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Total Synthesis of nor-1,6-Germacradien-5-ols

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The first total synthesis of (±)-nor-1,6-germacradien-5-ols is described. The synthetic route involves the RCM methodology for the ring formation and a selective 1,2 addition of MeLi to cyclodecenone. By altering the order of the last synthetic steps, TBSO-protected (±)-(1*Z*,6*E*)-nor-1,6-germacradien-5-ols (±)-(5*S**,8*R**)-16 and -(±)-(5*S**,8*S**)-16 were obtained. The synthetic strategy via cyclodecenone offers the possibility of preparing different analogues of the title compounds through addition of other nucleophiles. Moreover, nor-germacrene D could be accessed from the target molecule by methylenation of its carbonyl moiety. (±)-nor-1,6-Germacradien-5-ol [(±)-(1*E*,5*S**,6*E*,8*S**)-**2**] was synthesized in eight steps from isovaleric acid. The 10-membered ring was formed by RCM, and the tertiary alcohol moiety was introduced in the last step via a highly diastereoselective addition of MeLi to (±)-(1*E*,6*E*)-1,6-cyclodecen-5-one (±)-*E*,*E*-**5**. Addition of MeLi to cyclodecenone (±)-*Z*,*E*-**5** also occurred with complete selectivity to provide (±)-(1*Z*,5*S**,6*E*,8*S**)-**2**. A slightly different synthetic pathway was also explored, in which the order of the final synthetic steps was switched: the enone formation and the addition of MeLi were conducted prior to the cyclization. When the hydroxy group was protected as a TBS ether, the newly formed olefin had exclusively *Z* configuration. Thus, TBSO-protected (±)-(1*Z*,6*E*)-nor-1,6-germacradien-5-ols (±)-**16** were obtained as a 1:1 (5*S**,8*S**)/(5*R**,8*S**) mixture. The NMR spectra of these two diastereomers confirmed the relative stereochemistry of natural (−)-1,6-germacradien-5-ol (**1**) at C5 and C8.

Introduction

Extensive forest areas are defoliated every year by larvae of various insects. In Europe alone, thousands of hectares of pines are damaged by members of the *Diprionidae* family (conifer or pine sawflies).[1] The European pine sawfly *Neodiprion sertifer* exhibits outbreaks that last around 3 years at a time and cause an approximately 33% reduction in the growth of pine trees over a 10 year period. This outbreak corresponds to an important economic loss (of about 500 Euro/hectare),[1b] which makes monitoring the sawfly density a clear goal for forest research. Pesticides have been classically used for that purpose, despite their well-know drawbacks, such as polluting effects and killing other insects. More recently, pheromones have been studied as a means to control the population of sawfly species, and some progress has been achieved in this field.[1b] A different approach would be to elucidate the resistance mechanisms that pines use against *N. sertifer* and use the chemicals involved in those mechanisms as natural weapons against larvae. Various studies have shown that variations in the composition of the resin secreted by pines, as a part of the chemical defense of the tree against herbivores, affect the larval development time as well as the risk of mortality of the larvae.[2] Larvae sequester the resin of the host tree and use it as a defense secretion against its predators (ants, spiders, wasps, and birds). The defense secretion of larvae, similar to the needle resin, mainly consists of mono-, di-, and sesquiterpenes.[2] 1,6-Germacradien-5-ol **1**[3] (Scheme 1) is a major component of the sesquiterpene fraction of the resin of several pine varieties. To the best of our knowledge, no synthesis of **1** has yet been published.[4] Toward that direction, we recently reported[5] the formation of a 10-membered ring via ring-closing metathesis.[6] This ring is a direct precursor of (±)-nor-1,6-germacradien-5-ol [(±)-**2**].[7]We believe that **2** might exhibit properties similar to those of **1**, as the allylic alcohol is most likely the active moiety in the molecule. Here, we describe the total synthesis of (±)-nor-1,6-germacradien-5-ol [(±)-**2**], a direct analogue and a model compound for **1**.

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(1) (a) Wagner, M.; Raffa, K. F. *Sawfly Life Story: Adaptation to Woody Plants*; Academic Press: San Diego, 1993. (b) PHERODIP *Pine Sawfly Pheromones for Sustainable Management of European Forest*; European Community Contract No. FAIR1-CT95-0339. Final report.

(2) (a) Larsson, S.; Björkman, C.; Gref, R. *Oecologia* **1986**, *70*, 77−84. (b) Bergström, G.; Wassgren, A.-B.; Birgersson, G. *Acta Chem. Scand.* **1994**, *48*, 187−188.

(3) Bohlmann, F.; Knoll, K.-H.; Zdero, C.; Mahanta, P.; Grenz, M.; Suwita, A.; Ehlers, D.; Van, N. L.; Abraham, W.-R.; Natu, A. A. *Phytochemistry* **1977**, *16*, 965−985.

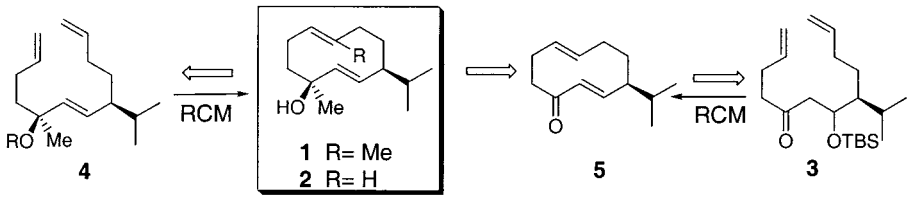
(4) A first attempt was carried out: Nordin, O. Ph.D. Thesis, Royal Institute of Technology, Stockholm, Sweden, 1999.

(5) Nevalainen, M.; Koskinen, A. M. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 4060−4062.

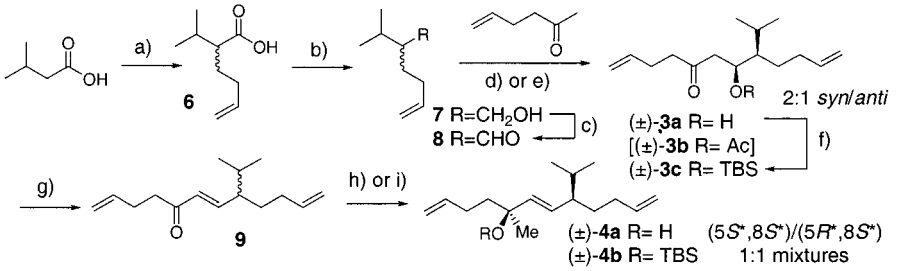
(6) (a) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073−2077. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (c) Trnka, T. M.; Grubbs, R. *Acc. Chem. Res.* **2001**, *34*, 18−29.

(7) Initially we believed that nor-1,6-germacradien-5-ol (**2**) was also a natural product (CA registry number: 71046-98-5) because it is described in the literature as a compound different from **1** (CA registry number: 74841-87-5). However, when the literature was carefully examined, it became clear that such a compound must have originated from a printing error (Zdero, C.; Bohlmann, F.; Solomon, J. C.; King, R. M.; Robinson, H. *Phytochemistry* **1989**, *28*, 531−542) and that the only naturally occurring sesquiterpene is **1**. This result is logical, as sesquiterpenes are biosynthetically formed from (*E*,*E*)-farnesyl diphosphate and therefore should incorporate the −CH═C(Me)− unit.

Scheme 1. Retrosynthetic Analysis for nor-1,6-Germacradien-5-ol (2)

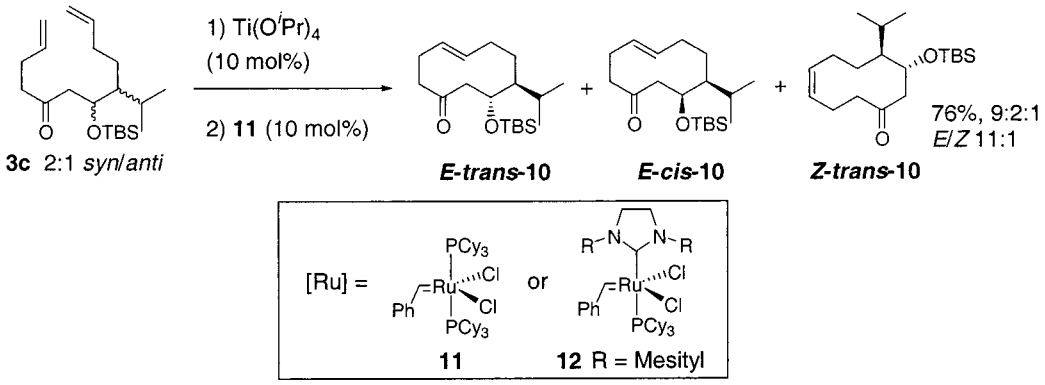


Scheme 2. Synthesis of Racemic Precursors 3 and 4[a]



[a] Reagents and conditions: (a) i. NaH; ii. LDA; iii. $Br(CH_2)_2CH{=}CH_2$; (b) $LiAlH_4$, THF; (c) PCC, NaOAc, CH_2Cl_2; (d) i. LDA, THF, −78 °C; ii. Ac_2O; (e) LDA, THF, −78 °C; (f) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (g) DBU, THF, 0 °C; (h) MeLi, Et_2O, −35 °C; (i) $AlMe_3$, MeLi, TBSOTf, THF, −78 °C.

Scheme 3. RCM Reaction of Bisolefin (±)-3c



Results and Discussion

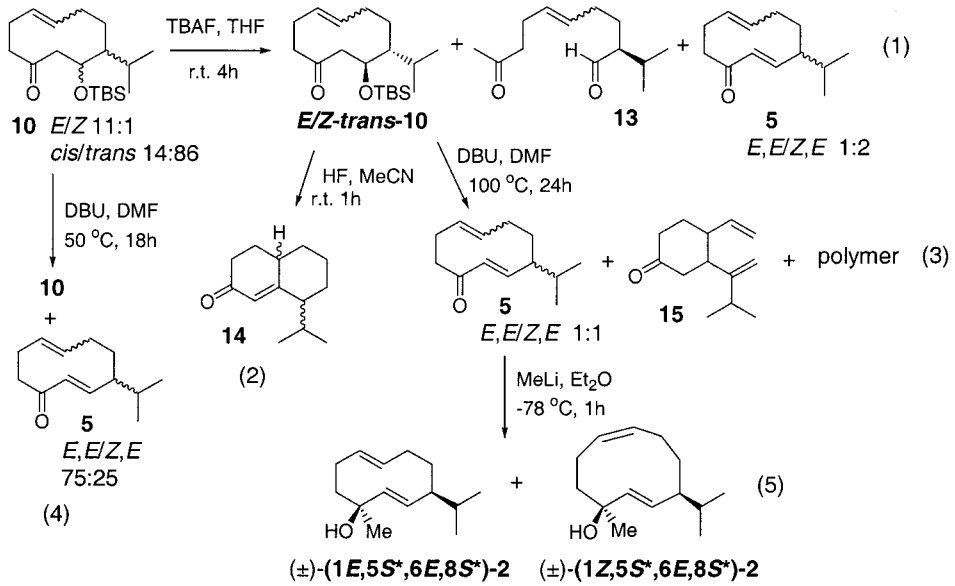
According to retrosynthetic analyses, (±)-nor-1,6-germacradien-5-ol [(±)-**2**] could be accessed by RCM from racemic bisolefins **3** and trisolefins **4** (Scheme 1), obtained from isovaleric acid as shown in Scheme 2.

Alkylation of isovaleric acid with 4-bromobutene gave acid **6**, which was reduced with $LiAlH_4$ and subsequently oxidized with buffered PCC to provide aldehyde **8**. Condensation of **8** with 5-hexen-2-one gave a 2:1 syn/anti mixture of aldol products (±)-**3a** in 43% overall yield from isovaleric acid. Protection of the hydroxy group with TBSOTf was achieved in 92% yield. Aldols (±)-**3a** were trapped in situ with excess acetic anhydride to give acetates (±)-**3b** (not isolated), which upon treatment with DBU underwent elimination to enone **9** (56% yield from **8**). 1,2 addition of MeLi to **9** provided a 1:1 (5*S**, 8*S**)/(5*R**, 8*S**) mixture of allylic alcohols (±)-**4a** in 85% yield. Attempted protection of alcohol (±)-**4a** with TBSOTf and 2,6-lutidine in CH_2Cl_2 at 0 °C gave the corresponding elimination products. One-pot MeLi addition−TBSO protection was achieved following the method of Kim and Park.[8] Thus, the silyl ethers (±)-**4b** were obtained as a 1:1 (5*S**, 8*S**)/(5*R**, 8*S**) mixture in 90% yield.

Cyclization of (±)-**3c** in the presence of 10 mol % of the binary system Grubbs' catalyst, $Ti(O^iPr)_4$, in refluxing dichloromethane (0.56 mM, 36 h) yielded an 11:1 *E*/*Z*−14:86 *cis*/*trans* mixture of cycles (±)-**10** in 76% yield (Scheme 3).[5] The unwanted *Z* isomer was the minor component of the mixture; therefore, we decided to explore the selectivity of the ring closure in the presence of the second-generation carbene complex **12**, as NHC-containing metathesis catalysts had been shown to be particularly *E* selective.[9] However, when (±)-**3c** was treated under the same RCM reaction conditions described above but with Ru carbene **12**, a 1:6 *E*/*Z* mixture of *trans*-**10** was obtained. *E*-*cis*-**10** was formed only in trace amounts, which along with the fact that no starting bisolefin was recovered indicates that (±)-*anti*-**3c** polymerizes instead of cyclizing in the presence of Nolan's catalyst (**12**). The TBSO moiety of bisolefin (±)-**3c** might be responsible for the formation of *Z*-**10** as the major diastereomer when **12** is used,[10] which is another example of the concept first introduced by Fürstner and co-workers that a distant hydroxy group can exert remote control over olefin geometry.[10] The authors concluded

(9) Lee, C. W.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 2145−2147.
(10) Fürstner, A.; Thiel, O. R.; Blanda, G. *Org. Lett.* **2000**, 2, 3731−3734.

Scheme 4. Synthesis of (±)-2 from Diastereomeric Cycles 10

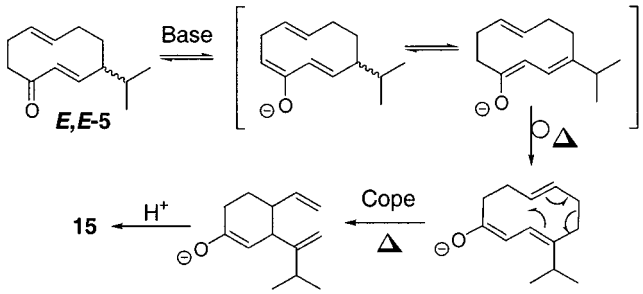


that the configuration of the newly formed olefin is dependent on the substrate rather than on the catalyst, even if second-generation ruthenium carbenes are used.

Our synthetic endeavors toward (±)-nor-1,6-germacradien-5-ol [(±)-**2**] from 10-membered rings **10** are outlined in Scheme 4.

An attempt to deprotect the TBSO ethers **10** with TBAF at rt gave a mixture of unreacted starting material, retroaldol product **13**,[5] and enone **5** (1:2 *E*,*E*/*E*,*Z* mixture) (Scheme 4, eq 1). This result indicates that the 10-membered aldol is unstable and either undergoes a retroaldol reaction to release its transannular strain or eliminates to form enone **5**. Indeed, the target aldol was also not obtained by treatment of *E*/*Z*-*trans*-**10** with 40% HF in acetonitrile at rt. Clean formation of bicyclic unsaturated ketone **14**[11] occurred instead (Scheme 4, eq 2). Similar cyclizations have been observed for germacradienol **1** in the presence of traces of acid or when promoted by heat.[12] In view of those results, we decided to explore the direct elimination of the TBSO group with DBU.[13] Treatment of **10** with DBU in CH_2Cl_2 at reflux for several hours was not effective. When more drastic conditions were used (DMF at 100 °C), the desired elimination took place, yielding the *E*-enone exclusively. However, a difference in the reaction rate of diastereomers **10** was observed, with the order of reactivity *E*-*cis*-**10** > *E*-*trans*-**10** > *Z*-*trans*-**10**. This difference in reactivity originates from steric hindrance at the C(6)H_2 protons. In the case of the cis isomer, those protons are more accessible to the bulky base than are those in the trans isomers. Indeed, on the basis of molecular models, the H6 protons of *trans*-**10** are located in a pocket-type cavity formed by the cycle and the isopropyl group. Consequently, the desilylation of a diastereomeric mixture of **10** requires a prolonged reaction time. After 24 h of treating an 11:1 *E*/*Z*-*trans*-**10** mixture at 100 °C, only some unreacted *Z*-**10** remained, but, to our surprise, enone **5** was obtained in low yield (39%) as a 1:1 inseparable *E*,*E*/*Z*,*E* mixture (Scheme 4, eq 3). NMR spectra of a series of experiments carried out at different reaction times revealed that at 100 °C enone *E*,*E*-**5** underwent a Cope rearrangement to give bisolefin **15** (Scheme 5), which in turn decomposed. A similar rearrangement does not take place on the *E*,*Z*-enoate because in that case it is electronically disfavored. This result explains the enrichment observed for the *E*,*Z* isomer. Lowering the temperature did not solve the problem. When an 11:1 *E*/*Z*−14:86 cis/trans mixture of **10** was treated with excess DBU at 50 °C for 18 h, enone **5** was obtained in 34% yield as a 75:25 *E*,*E*/*Z*,*E* mixture (Scheme 4, eq 4). Carbacycles **10** were recovered in 51% yield as a 9:1 *E*/*Z* mixture. Finally, *E*,*E*-**5** was obtained from *E*-*trans*-**10**, previously isolated by flash chromatography. To minimize decomposition, the reaction was stopped after 8 h, yielding 29% of the enone and 63% of the recovered cycle, which could be recycled.

Scheme 5. Cope Rearrangement of Enone *E*,*E*-5



Addition of MeLi to enone *E*,*E*-**5** proceeded with complete diastereoselection to give (±)-(1*E*,5*S**,6*E*,8*S**)-**2** (Scheme 4). The nucleophile attacked the less hindered side of the carbonyl, as shown in Scheme 6.

This selectivity was not exclusive for the *E*,*E* isomer but was also exhibited by *Z*,*E*-**5**. Thus, when a 1:1 mixture of *E*,*E*/*Z*,*E*-**5** was treated with MeLi under the same reaction conditions, only the (5*S**,8*S**) isomers *E*,*E*-**2** and *Z*,*E*-**2** were obtained (Scheme 4, eq 5). Although conformational analyses of *Z*,*E*-1,6-cyclodeca-

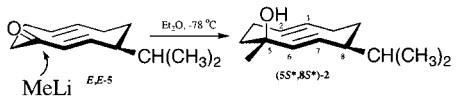
(11) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrel, R. *J. Am. Chem. Soc.* **1963**, *85*, 207−222.

(12) (a) Nordin, O.; Hedenström, E.; Högberg, H.-E. *Acta Chem. Scand.* **1999**, *53*, 124−132. (b) Schmaus, G.; Schultze, W.; Kubeczka, K.-H. *Planta Med.* **1989**, *55*, 482−487.

(13) Hareau, G. P-J.; Koiwa, M.; Hikichi, S.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 3640−3650.

(14) Neykov, G. D.; Ivanov, P. M.; Orahovats, A. S. *THEOCHEM* **1987**, *38*, 147−158.

Scheme 6. 1,2-Addition of MeLi to *E,E*-5 by the Less Hindered Carbonyl Face[a]



[a] The *E,E*-1,6-cyclodecadiene systems are drawn in the most stable "chair-chair" conformation based on computational studies conducted on their analogs.[14]

Table 1. ^{1}H NMR Data in $CDCl_3$ for 1,6-Germacradien-5-ol (1) and nor-1,6-Germacradien-5-ols 2 and 16

compound	configuration C5,C8	δ_{H6} (d)	δ_{H7} (dd)	reference
1	*R,S*	5.17	5.25	3, 15a
1	*S,S*	5.25	5.17	15a
1	*R*,S**	5.24	5.19	15b
1	*R,R*	5.25	5.18	15c
1	*S,S*	5.25	5.18	12
(*E,E*)-**2**	*S*,S**	5.13	5.02	[a]
(*Z,E*)-**2**	*S*,S**	5.21	5.11	[a]
(*Z,E*)-**16**	*S*,S**	5.26	4.90	[a]
(*Z,E*)-**16**	*R*,S**	4.94	5.22	[a]

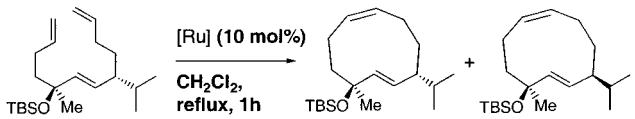
[a] This paper.

dienes are not described in the literature, it is clear that in the most stable conformation of *Z,E*-**5** only one of the faces of the carbonyl moiety must be accessible to the nucleophile. Even at higher temperature (i.e., −50 °C), the addition was completely face-selective. However, the formation of a side product was then observed, which on the basis of NMR was a dehydration product that was most likely nor-germacrene D (extra olefinic carbons at δ 151.5 and 100.7). This compound could be synthesized a priori via methylenation of enone *E,E*-**5**, for example, by means of the Tebbe reaction.

The relative configuration of 1,6-germacradien-5-ol (**1**) has been inconsistently assigned in the literature.[3,12,15] Different relative configurations have been reported for different samples. Recently, Högberg and co-workers[12] concluded that their (−)-**1** sample extracted from natural sources presented the (5*S*,8*S*) configuration. However, the authors pointed out that to confirm that result both isomers, (5*S*,8*S*)- and (5*R*,8*S*)-**1**, should be synthesized. Our synthesis of (5*S**,8*S**)-(*E,E*)-**2**, a close analogue of **1**, via selective MeLi addition to *E,E*-**5** should corroborate the relative stereochemistry proposed by the authors. Indeed, the ^{1}H NMR chemical shifts of (5*S**,8*S**)-(*E,E*)-**2** are analogous to those reported for (5*S*,8*S*)-**1** (Table 1). On the other hand, the only major difference reported between (5*S*,8*S*)- and (5*R*,8*S*)-**1** is that the chemical shifts for H6 and H7 switch places in the spectra of the two compounds.[15a] We have observed a similar phenomenon for TBSO-protected (5*S**,8*S**)- and (5*R**,8*S**)-(*Z,E*)-germacradienols (vide infra), which further corroborates the relative stereochemistry of synthetic (5*S**,8*S**)-(*E,E*)-**2** and (5*S**,8*S**)-(*Z,E*)-**2**.

With (±)-(1*E*,6*E*)-nor-1,6-germacradien-5-ol [(±)-**2**] in hand and aware of the sensitivity of its 10-membered precursors to acids, carbocation-forming reagents, and heat, we decided to attempt a slightly different route toward (±)-**2** in which we could avoid working on the 10-membered ring once it has been formed. We thus decided to incorporate the allylic alcohol moiety into the bisolefin precursor and to perform the RCM reaction as the last step. The RCM reaction on free alcohol (±)-**4a** (Scheme 2) failed, emphasizing the importance of the olefin substitution pattern for the successful ring-closure.[5] In light of this result, we attempted the cyclization of precursor (±)-**4b**, as shown in Scheme 7.

Scheme 7. RCM Reaction of Racemic Trisolefins 4b



(±)-**4b** 1:1 mixture — 67%, 1:1 *E/Z* 0:100 — (5*S**,8*R**)-*Z,E*-**16** — (5*S**,8*S**)-*Z,E*-**16**

To our surprise, the formation of 10-membered rings **16** in the presence of 10 mol % of Grubbs' catalyst (Scheme 7) was highly diastereoselective and much faster than in the case of **10** (1 versus 36 h, respectively). However, only the *Z* olefin was formed. The same result was obtained when Grubbs' catalyst (**11**) was substituted by Nolan's catalyst (**12**). Other protecting groups in place of TBS might dictate a different geometry for the newly formed olefin.[10] However, this concept was not studied. Because trisolefinic precursor (±)-**4b** was a 1:1 mixture of diastereomers, both (5*S**,8*S**)- and (5*R**,8*S**)-*Z,E*-**16** were obtained. The ^{1}H NMR spectra of the two *Z,E*-**16** diastereomers are very similar, and indeed, the H6 and H7 olefinic protons change position in their spectra, as reported for (5*S*,8*S*)- and (5*R*,8*S*)-**1** (Table 1). This result further confirms the relative stereochemistry of (−)-1,6-germacradien-5-ol (**1**).

Conclusions

In summary, we have presented the first total synthesis of (±)-nor-1,6-germacradien-5-ols (±)-(1*E*,5*S**,6*E*,8*S**)-**2** and (±)-(1*Z*,5*S**,6*E*,8*S**)-**2**. The synthetic route involves RCM methodology for ring formation and a selective 1,2 addition of MeLi to cyclodecenone **5**. By altering the order of the last synthetic steps, TBSO-protected (±)-(1*Z*,6*E*)-nor-1,6-germacradien-5-ols (±)-(5*S**,8*S**)- and (±)-(5*R**,-8*S**)-**16** were obtained. Our synthetic strategy via cyclodecenone **5** offers the possibility of preparing different analogues of **2** by the addition of nucleophiles other than MeLi to **5**. Moreover, (±)-nor-germacrene D can be accessed from **5** by methylenation of its carbonyl moiety.

Experimental Section

^{1}H NMR spectra were recorded on a Bruker Avance-400 operating at 400 MHz and are reported in ppm downfield from $SiMe_4$. *J* values are given in Hz. ^{13}C NMR spectra were recorded on a Bruker Avance-400 at 100 MHz. HRMS was conducted on a JEOL JMS-DX303 (EI+). Analytical thin-layer chromatography (TLC) was performed on Merck silica gel plates with QF-254 indicator. Visualization was accomplished with UV light or acidic PMA. Flash chromatography was performed using Merck silica gel 60 (40−63 μm).

Solvents were dried using standard procedures.[16] Reagents were purchased from Aldrich and Fluka, except DBU (Lancaster). Grubbs' and Nolan's catalysts were obtained from

(15) (a) Bohlmann, F.; Zdero, C.; King, R. M.; Robinson, H. *Phytochemistry* **1984**, *23*, 1798−1799. (b) Izac, R. R.; Bandurraga, M. M.; Wasylyk, J. M.; Dunn, F. W.; Fenical, W. *Tetrahedron* **1982**, *38*, 301−304. (c) Kitagawa, I.; Cui, Z.; Son, B. W.; Kobayashi, M.; Kyogoku, Y. *Chem. Pharm. Bull.* **1987**, *35*, 124−135.

(16) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Longman Scientific & Technical: Harlow, U.K., 1989.

Strem. All glassware was oven-dried (120 °C) overnight and allowed to cool to rt in a desiccator.

(±)-2-Isopropyl-5-hexenoic acid [(±)-6]. [17]In a 250 mL three-necked round-bottom flask under argon was placed (^{i}Pr)$_2$NH (14.2 mL, 0.11 mol, 120 mol %) in dry THF (90 mL). The contents of the flask were cooled to −10 °C, and BuLi (2.5 M in hex, 44.0 mL, 0.11 mol, 120 mol %) was added dropwise. The mixture was stirred at 0 °C for 30 min (flask A).

In a separate 500 mL three-necked round-bottom flask under argon was placed NaH (3.7 g, 92.5 mmol, 101 mol %) in dry THF (100 mL). Isovaleric acid (10.0 mL, 9.4 g, 91.7 mmol, 100 mol %) was added dropwise, and the resulting mixture was heated to reflux for 10 min and then cooled to 0 °C (flask B).

The contents of flask A were cannulated into isovaleric acid sodium salt (flask B). The mixture gelled in a few minutes. 4-Bromo-1-butene (9.5 mL, 12.6 g, 93.6 mmol, 102 mol %) was added, and the resulting cake was heated at 30 °C for 24 h (the gel disappeared after about 1 h), cooled to rt, and quenched with 1 N HCl (200 mL). The layers were separated, and the aqueous one was extracted with Et_2O (3 × 75 mL). The combined organic extracts were washed with H_2O (2 × 100 mL), dried ($MgSO_4$), and filtered, and the solvent was evaporated under reduced pressure to give **6** as a yellow oil (13.6 g, 87.1 mmol, 95%), which was used without further purification. ^{1}H NMR ($CDCl_3$) δ 11.8 (bs, 1H), 5.80 (m, 1H), 5.03 (dd, J = 17.1 Hz, J = 1.6 Hz, 1H), 4.97 (dd, J = 9.7 Hz, J = 0.7 Hz, 1H), 2.20−2.10 (m, 1H), 2.10−1.95 (m, 1H), 1.95−1.85 (m, 1H), 1.74−1.71 (m, 1H), 1.60−1.58 (m, 1H), 0.97 (2d, J = 7.0 Hz, 6H).

(±)-2-Isopropyl-5-hexenol [(±)-7]. In a 250 mL three-necked round-bottom flask under argon was placed $LiAlH_4$ (5.4 g, 141.4 mmol, 275 mol %) in dry THF (17 mL). The suspension was cooled to 0 °C, and 2-isopropyl-5-hexenoic acid (8.0 g, 51.3 mmol, 100 mol %) in dry THF (55 mL) was added dropwise. The resulting mixture was stirred at rt for 2 h, quenched at 0 °C with 10% NaOH (50 mL), diluted with Et_2O (50 mL), and saturated with Na_2SO_4. The white cake was filtered with Et_2O (3 × 25 mL), and the solvent was evaporated from the filtrate at reduced pressure. A liquid was obtained from which 3-methylbutanol (side product) was removed by distillation at reduced pressure (40 °C, 20 mmHg). The residue of the distillation was **7** (7.1 g, 50.3 mmol, 98%), which was sufficiently pure to be used directly in the next step. An analytical sample was purified by flash chromatography (hex/AcOEt 10:1). R_f = 0.16 (hex/AcOEt 8:1). ^{1}H NMR ($CDCl_3$) δ 5.70 (m, 1H), 5.00 (m, 2H), 3.60 (m, 2H), 2.14−2.05 (m, 2H), 1.85−1.78 (m, 1H), 1.73 (s, 3H), 1.46−1.30 (m, 2H), 1.27 (bs, 1H), 0.91 (d, J = 6.9 Hz, 3H), 0.90 (d, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 139.0, 125.4, 114.3, 63.4, 45.9, 32.0, 27.8, 26.9, 19.7, 19.1. HRMS: calcd for (M^+ − OH) (C_8H_{15}) 111.1175, found 111.1143.

(±)-2-Isopropyl-5-hexenal [(±)-8].[18] In a 250 mL three-necked round-bottom flask under argon were placed PCC (4.57 g, 21.3 mmol, 150 mol %) and NaOAc (346 mg, 4.2 mmol, 30 mol %) in dry CH_2Cl_2 (20 mL). To the resulting heterogeneous mixture, vigorously stirred and cooled to 0 °C, was added 2-isopropyl-5-hexenol (2.00 g, 14.1 mmol, 100 mol %) in dry CH_2Cl_2 (20 mL). The resulting mixture was stirred at rt for 1.5 h and diluted with Et_2O (20 mL), and the supernatant was separated by decantation. The black residue was washed with Et_2O (3 × 10 mL), and the combined ethereal extracts were filtered through a short pad of Florisil. Evaporation of the solvent under reduced pressure gave **8** as a yellowish liquid (1.51 g, 10.8 mmol, 77%), which was used without further purification. ^{1}H NMR ($CDCl_3$) δ 9.64 (d, J = 3.2 Hz, 1H), 5.80 (m, 1H), 5.00 (m, 2H), 2.13−1.96 (m, 4H), 1.82−1.74 (m, 1H), 1.57−1.51 (m, 1H), 0.98 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 205.6, 137.9, 115.2, 57.5, 31.7, 28.3, 25.0, 20.2, 19.6.

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(±)-8-Isopropyl-dodeca-1,6,11-triene-5-one [(±)-9]. In a 250 mL three-necked round-bottom flask under argon was placed (^{i}Pr)$_2$NH (1.66 mL, 1.19 g, 11.8 mmol, 110 mol %) in dry THF (93 mL). The solution was cooled to −10 °C, and BuLi (2.5 M in hex, 4.72 mL, 11.8 mmol, 110 mol %) was added dropwise. The resulting mixture was subsequently stirred at 0 °C for 15 min and cooled to −78 °C. 5-Hexen-2-one (1.38 mL, 1.16 g, 11.8 mmol, 110 mol %) was added dropwise, and the solution was stirred for 1 h. Aldehyde **8** (1.5 g, 10.7 mmol, 100 mol %) in THF (23 mL) was added slowly, and stirring was continued for 2 h. The reaction mixture was then treated with Ac_2O (11.7 mL, excess), allowed to warm to rt, and stirred for 20 min. H_2O (23 mL) and 1 N HCl (11.5 mL) were added, the layers were separated, and the aqueous one was extracted with Et_2O (2 × 50 mL). The combined organic extracts were stirred with saturated $NaHCO_3$ solution (100 mL) for 1 h. The organic phase was dried ($MgSO_4$) and filtered, and the solvent was eliminated under reduced pressure. A yellow liquid was obtained, which was dissolved in dry THF (115 mL) and treated with DBU (1.6 mL, 1.63 g, 10.7 mmol, 100 mol %) at 0 °C under argon. The resulting mixture was stirred at rt for 2.5 h, treated with H_2O (115 mL) and 1 N HCl (23 mL), and extracted with AcOEt (2 × 50 mL). The organic extracts were combined, washed with saturated $NaHCO_3$ solution (50 mL) and brine (50 mL), dried ($MgSO_4$) and filtered, and the solvent was removed under vacuum. The residue was purified by flash chromatography (hex/AcOEt 98:2), giving **9** as yellow liquid with a characteristic smell (1.3 g, 6.00 mmol, 56%). R_f = 0.48 (hex/AcOEt 9:1). ^{1}H NMR ($CDCl_3$) δ 6.63 (dd, J = 15.9 Hz, J = 9.8 Hz, 1H), 6.06 (d, J = 15.9 Hz, 1H), 5.90−5.71 (m, 2H), 5.07−4.94 (m, 4H), 2.66 (t, J = 7.2 Hz, 2H), 2.39 (m, 2H), 1.05−1.90 (m, 3H), 1.72−1.59 (m, 3H), 1.50−1.40 (m, 2H), 0.91 (d, J = 6.9 Hz, 3H), 0.86 (d, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 199.4, 149.5, 138.3, 137.2, 131.3, 115.1, 114.8, 48.8, 39.2, 31.7, 31.7, 30.7, 28.2, 20.6, 19.2. HRMS: calcd for M^+ ($C_{15}H_{24}O$) 220.1827, found 220.1792.

(±)-7-Hydroxy-8-isopropyl-dodeca-1,11-dien-5-one [(±)-3a]. In a 500 mL three-necked round-bottom flask under argon was placed (^{i}Pr)$_2$NH (1.66 mL, 1.19 g, 11.78 mmol, 110 mol %) in dry THF (93 mL). The solution was cooled to −10 °C, and BuLi (2.5M in hex, 4.72 mL, 11.78 mmol, 110 mol %) was added dropwise. The resulting mixture was subsequently stirred at 0 °C for 15 min and cooled to −78 °C. 5-Hexen-2-one (1.38 mL, 1.16 g, 11.78 mmol, 110 mol %) was added dropwise, and the solution was stirred for 1 h. Aldehyde **8** (1.5 g, 10.73 mmol, 100 mol %) was added dropwise and stirring was continued for 2 h. The reaction mixture was quenched with saturated $NaHCO_3$ (5.4 mL) and then allowed to warm to rt. Additional saturated $NaHCO_3$ (107 mL) was added, the layers were separated, and the aqueous one was extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. A yellow liquid was obtained, which was purified by flash chromatography (hex/AcOEt 15:1), giving **3a** as a clear liquid (1.56 g, 6.55 mmol, 61%) that was a 2:1 syn/anti mixture of diastereomers. R_f = 0.17 (hex/AcOEt 15:1). ^{1}H NMR ($CDCl_3$) δ 5.80 (m, 2H), 5.02 (m, 4H), 4.20 (major) and 4.10 (minor) (ddd, J = 10.1 Hz, J = 6.5 Hz, J = 3.7 Hz, and ddd, J = 9.6 Hz, J = 6.0 Hz, J = 3.7 Hz, 1H), 2.94 (minor) and 2.81 (major) (2d, J = 3.7 Hz, 1H), 2.63−2.49 (m, 4H), 2.36 (dd, J = 14.0 Hz, J = 7.5 Hz, 2H), 2.15−2.10 (m, 2H), 2.00−1.85 (minor) and 1.85−1.72 (major) (2m, 1H), 1.52−1.40 (major) and 1.40−1.30 (minor) (2m, 2H), 1.30−1.20 (minor) and 1.11 (major) (m and dt, J = 9.6 Hz, J = 4.9 Hz, 1H), 0.96 (major) and 0.91 (minor) (2d, J = 7.0 Hz and J = 6.5 Hz, 3H), 0.91 (major) and 0.90 (minor) (2d, J = 7.0 Hz and J = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 211.7 (minor), 211.5, 139.1, 138.8 (minor), 136.8, 115.4, 114.5 (minor), 114.3, 68.7 (minor), 68.3, 48.1 (minor), 47.9, 42.6 (minor), 42.6, 33.6 (minor), 33.5, 28.6, 27.6, 27.5, 25.7, 25.4 (minor), 21.2 (minor), 20.5, 19.7, 18.6 (minor). HRMS: calcd for M^+ ($C_{15}H_{26}O_2$) 238.1933, found 238.1906.

(±)-7-(*tert*-Butyl-dimethyl-silanyloxy)-8-isopropyl-dodeca-1,11-dien-5-one [(±)-3c]. In a 100 mL three-necked round-bottom flask under argon was placed aldol **3a** (2:1 syn/anti) (1.0 g, 4.2 mmol) in dry CH_2Cl_2 (20 mL), and the solution was

cooled to 0 °C. 2,6-Lutidine (980 μL, 8.4 mmol, 200 mol %) and TBSOTf (1.16 mL, 5.0 mmol, 120 mol %) were added sequentially, dropwise, and the resulting mixture was stirred for 2 h and quenched with saturated K_2CO_3 solution (20 mL) before the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic extracts were washed with brine (2 × 10 mL), dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo. The residue was purified by flash chromatography (hex/$CHCl_3$ 3:1) to give **3c** as a clear liquid (1.36 g, 3.8 mmol, 92%) (2:1 syn/anti mixture). R_f = 0.35 (hex/ $CHCl_3$ 2:1). ^{1}H NMR ($CDCl_3$) δ 5.80 (m, 2H), 5.00 (m, 4H), 4.40 (m, 1H), 2.63 (m, 1H), 2.53 (m, 2H), 2.42 (m, 1H), 2.32 (m, 2H), 2.10 (m, 2H), 1.87 (m, 1H), 1.58 (m, 1H), 1.38 (m, 1H), 1.25 (m, 2H), 0.95 (major) and 0.95 (minor) (2d, J = 6.9 Hz, 3H), 0.90 (minor) and 0.87 (major) (2d, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 209.1, 139.3 (minor), 139.1, 137.1, 115.2, 114.5, 114.1 (minor), 70.1, 69.9 (minor), 49.6 (minor), 49.1, 47.4, 46.7 (minor), 43.7 (minor), 43.6, 33.6 (minor), 33.1, 28.9, 27.5, 27.2, 26.4, 26.0 (minor), 25.9, 22.6, 21.6 (minor), 20.5 (minor), 19.9, 18.0, −4.5, −4.6, −4.8 (minor). HRMS: calcd for (M^+ − ^{t}Bu) ($C_{17}H_{31}O_2Si$) 295.2096, found 295.2047.

(±)-*cis*/*trans*-9-(*tert*-Butyl-dimethyl-silanyloxy)-8-isopropyl-cyclodec-4(*E*/*Z*)-enone [(±)-10]. In a 1 L three-necked round-bottom flask under argon was placed bisolefin **3c** (180 mg, 0.51 mmol) in degassed CH_2Cl_2 (888 mL) and Ti(O^iPr)$_4$ (16 μL, 51 μmol, 10 mol %), and the solution was heated to reflux for 1 h. A solution of Grubbs' catalyst (43 mg, 51 μmol, 10 mol %) in degassed CH_2Cl_2 (17 mL) was cannulated over the bisolefin solution, and the resulting mixture was heated under reflux for another 36 h. The reaction mixture was allowed to cool to rt, a stream of air was bubbled through it, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (hex/$CHCl_3$, 3:1) to give (±)-*E*-*trans*-**10** (47% yield), (±)-*E*-*cis*-**10** (21% yield), and (±)-*Z*-*trans*-**10** (8% yield) all as clear oils. $R_{f\,(E-trans)}$ = 0.24, $R_{f\,(E-cis)}$ = 0.19, and $R_{f\,(Z-trans)}$ = 0.24 (hex/ $CHCl_3$, 1:1).

(±)-*E*-*trans*-10: ^{1}H NMR ($CDCl_3$) δ 5.57 (ddd, J = 15.3 Hz, J = 7.6 Hz, J = 7.6 Hz, 1H), 5.52−5.40 (m, 1H), 4.38 (dd, J = 10.7 Hz, J = 3.8 Hz, 1H), 2.92 (dd, J = 17.7 Hz, J = 10.7 Hz, 1H), 2.72−2.57 (m, 1H), 2.45−2.30 (m, 2H), 2.30−2.05 (m, 3H), 1.80−1.60 (m, 1H), 1.65−1.50 (m, 3H), 1.35−1.25 (m, 1H), 0.96 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H), 0.85 (s, 9H), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 212.0, 135.3, 128.3, 68.6, 51.4, 44.8, 42.4, 31.4, 30.0 (bs), 28.9 (bs), 27.9 (bs), 25.8, 21.3, 21.2, 18.1, −3.8, −4.7. HRMS: calcd for M^+ ($C_{19}H_{36}O_2Si$) 324.2485, found 324.2475.

(±)-*E*-*cis*-10: ^{1}H NMR ($CDCl_3$) δ 5.60−5.30 (m, 2H), 4.32 (ddd, J = 9.5 Hz, J = 6.5 Hz, J = 2.7 Hz, 1H), 3.14 (dd, J = 15.6 Hz, J = 10.4 Hz, 1H), 2.55−2.35 (m, 4H), 2.35−1.80 (m, 4H), 1.55−1.40 (m, 1H), 1.25−1.15 (m, 2H), 0.90 (d, J = 6.9 Hz, 3H), 0.89 (s, 9H), 0.76 (d, J = 6.9 Hz, 3H), 0.09 (2s, 6H). ^{13}C NMR ($CDCl_3$) δ 209.7, 131.8, 127.4, 68.9, 51.3, 48.9, 44.2, 42.3, 26.4, 26.3, 25.8, 23.7, 23.6, 22.0, 17.0, −4.3, −4.6.

(±)-*Z*-*trans*-10: ^{1}H NMR ($CDCl_3$) δ 5.47 (dddd, J = 11.1 Hz, J = 11.1 Hz, J = 5.6 Hz, J = 1.1 Hz, 1H), 5.32 (ddd, J = 11.1 Hz, J = 11.1 Hz, J = 5.0 Hz, 1H), 4.43 (dd, J = 11.1 Hz, J = 5.9 Hz, 1H), 3.33 (dd, J = 16.8 Hz, J = 11.1 Hz, 1H), 2.95 (m, 1H), 2.61 (m, 1H), 2.53 (td, J = 13.6 Hz, J = 4.5 Hz, 1H), 2.31 (dd, J = 13.2 Hz, J = 4.2 Hz, 1H), 2.24 (dd, J = 16.8 Hz, J = 5.9 Hz, 1H), 2.12 (m, 1H), 2.02 (m, 1H), 1.90 (m, 1H), 1.54 (m, 1H), 1.31 (m, 1H), 1.20 (m, 1H), 0.90 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.87 (d, J = 6.8 Hz, 3H), 0.06 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 211.1, 131.7, 127.3, 70.3, 46.3, 44.5, 43.7, 32.1, 26.5, 25.9, 23.2, 22.9, 21.5, 20.8, 18.0, −3.6, −4.7.

(±)-4-Isopropyl-cyclodeca-2,7(*E*/*E*)-dienone [(±)-5]. In a 10 mL round-bottom flask under argon was placed **10** (*E*/*Z*, 11:1; *cis*/*trans*, 14:86) (100 mg, 0.31 mmol) in dry DMF (2.5 mL), and DBU (135 μL, 0.90 mmol, 290 mol %) was added dropwise at rt. The resulting mixture was stirred at 50 °C for 18 h, allowed to cool to rt, and poured into Et_2O (20 mL) and brine (20 mL), and the biphasic mixture was stirred for 30 min. The layers were separated. The organic layer was dried ($MgSO_4$) and filtered, and the solvent was removed in vacuo. The residue was purified by flash chromatography (hex/$CHCl_3$ 3:1) to give **5** as a clear oil (20 mg, 0.10 mmol, 34%) as a 75:25 *E*,*E*/*Z*,*E* mixture, along with recovered starting material (51 mg, 0.16 mmol, 51%) (9:1 *E*/*Z*). R_f = 0.33 (hex/$CHCl_3$, 1:2).

(±)-*E*,*E*-5: ^{1}H NMR ($CDCl_3$) δ 6.02 (d, J = 16.1 Hz, 1H), 5.94 (dd, J = 16.1 Hz, J = 9.3 Hz, 1H), 5.06 (dddd, J = 15.6 Hz, J = 10.3 Hz, J = 3.7 Hz, J = 1.5 Hz, 1H), 4.98 (ddd, J = 15.6 Hz, J = 10.6 Hz, J = 2.7 Hz, 1H), 2.53 (m, 2H), 2.43 (m, 2H), 2.30−2.10 (m, 3H), 1.83 (m, 1H), 1.58 (m, 1H), 1.38 (m, 1H), 0.90 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 202.0, 150.9, 140.6, 136.4, 131.3, 52.9, 42.1, 33.7, 32.3, 30.9, 30.7, 20.8, 19.4. HRMS: calcd for M^+ ($C_{13}H_{20}O$) 192.1514, found 192.1521.

(±)-(1*S,4*S**)-4-Isopropyl-1-methyl-cyclodeca-2,7(*E*/*E*)-dienol [(±)-2].** In a 25 mL two-necked round-bottom flask under argon was placed enone *E*,*E*-**5** (20 mg, 104 μmol) in dry Et_2O (1.7 mL), and the solution was cooled to −78 °C. MeLi (1.6 M) in Et_2O (130 μL, 208 μmol, 200 mol %) was added dropwise, and the resulting mixture was stirred at −78 °C for 1 h, quenched with ice water (2 mL), and then allowed to warm to rt. The layers were separated, and the aqueous one was extracted with Et_2O (2 × 2 mL). The combined organic extracts were washed with brine (2 × 5 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (hex/AcOEt, 15:1) to give **2** as a clear oil (18.8 mg, 90.4 μmol, 94%). R_f = 0.25 (hex/AcOEt, 9:1). ^{1}H NMR ($CDCl_3$) δ 5.13 (d, J = 15.9 Hz, 1H), 5.02 (dd, J = 15.9 Hz, J = 9.5 Hz, 1H), 4.97 (m, 2H), 2.55−2.35 (m, 1H), 2.25−2.15 (m, 2H), 2.15−2.05 (m, 1H), 2.0−1.75 (m, 1H), 1.70−1.60 (m, 3H), 1.55−1.40 (m, 2H), 1.35−1.15 (m, 1H), 1.21 (s, 3H), 0.84 (d, J = 6.8 Hz, 3H), 0.79 (d, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 141.1, 135.2, 132.4, 130.9, 73.6, 52.5, 38.5, 34.3, 33.0, 31.1, 29.9, 28.9, 20.6, 18.9. HRMS: calcd for M^+ ($C_{14}H_{24}O$) 208.1827, found 208.1825.

(±)-8-Isopropyl-5-methyl-dodeca-1,6(*E*),11-trien-5-ol [(±)-4a]. In a 25 mL two-necked round-bottom flask under argon was placed enone **9** (100 mg, 0.45 mmol) in dry Et_2O (7 mL), and the solution was cooled to −78 °C. MeLi (1.6 M) in Et_2O (0.56 mL, 0.90 mmol, 200 mol %) was added dropwise, and the resulting mixture was stirred for 30 min at −78 °C and then allowed to warm slowly to −20 °C before being quenched with ice water (10 mL) and allowed to warm to rt. The layers were separated and the aqueous one was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (hex/AcOEt, 15:1) to give **4a** as a colorless oil (102 mg, 0.43 mmol, 85%) in a 1:1 mixture of diastereomers. R_f = 0.34 (hex/AcOEt, 15:1). ^{1}H NMR ($CDCl_3$) δ 5.83 (m, 2H), 5.47 (2d, J = 15.6 Hz, 1H), 5.37 and 5.34 (2d, J = 15.6 Hz, 1H), 4.98 (m, 4H), 2.15−2.05 (m, 3H), 1.98−1.85 (m, 1H), 1.80 (m, 1H), 1.70−1.45 (m, 5H), 1.40−1.25 (m, 1H), 1.29 (s, 3H), 0.89 and 0.87 (2d, J = 6.8 Hz, 3H), 0.84 and 0.83 (2d, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 139.10, 139.09, 139.01, 138.98, 138.27, 129.65, 129.58, 114.37, 114.23, 73.03, 72.99, 48.45, 41.77, 31.89, 31.85, 31.67, 31.54, 28.70, 28.67, 28.56, 20.80, 20.76, 19.03, 18.97. HRMS: calcd for (M^+ − OH) ($C_{16}H_{27}$) 219.2113, found 219.2137.

(±)-[1-But-3-enyl-4-isopropyl-1-methyl-octa-2,7-dienyloxy]-*tert*-butyl-dimethyl-silane [(±)-4b]. In a 25 mL two-necked round-bottom flask under argon was placed Me_3Al (2 M) in hex (348 μL, 0.68 mmol, 150 mol %) in dry THF (6 mL), and the solution was cooled to −78 °C. MeLi (1.6 M) in Et_2O (426 μL, 0.68 mmol, 150 mol %) was added dropwise, and the resulting mixture was stirred for 30 min and then cannulated into a solution of enone **9** (100 mg, 0.45 mmol) and TBSOTf (125 μL, 144 mg, 0.54 mmol, 120 mol %) in THF (3 mL) at −78 °C. The resulting mixture was stirred for another 1 h at −78 °C, quenched with sat. K_2CO_3 solution (5 mL), and allowed to warm to rt. The layers were separated, and the aqueous one was extracted with Et_2O (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (hex) to give **4b** as a clear oil (142 mg, 0.41 mmol, 90%) in a 1:1 mixture of diastereomers. R_f = 0.46 (hex). ^{1}H NMR ($CDCl_3$) δ 5.82 (m, 2H), 5.42 and 5.41 (2d, J =

15.5 Hz, 1H), 5.33 and 5.30 (2dd, J = 15.5 Hz, J = 9.0 Hz, 1H), 4.95 (m, 4H), 2.11 (m, 3H), 1.93 (m, 1H), 1.78 (m, 1H), 1.65−1.45 (m, 4H), 1.40−1.25 (m, 1H), 1.31 (s, 3H), 0.90 (s, 3H), 0.89, 0.88, 0.87 and 0.84 (4d, J = 6.8 Hz, 6H), 0.09, 0.08, 0.08 (3s, 6H). ^{13}C NMR ($CDCl_3$) δ 139.54, 139.52, 139.24, 138.91, 138.81, 129.30, 114.14, 114.11, 113.75, 75.22, 75.19, 48.40, 48.39, 43.73, 43.71, 32.06, 31.98, 31.94, 31.90, 31.86, 31.75, 28.75, 28.32, 28.21, 20.85, 20.82, 18.95, 18.84, 18.34, 18.33, −1.97, −1.99, −2.02. HRMS: calcd for M^+ ($C_{22}H_{42}OSi$) 350.3005, found 350.2975.

***(±)-tert*-Butyl-[(1*S**,4*S**)/(1*S**,4*R**)-4-isopropyl-1-methyl-cyclodeca-2,7(*Z*/*E*)-dienyloxy]-dimethyl-silane [(±)-16].** In a 500 mL three-necked round-bottom flask under argon was placed bisolefin **4b** (50 mg, 0.14 mmol) in degassed CH_2Cl_2 (250 mL). A solution of Grubbs' catalyst (12 mg, 10 mol %) in degassed CH_2Cl_2 (5 mL) was cannulated over the bisolefin solution, and the resulting mixture was heated under reflux for 1 h. The reaction mixture was allowed to cool to rt, a stream of air was bubbled through it, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (hex) to give a 1:1 (*S**,*R**)/(*S**,*S**) mixture of **16** (28 mg, 87 μmol, 62% yield) as a clear oil. $R_{f(S^*,R^*)}$ = 0.55, $R_{f(S^*,S^*)}$ = 0.41 (hex). ^{1}H NMR ($CDCl_3$) δ 5.30−5.15 (m, 1H), 5.22 (dd, J = 14.9 Hz, J = 10.6 Hz, 1H), 5.08 (ddd, J = 11.2 Hz, J = 11.2 Hz, J = 3.8 Hz, 1H), 4.94 (d, J = 14.9 Hz, 1H), 2.40 (m, 2H), 1.70 (m, 3H), 1.53 (m, 1H), 1.45−1.15 (m, 4H), 1.28 (s, 3H), 0.95 (s, 9H), 0.86 (d, J = 6.6 Hz, 3H), 0.81 (d, J = 6.7 Hz, 3H), 0.10 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 138.68, 132.22, 127.27, 124.58, 48.49, 42.56, 32.66, 29.71, 29.60, 26.81, 26.10, 24.56, 22.20, 20.46, 20.05, 18.58, −1.86, −1.92. HRMS: calcd for M^+ ($C_{20}H_{38}OSi$) 322.2692, found 322.2681.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of compounds **2**−**5**, **9**, **10**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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