 1. The most commonly used palladium-catalyzed cross-coupling reactions.



Scheme 1. Palladium-catalyzed cross-coupling of alkenyl halides and alkenylcuprates in the presence of $ZnBr_2$.

giving rise to the formation of intermediate cuprates, which react with electrophiles to afford either vinyl or allylsilanes.[21] The regiochemistry of the addition depends on various factors such as the nature of the cuprate, the substitution of the allene, the temperature of the reaction, the nature of the silyl group, and the nature of the electrophile. Thus, the reaction of 1,2-propadiene with higher order silylcyanocuprates **1** containing the phenyldimethylsilyl group gives, at any temperature between −78 °C and 0 °C, a vinylsilane-allylcuprate intermediate **2**, which readily reacts with a wide variety of electrophiles leading to the corresponding vinylsilanes.[21] However, the use of a lower order cuprate $PhMe_2SiCu(CN)Li$ **3** shows the opposite regioselectivity pattern, giving now an allylsilane-vinylcopper intermediate **4**, which offers the possibility of obtaining functionalized allylsilanes (Scheme 2).[22,23]



Scheme 2. Silylcupration of 1,2-propadiene using higher order or lower order cuprates.

In a preliminary communication we reported the palladium mediated coupling reaction of the allylsilane-vinylcopper reagent **3** with alkenyl halides as an alternative isoprenylation method, which can be applied to the construction of terpenoid structures.[24] Here we report in full the scope of this methodology depending on the nature of the catalyst and the vinyl halide used and their application in the synthesis of natural mono- and sesquiterpenes.

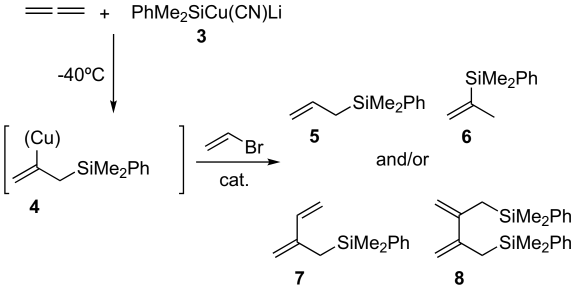
2. Results and discussion

Silylcupration of allene, at −40 °C, using the lower order cuprate **3** gives an allylsilane-vinylcuprate intermediate **4**, which upon treatment with a wide variety of electrophiles affords functionalized allylsilanes in high yields. The only limitation to this otherwise general method is the lack of reactivity of the intermediate **4** with vinyl halides. Encouraged by previous results[16–18] we decided to explore the palladium-catalyzed reaction of our vinylcuprate **4** with vinyl bromide. The results are shown in Table 1.

As it is shown in Table 1 the Pd(II) catalyst, used in entries 1 and 2, is ineffective toward the cross-coupling reaction, giving rise to a rather complex mixture of byproducts (the hydrolysis products **5** and **6**,[25] together with the dimer **8** obtained by homocoupling of the copper reagent). Better results are achieved in the nickel-catalyzed coupling, though the reaction is not clean and moderated yields are obtained. In contrast, the best results are achieved using palladium(0) $Pd(PPh_3)_4$ as the catalyst (Table 1, entries 5 and 6). Moreover an increase of the reaction temperature (from −40 to 0 °C) produces more side products (Table 1, entry 7). The fact that the homo-coupled dimer **8** was obtained as a minor side product in every reaction was not an inconvenient since it could be easily separated on chromatography. We then examined the reaction with other substrates to evaluate the generality of the reaction and the influence of the nature of the halide (Table 2).

The results shown in Table 2 indicate that $Pd(PPh_3)_4$ is always more effective for this coupling than $Ni(acac)_2$. Moreover vinyl iodides give better yields of the Pd-catalyzed cross-coupling product than the bromide derivatives (Table 2, entries 8 and 10) though both are reasonable. On the contrary, the Ni-catalyzed reaction is only acceptable when vinyl bromides are used (Table 2, entries 2

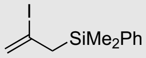
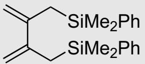
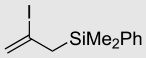
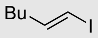
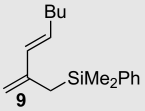
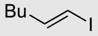
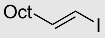
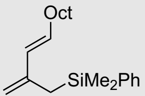
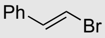
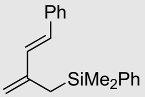
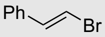
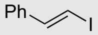
Table 1
Cross-coupling reaction of vinylcuprate **4** with vinyl bromide under different catalysts



Entry	Catalyst[a]	Conditions[b]	5	6	7	8
1	$PdCl_2(MeCN)_2$	**A**	35%	40%	10%	10%
2	$PdCl_2(MeCN)_2$	**B**	30%	35%	15%	10%
3	$Ni(acac)_2$	**A**	10%	20%	60%	5%
4	$Ni(acac)_2$	**B**	5%	15%	65%	10%
5	$Pd(PPh_3)_4$	**A**			85%	8%
6	$Pd(PPh_3)_4$	**B**			86%	10%
7	$Pd(PPh_3)_4$	**C**		10%	50%	30%

[a] 10 mol % of catalyst is used.
[b] Conditions A: −40 °C, 2 h; then −40 to 0 °C, 1 h; conditions B: −40 °C, 4 h; then −40 to 0 °C, 1 h; conditions C: 0 °C, 4 h.

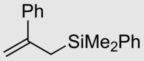
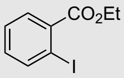
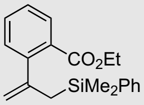
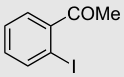
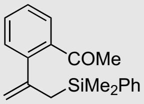
Table 2
Cross-coupling reaction of vinylcuprate **4** with vinyl halides

Entry	Vinyl halide	Catalyst[a]	Product[b]	Yield (%)
1		$Pd(PPh_3)_4$	 **8**	90
2		$Ni(acac)_2$	N.R.	
3		$Pd(PPh_3)_4$	 **9**	89
4		$Ni(acac)_2$	N.R.	
5		$Pd(PPh_3)_4$	 **10**	81
6		$Pd(PPh_3)_4$	 **11**	75
7		$Ni(acac)_2$	**11**	30
8		$Pd(PPh_3)_4$	**11**	87

[a] Compound **4** is added to a cooled solution of the catalyst (10 mol %) and the vinyl halide in THF at −40 °C.

[b] Reaction conditions A shown in Table 1.

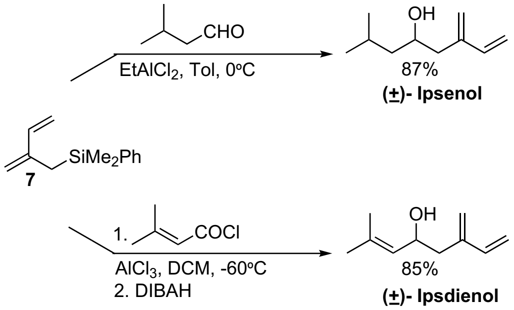
Table 3
Cross-coupling reaction of vinylcuprate **4** with aryl halides

Entry	Aryl halide	Catalyst[a]	Product	Yield (%)
1	PhI	$Pd(PPh_3)_4$	 **12**	88
2	PhBr	$Pd(PPh_3)_4$	N.R.	
3	PhBr	$Ni(acac)_2$	N.R.	
4		$Pd(PPh_3)_4$	 **13**	70
5		$Pd(PPh_3)_4$	 **14**	73

[a] Catalytical amount (10 mol %) of catalyst is used.

and 9 vs 4 and 6). In general, all the reactions proceeded in high yields when 10 mol % of the palladium catalyst is used. Moreover, inverse addition was proved to be advantageous for both higher yield and purity.

As expected, aryl halides also undergo cross-coupling with our allylsilane-vinylcuprate **4** providing excellent coupling partners (Table 3). However, whereas aryl iodides are coupled in high yield (Table 3, entries 1, 4, and 5) the reaction is ineffective with the bromide derivatives (Table 3, entries 2 and 3), which may be ascribed to their lower ability to undergo oxidative addition to Pd(0) in the catalytic cycle. Remarkably, an array of functionality is tolerated including esters and ketones (Table 3, entries 4 and 5).



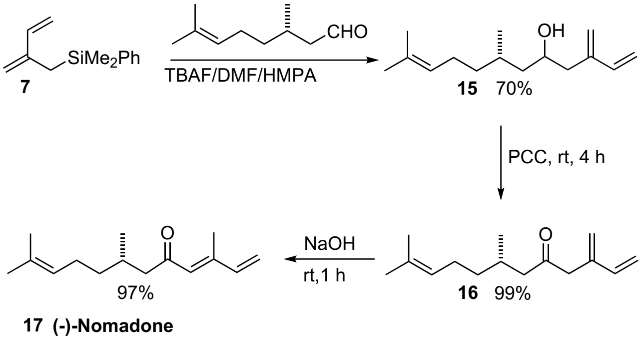
Scheme 3. Synthesis of (±)-ipsenol and (±)-ipsdienol.

The most attractive aspect of this strategy is the possibility of introducing an isoprenyl moiety in a single and high yielding step. In effect, diene **7** can be formally considered as a synthetic equivalent of an isoprenyl anion since allylsilanes are known to be excellent nucleophiles. This methodology has been successfully applied to the synthesis of three isoprenylated naturally occurring products, which are (±)-ipsenol, (±)-ipsdienol and (−)-nomadone. Natural monoterpenes ipsenol and ipsdienol are the principal components of the aggregation pheromones of the bark beetle of California Ponderosa Pine *Ips Paraconfusus Lanier* and have been synthesized several times using different approaches.[26,27]

Thus reaction of isoprenylsilane **7** with isovaleraldehyde in the presence of ethyldichloroaluminum in toluene at 0 °C afforded in 87% yield natural (±)-ipsenol. The use of other catalysts such as BF_3, $TiCl_4$ or TBAF lowers significantly the yield. The corresponding synthesis of (±)-ipsdienol was done by reaction of **7** with 3,3-dimethylacryloyl chloride and subsequent reduction of the enone derivative (Scheme 3).

The interesting acyclic sesquiterpene nomadone **17**, which is a constituent of the mandibular gland secretion of *Nomada* bees that plays an important role in intra- and interspecific territorial behavior, has received much less attention.[28,29] This compound was first described by Francke et al. in 1989,[28] which suggested the name 'nomadone' for the most common sesquiterpene of the genus *Nomada*. It was synthesized[29] in 1991 by the former group as a mixture of *Z*/*E* stereoisomers in racemic form and used for identification purposes. However, investigation of the absolute configuration of the natural nomadone was never attempted and remains unknown.[30] In any case, whatever is the chiral configuration of natural nomadone, it can be easily achieved following the methodology depicted in Scheme 4 and choosing simply (*R*) or (*S*)-citronellal as starting material.

The synthesis of natural (−)-nomadone was accomplished in three high yielding steps. Thus reaction of (*S*)-citronellal with isoprenylsilane **7** under fluoride catalysis (TBAF) gave the Sakurai



Scheme 4. Synthesis of (−)-nomadone.

alcohol in 70% yield. Two standard transformation such as the PCC oxidation of the alcohol to the ketone and a basic catalyzed isomerization of the double bond to the conjugate position afforded natural (−)-nomadone in 67% overall yield (Scheme 4). To our knowledge, the reported synthesis of (−)-nomadone constitutes the first total synthesis described for this compound.

3. Conclusion

The silylcupration of allene, at −40 °C, using a lower order cuprate affords an allylsilane-vinylcuprate intermediate **4**, which effectively participates in metal-catalyzed cross-coupling reactions with vinyl halides. The scope and yield of the reaction are influenced by the choice of the transition metal, the ligands, the temperature of the reaction, and the nature of the reaction partners. The best results are obtained when a 10 mol % of the palladium(0) catalyst is used and the reaction is carried out at −40 °C. Both vinyl and aryl halides are effective as the coupling partner. However, whereas coupling with both vinyl iodides and bromides is allowed, for the aryl derivatives only the iodides are coupled in high yield (possibly due to the lower ability of aryl bromides to undergo oxidative addition to Pd(0) in the catalytic cycle).

The most interesting aspect of this reaction is the possibility of obtaining the isoprenyl intermediate **7** in a single a high yielding step. Moreover diene **7** contains a nucleophilic allylsilane unit, which can participate in Sakurai type's reactions. We have successfully applied this methodology to the synthesis of three natural occurring terpenes, which are (−)-nomadone, (±)-ipsenol, and (±)-ipsdienol.

Thus, starting from allene and in two simple and high yielding steps we are able to obtain natural ipsenol and ipsdienol, which are the principal components of the aggregation pheromones of the bark beetle of California Ponderosa Pine *I. Paraconfusus Lanier*. On the other hand, the *Nomada*-sesquiterpene 3,7,11-trimethyl-1,3,10-dodecatrien-4-one (commonly known as nomadone) is a constituent of the mandibular gland secretion of *Nomada* bees that plays an important role in intra- and interspecific territorial behavior. We here present the total synthesis of the acyclic (*S*)-(−)-sesquiterpene starting from natural monoterpene (*S*)-(−)-citronellal, which undergoes addition of the isoprenylsilane **7**, in the presence of TBAF, to give an intermediate, which is converted into the desired natural product by means of standard transformations. As far as we know this is the first reported total synthesis of (−)-nomadone.

4. Experimental section

4.1. General

All experiments were carried out under a nitrogen atmosphere. Unless otherwise stated, commercial reagents were used as received without further purification. The reactions were carried out in solvents distilled from standard drying agents. THF were freshly distilled from sodium benzophenone ketyl under nitrogen. Aldehydes were freshly distilled under reduced pressure before use. Reactions were monitored by analytical thin-layer chromatography on commercial aluminum sheets pre-coated (0.2 mm layer thickness) with silica gel 60. Product purification by flash chromatography was performed on silica gel (E. Merck 230–400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 300 spectrometer. Optical rotations were determined on a Perkin–Elmer polarimeter at rt.

4.2. General conditions for the obtention of the allylsilane-vinylcopper reagent 4

A solution of dimethylphenylsilyl-lithium (6 mmol) in THF was added by syringe to a stirred suspension of copper(I) cyanide (6 mmol) in THF at 0 °C. After 30 min at this temperature the solution of dimethylphenylsilylcopper **3** (6 mmol) was cooled at −40 °C and a slight excess of allene was added from a balloon. The mixture was stirred for 1 h and then used immediately.

4.3. General conditions for the cross-coupling reaction between vinyl halides and the allylsilane-vinylcopper 4

The solution previously prepared was added, over a period of 30 min, to a flask containing a solution of the vinyl halide (6 mmol) and the catalyst (0.6 mmol) in 10 ml of dry THF at −40 °C. The mixture was stirred for an additional period of 2 h at −40 °C and then allowed to warm to 0 °C. The reaction mixture was then quenched with basic saturated ammonium chloride solution and extracted with ether. The organic layer was dried (MgSO$_4$), evaporated, and chromatographed to give the corresponding products: **5**,[25] **6**,[25] **7**,[31] and **8**–**11** in good yields (see Tables 1 and 2).

4.3.1. 2,3-Bis(dimethylphenylsilylmethyl)butadiene ***8***

Colorless oil; IR: ν_{max} 1600, 1240, 1110, 875 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.59–7.39 (m, 10H), 4.98 (s, 2H), 4.76 (s, 2H), 2.03 (s, 4H), 0.33 (s, 12H); ^{13}C NMR (CDCl$_3$) δ 145.2, 139.4, 133.6, 128.9, 127.7, 111.9, 23.2, −2.6; MS (CI) *m*/*z* 350 [M]$^+$, 335, 270, 135. Anal. Calcd for C$_{22}$H$_{30}$Si$_2$: C, 75.36; H, 8.6. Found: C, 75.02; H, 8.30.

4.3.2. (E)-2-(Dimethylphenylsilylmethyl)octa-1,3-diene ***9***

Colorless oil; IR: ν_{max} 1600, 1250, 1110, 965 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.58–7.38 (m, 5H), 6.08 (d, J=15.6 Hz, 1H), 5.57 (dt, J=15.6 and 7.0 Hz, 1H), 4.83 (s, 1H), 4.67 (s, 1H), 2.08 (q, J=7.0 Hz, 2H), 1.97 (s, 2H), 1.35 (m, 4H), 0.93 (t, J=7.0 Hz, 3H), 0.32 (s, 6H); ^{13}C NMR (CDCl$_3$) δ 143.3, 139.3, 133.6, 132.7, 131.2, 128.8, 127.6, 112.2, 32.4, 31.5, 22.3, 21.3, 13.9, −2.8; MS (CI) *m*/*z* 258 [M]$^+$, 201, 183, 167, 135. Anal. Calcd for C$_{17}$H$_{26}$Si: C, 79.00; H, 10.14. Found: C, 79.41; H, 10.40.

4.3.3. (E)-2-(Dimethylphenylsilylmethyl)dodeca-1,3-diene ***10***

Colorless oil; IR: ν_{max} 1600, 1250, 970 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.56–7.35 (m, 5H), 6.06 (d, J=15.6 Hz, 1H), 5.54 (dt, J=15.6 and 7.0 Hz, 1H), 4.81 (s, 1H), 4.65 (s, 1H), 2.04 (q, J=7.0 Hz, 2H), 1.95 (s, 2H), 1.41–1.20 (m, 12H), 0.91 (t, J=7.0 Hz, 3H), 0.30 (s, 6H); ^{13}C NMR (CDCl$_3$) δ 143.3, 139.3, 133.6, 132.7, 131.2, 128.9, 127.6, 112.2, 32.8, 31.9, 29.5, 29.4, 22.7, 21.4, 14.1, −2.8; MS (CI) *m*/*z* 314 [M]$^+$, 223, 201, 169, 135. Anal. Calcd for C$_{21}$H$_{34}$Si: C, 80.18; H, 10.89. Found: C, 79.85; H, 10.55.

4.3.4. (E)-3-(Dimethylphenylsilylmethyl)-1-phenylbuta-1,3-diene ***11***

Colorless oil; IR: ν_{max} 1600, 1580, 1250, 1110, 950 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.61–7.27 (m, 10H), 6.81 (d, J=16.2 Hz, 1H), 6.40 (d, J=16.2 Hz, 1H), 5.08 (s, 1H), 4.88 (s, 1H), 2.10 (s, 2H), 0.35 (s, 6H); ^{13}C NMR (CDCl$_3$) δ 145.7, 143.4, 139.1, 132.9, 132.7, 131.8, 129.1, 127.9, 127.8, 127.4, 127.7, 115.6, 21.6, −2.7; MS (CI): *m*/*z*: 278 [M]$^+$, 200, 187, 183, 136, 135. Anal. Calcd for C$_{19}$H$_{22}$Si: C, 81.95; H, 7.96. Found: C, 82.32; H, 8.28.

4.4. General conditions for the cross-coupling reactions between aryl halides and the allylsilane-vinylcopper 4

A solution of **7** (6 mmol) was added, over a period of 30 min, to a flask containing a solution of the aryl halide (6 mmol) and the catalyst (0.6 mmol) in 10 ml of dry THF at −40 °C. The mixture was stirred for an additional period of 2 h at −40 °C and then allowed to warm to 0 °C. The reaction mixture was then quenched with basic saturated ammonium chloride solution and extracted with ether. The organic layer was dried (MgSO$_4$), evaporated, and chromatographed to give products **12**–**14** in good yields (see Table 3).

*4.4.1. 2-Phenyl-3-dimethylphenylsilylprop-1-ene **12***

Colorless oil; IR: ν_{max} 1610, 1250, 1110, 880 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.53–7.26 (m, 10H), 5.19 (d, J=1.2 Hz, 1H), 4.89 (d, J=1.2 Hz, 1H), 2.30 (s, 2H), 0.20 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 146.0, 142.7, 138.9, 133.6, 129.0, 128.2, 127.8, 127.3, 126.5, 111.1, 25.3, −2.9; MS (CI): *m*/*z*: 252 [M]$^+$, 197, 174, 159, 135. Anal. Calcd for $C_{17}H_{20}Si$: C, 80.89; H, 7.99. Found: C, 81.11; H, 8.22.

*4.4.2. Ethyl 2-(3-(dimethylphenylsilyl)prop-1-en-2-yl)benzoate **13***

Colorless oil; IR: ν_{max} 1720, 1600, 1280, 1110, 880 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.78 (dd, J=7.6 and 1.6 Hz, 1H), 7.49–7.26 (m, 7H), 7.13 (dd, J=7.6 and 1.6 Hz, 1H), 4. 79 (s, 1H), 4.91 (s, 1H), 4.36 (q, J=7.1 Hz, 2H), 2.91 (s, 2H), 1.39 (t, J=7.1 Hz, 3H), 0.18 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 168.1, 147.5, 145.2, 138.6, 133.5, 131.2, 129.9, 129.5, 128.8, 127.6, 126.9, 112.3, 61.0, 27.8, 14.1, −3.0. Anal. Calcd for $C_{20}H_{24}SiO_2$: C, 74.03; H, 7.45. Found: C, 74.37; H, 7.79.

*4.4.3. 2-(3-(Dimethylphenylsilyl)prop-1-en-2-yl)phenyl methyl ketone **14***

Colorless oil; IR: ν_{max} 1680, 1620, 1250, 1110, 880 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.40–7.30 (m, 9H), 5.00 (s, 1H), 4.96 (s, 1H), 2.54 (s, 3H), 2.11 (s, 2H), 0.17 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 203.6, 147.3, 143.2, 138.9, 138.3, 133.5, 130.8, 129.7, 128.9, 128.0, 127.6, 127.2, 126.5, 113.6, 29.9, 28.2, −3.1. Anal. Calcd for $C_{19}H_{22}SiO$: C, 77.50; H, 7.53. Found: C, 77.81; H, 7.82.

4.5. Synthesis of (±)-ipsenol

To a solution of $EtAlCl_2$ (1 mmol, 1.8 M in toluene) in 5 ml of dry toluene, at 0 °C and under nitrogen, was added dropwise a mixture of isovaleraldehyde (1 mmol) and the diene **7** (1.2 mmol) in 2 ml of dry toluene. The mixture is stirred for 30 min at 0 °C and then quenched with $NaHCO_3$ satd solution, and extracted with ether. The organic layer was dried ($MgSO_4$), evaporated, and chromatographed to give the corresponding natural product in 87% yield. All the analytical data were in agreement with those reported in the literature.[26e]

4.6. Synthesis of (±)-ipsdienol

To a solution of $AlCl_3$ (1 mmol, 134 mg) in 3 ml of dry DCM, at −60 °C and under nitrogen, was added dropwise a solution of 3,3-dimethylacryloyl chloride (1 mmol) in 1 ml of dry DCM. This solution was transferred to another flask containing a solution of 1 mmol of diene **7** in 3 ml of dry DCM at −60 °C. The mixture is stirred for 15 min, then quenched with saturated ammonium chloride and extracted with ether. The organic layer was dried ($MgSO_4$), evaporated, and used immediately.

To a solution of the previously prepared enone in 5 ml of dry toluene, at −40 °C and under nitrogen, was added 2 mmol of DIBAL (1.33 ml, 1.5 M in toluene). The mixture is stirred for 4 h at −40 °C and then allowed to warm to 0 °C. The reaction mixture is quenched with saturated ammonium chloride and extracted with ether. The organic layer was dried ($MgSO_4$), evaporated, and chromatographed to give the natural product in 85% overall yield. All the analytical data were in agreement with those reported in the literature.[26d]

4.7. Synthesis of (−)-nomadone

*4.7.1. (7S)-7,11-Dimethyl-3-methylenedodeca-1,10-dien-5-ol **15***

To a solution of (*S*)-citronellal (0.2 ml, 1.2 mmol) and 7 (1.5 mmol), in a mixture of DMF (2 ml) and HMPA (0.32 ml, 1.8 mmol) at 45 °C and under nitrogen, was added TBAF (0.25 ml, 1 M in THF). The mixture was stirred for 2 h at 45 °C and then quenched with brine, extracted with ether, dried, evaporated, and chromatographed to give a mixture of diastereomeric alcohols **15** in 69% yield as a colorless oil; IR: ν_{max} 3600, 3500, 1600, 1000, 900 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.40 (dd, J=17.6 and 10.7 Hz, 1H), 5.25 (d, J=17.6 Hz, 1H), 5.18–5.17 (m, 4H), 3.84 (m, 1H), 2.51 (td, J=13.8 and 3.5 Hz, 1H), 2.17 (dd, J=13.8 and 8.8 Hz, 1H), 1.98 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.64–1.20 (m, 5H) 0.94 (d, J=6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 143.1, 138.4, 131.2, 124.7, 118.5, 114.2, 67.5, 44.7, 40.7, 36.6, 29.3, 25.7, 25.4, 20.2, 19.1; MS (CI) *m*/*z* 222 [M]$^+$, 207, 205, 195, 193, 189, 136, 135, 121, 109. Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.36; H, 12.09.

*4.7.2. (S)-7,11-Dimethyl-3-methylenedodeca-1,10-dien-5-one **16***

A suspension of the alcohols **15** and PCC/aluminium oxide in hexane was stirred for 4 h at rt. The solution is filtered and the oxidation reagent washed three times with ether. The combined filtrates are evaporated to give compound **16** in 99% yield as a colorless oil, which doesn't need further purification; $[\alpha]_D^{20}$ −14 (*c* 0.5, $CHCl_3$); IR: ν_{max} 1710, 1600, 930, 850 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.42 (dd, J=17.5 and 10.8 Hz, 1H), 5.26 (s, 1H), 5.13 (d, J=17.5 Hz, 1H), 5.12 (s, 1H), 5.11 (d, J=10.8 Hz, 1H), 5.08 (t, J=6.5 Hz, 1H), 3.27 (s, 2H), 2.44 (dd, J=16.5 and 5.5 Hz, 1H), 2.27 (dd, J=16.5 and 8.0 Hz, 1H), 2.04–1.89 (m, 3H), 1.68 (s, 3H), 1.59 (s, 3H), 1.35–1.23 (m, 2H), 0.88 (d, J=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 208.4, 140.0, 138.0, 131.4, 124.3, 120.2, 115.0, 48.5, 47.4, 36.8, 28.5, 25.7, 25.4, 19.6, 17.6; MS (CI) *m*/*z* 220 [M]$^+$, 207, 202, 187, 177, 159, 109, 69, 41. Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 82.06; H, 11.26.

*4.7.3. (S)-3,7,11-Trimethyldodeca-1,3,10-trien-5-one **17***

To a solution of the enone **16** in 2 ml of H_2O, 2 ml of EtOH, and 2 ml of THF was added 5 ml of a solution of 0.5 M NaOH. The mixture was stirred at rt for 1 h and then extracted with ether, washed with brine, dried, evaporated, and chromatographed to give (−)-nomadone **17** in 90% yield as a colorless oil; $[\alpha]_D^{20}$ −21.3 (*c* 1.0, $CHCl_3$); IR: ν_{max} 1680, 1620, 1590, 1050, 980 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.35 (dd, J=17.4 and 10.6 Hz, 1H), 6.12 (s, 1H), 5.64 (d, J=17.4 Hz, 1H), 5.43 (d, J=10.6 Hz, 1H), 5.08 (br t, J=7.1 Hz, 1H), 2.46 (dd, J=15.1 and 5.7 Hz, 1H), 2.25 (dd, J=15.1 and 8.1 Hz, 1H), 2.22 (s, 3H), 2.04–1.92 (m, 3H), 1.66 (s, 3H), 1.58 (s. 3H), 1.38–1.20 (m, 2H), 0.90 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 201.9, 149.6, 140.5, 131.3, 127.3, 124.3, 120.3, 52.1, 37.0, 29.4, 25.7, 25.4, 19.7, 17.6, 13.3; MS (CI) *m*/*z* 220 [M]$^+$, 203, 193, 187, 177, 163, 135, 109, 69, 43, 41. Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 82.12; H, 11.31.

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