Stereoselective Synthesis of (+)-Nephrosteranic Acid, (+)-*trans*-Cognac Lactone, and (+)-*trans*-Whisky Lactone using a Chiral Cyclohexadienyl Ti Compound

Florian Schleth,[a, b] Thomas Vogler,[a] Klaus Harms,[a] and Armido Studer*[a, b]

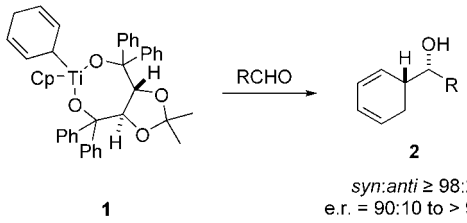
Abstract: We present the stereoselective transfer of cyclohexadienyl from 3-metalated 1,4-cyclohexadienes to various aldehydes. Lewis-acid-mediated "allylation" of aldehydes by treatment with 3-silylated and 3-stannylated 1,4-cyclohexadienes could not be achieved with high diastereoselectivity. In contrast, cyclohexadienyl titanium compounds reacted with both aliphatic and aromatic aldehydes with good-to-excellent diastereoselectivities. Reaction of a chiral TADDOL-derived (TADDOL, 2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolandimethanol) cyclohexadienyl Ti derivative with various aldehydes led to the corresponding homoallylic alcohols with excellent diastereo- and enantioselectivities. Lower selectivities were obtained with chiral *B*-cyclohexadienyldiisopinocampheylborane. The 1,3-cyclohexadienes are very useful building blocks for the preparation of biologically important γ-butyrolactones. Short efficient syntheses of (+)-nephrosteranic acid, (+)-*trans*-whisky lactone, and (+)-*trans*-cognac lactone by desymmetrization of 1,4-cyclohexadiene are described.

Keywords: asymmetric synthesis · cyclohexadienes · lactones · natural products · synthetic methods · titanates

Introduction

Nucleophilic addition of allyl metals to carbonyl compounds has been widely used for the introduction of the synthetically useful allyl moiety. Secondary and tertiary homoallyl alcohols have been prepared by this method. Many applications in complex natural product synthesis have been reported. In the last fifteen years, many papers on stereoselective allylation have appeared.[1] Various "metals" have been used in these processes: Allylation of aldehydes with allyl silanes in the presence of chiral Lewis acids has been described.[2] More recently, stereoselective allylation with allyl silanes in the presence of chiral Lewis bases has been achieved.[3] Chiral allyl silanes can also be used in stereoselective allylations.[4] Allyl stannanes in the presence of Lewis acids[5] and chiral allylboron compounds[6] have been used successfully for stereoselective allylations. Recently, Lewis-acid-mediated low-temperature allylations involving allylboron compounds have been reported.[7] Li,[8] Ti-derived compounds,[9] and other allyl "metal" compounds have also been applied in asymmetric allylations.

We recently published our first results from studies on the desymmetrization of chiral cyclohexadiene Ti compound **1**.[10] Treatment of this compound with various aldehydes provided the corresponding 1,3-cyclohexadienes **2** in good yields with excellent diastereo- and enantioselectivities [Eq. (1)]. These dienes are very interesting chiral building blocks, as has been shown by their use in the synthesis of nephrosteranic acid. Herein we report the desymmetrization of metalated cyclohexadienes in full detail. In addition, we describe the synthesis of (+)-nephrosteranic acid, (+)-*trans*-cognac lactone, and (+)-*trans*-whisky lactone by our new method.



1 **2**

syn:*anti* ≥ 98:2
e.r. = 90:10 to > 99:1

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[a] Dipl. Chem. F. Schleth, T. Vogler, Dr. K. Harms, Prof. Dr. A. Studer
Fachbereich Chemie der Universität Marburg
Hans-Meerwein-Strasse, 35032 Marburg (Germany)
E-mail: studer@uni-muenster.de

[b] Dipl. Chem. F. Schleth, Prof. Dr. A. Studer
New address:
Organisch Chemisches-Institut
Westfälische Wilhelms Universität
Corrensstrasse 40, 48149 Münster (Germany)
Fax: (+49) 251-8336523

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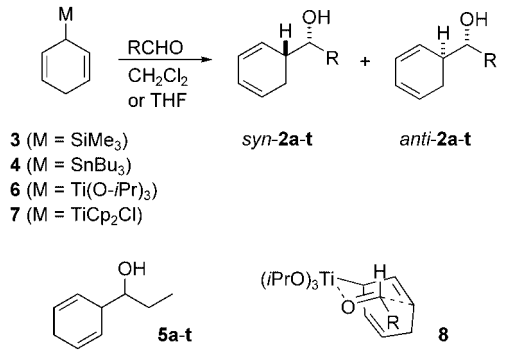
Results and Discussion

Several issues have to be considered to achieve highly stereoselective allylation of aldehydes by using 3-metalated 1,4-cyclohexadienes. The first problem to be solved is how the diastereoselectivity of the reaction can be controlled. This can be achieved by controlling the face selectivity of the electrophilic attack. By analogy with the parent allylations involving allyl metal derivatives, it is likely that the face selectivity can be controlled by the choice of metal (open versus closed transition state). In addition, the effect of possible metallotropic 1,3 shifts must be considered.[1] A big challenge for an allylation method that uses 3-metalated 1,4-cyclohexadienes is the desymmetrization of the 1,4-cyclohexadiene moiety (differentiation of the two enantiotopic double bonds).[11]

Our first experiments were conducted with silylated cyclohexadienes.[12,13] Diene **3** was treated with propanal in CH_2Cl_2 in the presence of various achiral Lewis acids (LAs, −78–25°C, Scheme 1) with the aim of producing **2a**. When $BF_3{\cdot}OEt_2$, $SnCl_4$, or trimethylsilyl triflate (TMS-OTf) was used as the Lewis acid, the desired product was not obtained. A moderate yield and low *syn* selectivity were achieved by using $TiCl_4$ (Table 1, entry 1). Reaction of the diene with *i*PrCHO (→**2b**), *t*BuCHO (→**2c**), and PhCHO (→**2d**)[14] provided similar results (entries 2–4). We next focused on the LA-mediated allylation of propanal with stannylated diene **4**. It is well known that allyl stannanes are more reactive nucleophiles than the corresponding silanes.[15] A satisfactory yield (75%) was obtained with $BF_3{\cdot}OEt_2$ as the LA, but *syn* selectivity remained low (entry 5). The regioisomer **5a**, derived from an LA-mediated 1,3-stannyl shift[3] and subsequent allylation, was formed as a byproduct in 13% yield. A lower yield of the desired product was obtained when $AlCl_3$ was used as the LA (entry 6), and **2a** was not formed at all in the presence of $Ti(O\text{-}iPr)_4$, $SnCl_4$, or TMS-OTf. The $BF_3{\cdot}OEt_2$-mediated reaction was also conducted with *i*PrCHO and PhCHO to afford **2b** and **2d** in moderate-to-good yields but with low selectivities (entries 7 and 8). Regioisomers **5b** and **5d** were formed in 20 and 33% yield, respectively.

LA-catalyzed allylation of aldehydes with allyl stannanes and allyl silanes proceeds through an open transition state.[1] We decided to use cyclohexadienyl titanium compounds, which are known to form rigid cyclic transition states, to try to increase the diastereoselectivity of the reactions. The Ti compounds were readily prepared from 1,4-cyclohexadiene by lithiation (*s*BuLi, tetramethylethylenediamine (TMEDA), THF, −78°) and transmetalation by treatment with $Ti(O\text{-}iPr)_4$ or Cp_2TiCl_2. Addition of **6** to propanal at −78°C occurred in excellent yield and with high selectivity (91%, *syn*:*anti* = 11:1, entry 9). Use of reagent **7**, derived from Cp_2TiCl_2, provided worse results (entry 10) so all further experiments were conducted with **6** (→**2e**–**t**).



Scheme 1. The various achiral cyclohexadienyl "metal" compounds tested.

Linear aliphatic aldehydes provide better selectivities (up to 13:1) than secondary aliphatic aldehydes (d.r. ≈ 3:1, entries 11–13). Reaction of **6** with pivalaldehyde afforded **2c**

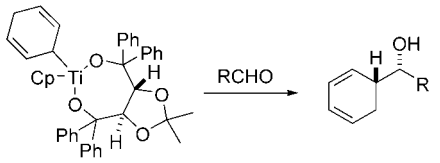
Table 1. Reaction of **3**, **4**, **6**, and **7** with various aldehydes.

	M	LA	R	Product	Yield [%]	d.r.[a] (*syn*:*anti*)
1	$SiMe_3$	$TiCl_4$	Et	**2a**	36	1.4:1[b]
2	$SiMe_3$	$TiCl_4$	*i*Pr	**2b**	35	1.6:1[b]
3	$SiMe_3$	$TiCl_4$	*t*Bu	**2c**	11	n.d.[c]
4	$SiMe_3$	$TiCl_4$	Ph	**2d**	31	1.6:1[b]
5	$SnBu_3$	$BF_3{\cdot}OEt_2$	Et	**2a**	75	1.7:1[b]
6	$SnBu_3$	$AlCl_3$	Et	**2a**	25	2.5:1[b]
7	$SnBu_3$	$BF_3{\cdot}OEt_2$	*i*Pr	**2b**	45	1.6:1[b]
8	$SnBu_3$	$BF_3{\cdot}OEt_2$	Ph	**2d**	77	1:3[b]
9	$Ti(O\text{-}iPr)_3$	–	Et	**2a**	91	11.0:1[b]
10	$TiCp_2Cl$	–	Et	**2a**	23	5.1:1[b]
11	$Ti(O\text{-}iPr)_3$	–	$C_{11}H_{23}$	**2e**	96	13.3:1[d]
12	$Ti(O\text{-}iPr)_3$	–	*i*Pr	**2b**	91	2.9:1[b]
13	$Ti(O\text{-}iPr)_3$	–	C_6H_{11}	**2f**	59	2.7:1[d]
14	$Ti(O\text{-}iPr)_3$	–	*t*Bu	**2c**	87	6.5:1[b]
15	$Ti(O\text{-}iPr)_3$	–	Ph	**2d**	99	9.0:1[d]
16	$Ti(O\text{-}iPr)_3$	–	4-Me−Ph	**2g**	98	14.4:1[d]
17	$Ti(O\text{-}iPr)_3$	–	4-MeO−Ph	**2h**	99	32:1[d]
18	$Ti(O\text{-}iPr)_3$	–	4-Br−Ph	**2i**	96	2.5:1[d]
19	$Ti(O\text{-}iPr)_3$	–	4-NO_2−Ph	**2j**	23	1.9:1[d]
20	$Ti(O\text{-}iPr)_3$	–	3-MeO−Ph	**2k**	98	11.9:1[e]
21	$Ti(O\text{-}iPr)_3$	–	2-MeO−Ph	**2l**	96	39:1[d]
22	$Ti(O\text{-}iPr)_3$	–	2-Me−Ph	**2m**	98	21:1[d]
23	$Ti(O\text{-}iPr)_3$	–	2-Br−Ph	**2n**	98	2.8:1[d]
24	$Ti(O\text{-}iPr)_3$	–	furyl	**2o**	94	13.2:1[d]
25	$Ti(O\text{-}iPr)_3$	–	α-naphthyl	**2p**	99	2.0:1[e]
26	$Ti(O\text{-}iPr)_3$	–	β-naphthyl	**2q**	99	9.4:1[e]
27	$Ti(O\text{-}iPr)_3$	–	PhCH=CH	**2r**	89	2.7:1[e]
28	$Ti(O\text{-}iPr)_3$	–	PhC≡C	**2s**	93	1.9:1[e]
29	$Ti(O\text{-}iPr)_3$	–	$C_9H_{19}C{\equiv}C$	**2t**	92	1.9:1[e]

[a] d.r., diastereomeric ratio. [b] Ratio determined by ^1H NMR spectroscopy. [c] n.d., not determined. [d] Ratio determined by GC analysis. [e] Ratio determined by HPLC analysis.

in high yield with good stereoselectivity (d.r. = 6.5:1, entry 14). A better result was obtained by using benzaldehyde (d.r. = 9:1, entry 15). Treatment of 4-MeO–PhCHO and 4-Me–PhCHO with **6** afforded **2g** and **2h**, respectively, with excellent selectivities (d.r. = 32:1 for 4-MeO–PhCHO, entries 16 and 17). Allylation of 4-Br–PhCHO led to **2i** with only moderate stereocontrol (d.r. = 2.5:1, entry 18). A change in the mechanism from an ionic to a single-electron-transfer (SET) process probably occurred for this aldehyde.[16] Indeed, reaction of **6** with SET substrate 4-NO_2–PhCHO gave **2j** with low selectivity (d.r. = 1.9:1, entry 19). Excellent stereocontrol was achieved with *ortho*-substituted benzaldehyde derivatives (entries 21 and 22). Use of the Br congener again resulted in only moderate selectivity (entry 23). Furfural and β-naphthaldehyde afforded good selectivities, whereas α-naphthaldehyde and cinnamaldehyde provided moderate selectivities (entries 24–27). Alkynals reacted with low selectivity (entries 28 and 29). These *syn* selectivities can be explained by the occurrence of a six-membered chair transition state **8** in which the R group of the aldehyde is located in a pseudoequatorial position.[1]

Table 2. Reaction of **1**, **9**, and **10** with various aldehydes.



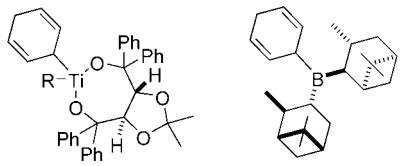
1 **2a, d, g-u**

	R	Reagent	Product	Yield [%]	d.r. (*syn*:*anti*)	e.r.
1	Ph	**1**	**2d**	83	>99:1[a]	98:2[a]
2	Ph	**9**	**2d**	83	8:1[a]	90.5:9.5[a]
3	Ph	**10**	**2d**	40	24:1[a]	89.5:10.5[a]
4	4-Me–Ph	**1**	**2g**	82	>99:1[a]	95:5[a]
5	4-MeO–Ph	**1**	**2h**	63	>99:1[b]	95:5[b]
6	4-Br–Ph	**1**	**2i**	94	>99:1[a]	97:3[a]
7	3-MeO–Ph	**1**	**2k**	58	>99:1[a]	97:3[b]
8	2-MeO–Ph	**1**	**2l**	61	>99:1[a]	>99:1[a]
9	2-Me–Ph	**1**	**2m**	56	>99:1[a]	96:4[a]
10	2-Br–Ph	**1**	**2n**	92	>99:1[c]	>99:1[c]
11	furyl	**1**	**2o**	72	98:2[a]	93:7[b]
12	α-naphthyl	**1**	**2p**	96	>99:1[b]	>99:1[b]
13	β-naphthyl	**1**	**2q**	81	>99:1[b]	90:10[b]
14	PhCH=CH	**1**	**2r**	93	>99:1[b]	90:10[b]
15	PhC≡C	**1**	**2s**	86	>99:1[b]	99:1[b]
16	$C_9H_{19}C\equiv C$	**1**	**2t**	83	>99:1[b]	98.5:1.5[b]
17	Et	**1**	**2a**	40[d]	>99:1[a]	91:9[e]
18	C_5H_{11}	**1**	**2u**	49[f]	>99:1[a]	92:8[a]

[a] Ratio determined by GC analysis. [b] Ratio determined by HPLC analysis. [c] Determined by GC analysis after transformation into **2d** (*t*BuLi, THF, −78 °C; H_2O). [d] The 1,4-diene **5a** was formed as a side product and could not be separated from the product. **2a**:**5a** = 89:11. [e] Determined by GC analysis after oxidation to (*R*)-1-phenylethanol. [f] The 1,4-diene **5u** was formed as a side product and could not be separated from the product. **2u**:**5u** = 88:12.

With a protocol for the diastereoselective addition of 1,4-cyclohexadienes to aldehydes in hand, we attempted the challenging task of differentiating between the enantiotopic double bonds in the cyclohexadienyl Ti compounds. Duthaler has successfully used 2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolandimethanol (TADDOL)-derived[17] allyl Ti derivatives in highly enantioselective allylations.[18] We prepared the analogous chiral Ti cyclohexadienyl compound **1** and found that the reaction of **1** with benzaldehyde (THF, −78 °C) occurs with excellent diastereoselectivity (*syn*:*anti* > 99:1). A promising enantioselectivity was also measured (enantiomeric ratio, e.r. = 91:9, chiral GC) but *syn*-**2d** was formed in low yield (19 %). Some decomposition of **1** probably occurred at −78 °C; when the same reaction was carried out at a lower temperature (−100 to −110 °C, THF/Et_2O) *syn*-**2d** was produced in 83 % yield (*syn*:*anti* > 99:1) with high enantioselectivity (e.r. = 98:2, Table 2, entry 1).

We also tested the isopropoxy Ti derivative **9** (Scheme 2) in the desymmetrization reaction.[19] Compound **9** provided lower selectivities than **1** upon reaction with benzaldehyde (83 % yield, *syn*:*anti* = 8:1, e.r.(*syn*) = 90.5:9.5, entry 2). Chiral *B*-cyclohexadienyldiisopinocampheylborane (**10**) afforded a moderate yield with good diastereoselectivity upon



1 (R = Cp)
9 (R = O-*i*Pr)

10

Scheme 2. Chiral cyclohexadienes **1**, **9**, and **10**, tested in the desymmetrization of 1,4-cyclohexadiene.

treatment with benzaldehyde under analogous conditions (40 % yield, *syn*:*anti* = 24:1, entry 3).[20] However, only moderate enantioselectivity was obtained (e.r.(*syn*) = 89.5:10.5). All further experiments were conducted with Ti derivative **1**.

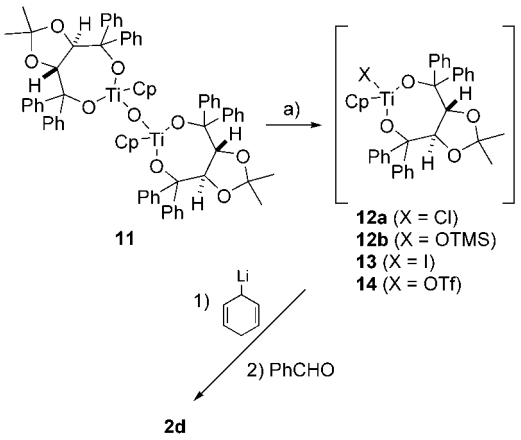
Compound **1** reacted with *para*, *meta*, and *ortho*-substituted benzaldehyde derivatives with excellent diastereoselectivity and high enantioselectivity (Table 2, entries 4–10). In contrast to **6**, chiral Ti reagent **1** reacted with Br-substituted aromatic aldehydes with excellent stereoselectivity (entries 6 and 10). The SET pathway is clearly not a problem in reactions with **1**. α-Naphthaldehyde and phenylpropargyl aldehyde reacted with **1** with "perfect" stereoselectivity, whilst furfural and β-naphthaldehyde provided lower, although good, enantioselectivities and excellent diastereoselectivities (entries 11–14). Reaction of **1** with alkynals provided the corresponding dienes in good yields with high stereoselectiv-

ities (entries 15 and 16). Linear aliphatic aldehydes such as propanal and hexanal gave slightly lower yields but excellent diastereoselectivities and good enantioselectivities (entries 17 and 18). The 1,4-dienes **5a** and **5u** were formed as side products of these reactions.

The absolute configuration for all the major isomers of the new compounds was assigned by considering the rearomatization of **2a** ($Pd(OAc)_2/Cu(OAc)_2$, MeOH), which led to (*R*)-1-phenyl-ethanol (e.r. = 91:9). This reaction shows that, in analogy to the Duthaler allylation, addition of **1** occurs on the *Si* face of the aldehyde.

The stable Ti complex **11** was formed during workup.[21] Complex **11** is apolar and can readily be isolated by chromatography (60–80%). The complex can also be prepared from the corresponding chloride **12a** by treatment of the chloride with saturated aqueous $NaHCO_3$. We envisioned that this complex could be used as a bench-stable precursor for the chiral cyclohexadienyl Ti complex **1**. Since stoichiometric amounts of the chiral Ti compound are needed in each experiment, recovery of this compound is a very important issue.

Compound **11** does not react with lithiated cyclohexadiene and was therefore transformed in situ into a more reactive species. The electrophiles TMSCl, TMSI, MeOTf, and TMSOTf were used to generate the corresponding Ti complexes **12**–**14**. To this end, **11** (in THF/Et_2O) was treated with 2 equiv alkylating reagent (1–3 h) at room temperature. Transmetalation and desymmetrization were performed by a method analogous to that described above (Scheme 3), with benzaldehyde as the aldehyde. In these reactions benzaldehyde was used as electrophile.



Scheme 3. Reuse of dimer **11**. a) TMSCl, TMSI, or TMSOTf in THF/Et_2O.

Regeneration of the active complex with TMSCl (room temperature for 3 h) and subsequent transmetalation and reaction with PhCHO afforded the desired diene **2d** in 68% yield. Diastereoselectivity remained high (*syn*:*anti* > 99:1) but enantioselectivity dropped (e.r. = 93:7) compared to that achieved with our original protocol (e.r. = 98:2, see Table 2, entry 1). The desired diene was not formed when MeOTf was used as the activating species; unidentified products were obtained. Reaction with TMSI and subsequent treatment with PhCHO provided the diene **2d** in 70% yield. TMSCl activation resulted in excellent diastereoselectivity (*syn*:*anti* > 99:1) but enantioselectivity dropped slightly (e.r. = 94:6) compared to that achieved with our original protocol. The best results were obtained with TMSOTf. The diene **2d** was isolated in 71% yield with "perfect" diastereoselectivity (*syn*:*anti* > 99:1) and an enantiomeric ratio of 97:3.

We studied the reactivation of dimer **11** in detail by using ^1H NMR spectroscopy. As can be seen in Figure 1a, reaction of **11** with TMSCl at room temperature produced the corresponding chloride **12a** (typical signals: singlet at δ = 6.40 ppm and doublets at δ = 5.10 and 4.93 ppm, respectively). The reaction was stopped after 240 minutes. Along with the signals corresponding to the desired chloride, a singlet was observed at δ = 6.32 ppm, caused by the presence of an unidentified Ti complex. Doublets occurred at δ = 5.00 and 4.89 ppm, which indicates that reactivation with TMSCl is not complete after 4 h. The side product was tentatively assigned as silyloxy TADDOLate **12b**, which we propose as an intermediate formed on the way to **12a**. A repeat NMR experiment clearly showed that a reaction time of 13 h is necessary to complete the transformation of **12b** into chloride **12a** (Figure 1b). This long reaction time for the generation of **12a** was taken into account and the original TMSCl experiment was repeated (TMCSCl and **11** were stirred for 18 h before addition of the lithiated cyclohexadiene). Enantioselectivity increased to 98:2 with this increase in reaction time.

In contrast to TMSCl reactivation, treatment of **11** with TMSOTf (→**14**) leads to complete reactivation after five minutes (Figure 1c). Reaction of **11** with TMSI to generate **13** is a clean process and is also complete after five minutes (^1H NMR spectra not shown). The allylation reaction with **13** occurs with a lower enantioselectivity than that with **12**; we do not yet understand why.

We initially applied our new method to the synthesis of nephrosteranic acid.[22] We presented the synthesis of scalemic nephrosteranic acid (*ee* = 83.5%) in a previous communication.[10] Our studies have revealed that alkynals provide far better stereoselectivities in the key desymmetrization reaction than aliphatic aldehydes (see Table 2). We therefore decided to use aldehyde **15**[23] in the reaction with **1**. Reduction of the triple bond at a later stage in the synthesis leads to the desired linear unsaturated alkyl chain of nephrosteranic acid.

Treatment of **1** with aldehyde **15** provided **2t** (83%, *syn*:*anti* > 99:1, e.r. = 98.5:1.5, see Table 2, entry 16). The Os-mediated dihydroxylation/diol cleavage protocol reported in our previous communication could be replaced by a more convenient ozonolysis to convert **2t** into the corresponding lactol (Scheme 4). The triple bond in the side chain of the crude lactol was hydrogenated (H_2, Pd/C) to form **16**. Crude **16** was oxidized to γ-butyrolactone **17** under Jones conditions (21% overall, steps b–d). Methylation by a literature procedure[22c] afforded (+)-nephrosteranic acid (89% after recrystallization, 15.5% overall yield, $[\alpha]_{25}^{D} = +27.3°$, $c = 0.97$ in $CHCl_3$); ref. [22a]: $[\alpha]_{25}^{D} = +27.2°$, $c = 1.45$ in $CHCl_3$). We

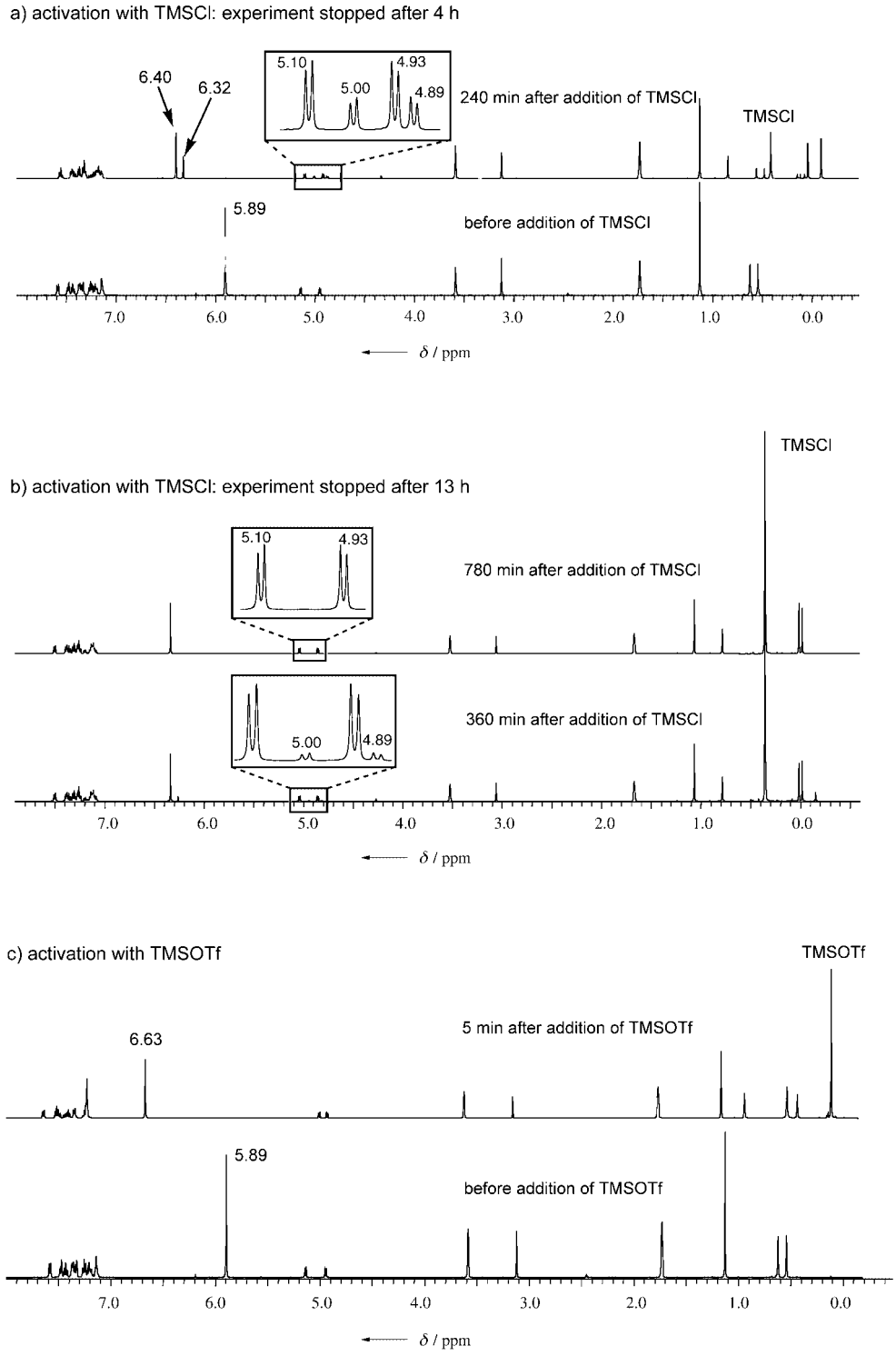
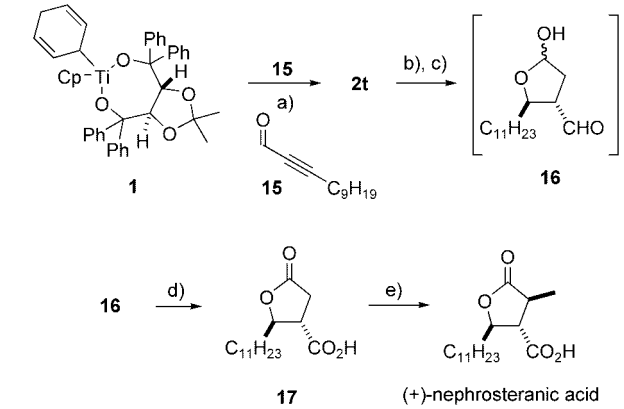


Figure 1. Reactivation of dimer **11** with TMSCl (a and b) and TMSOTf (c) was monitored by ^{1}H NMR spectroscopy. All experiments were carried out in [D_8]THF.

obtained crystals suitable for x-ray analysis. The structure of nephrosteranic acid is shown in Figure 2.[24]

We next applied our method to other γ-butyrolactones. We targeted the compounds *trans*-whisky and *trans*-cognac lactone.[25] The syntheses of these compounds are depicted in Scheme 5. The first four steps were conducted as described for the synthesis of nephrosteranic acid.

Compound **1** was trapped with aldehyde **18a** to give diene **19a** in 66% yield (*syn*:*anti* > 99:1; e.r. not determined). Ozonolysis and subsequent hydrogenation gave lactole **20a**. Jones oxidation led to the corresponding acid, which was immediately reduced by addition of $BH_3{\cdot}SMe_2$ to afford alcohol **21a** (13% for steps b–e). The Appel reaction (→**22a**, 79%) and radical debromination with our recently intro-



Scheme 4. Synthesis of nephrosteranic acid: a) THF/Et_2O, −100 to −110 °C; b) O_3, Me_2S, CH_2Cl_2, −78 °C; c) H_2, Pd/C, EtOH; d) CrO_3/H_2SO_4, acetone; e) NaHMDS, MeI, THF. HMDS = 1,1,1,3,3,3-hexamethyldisilazane.

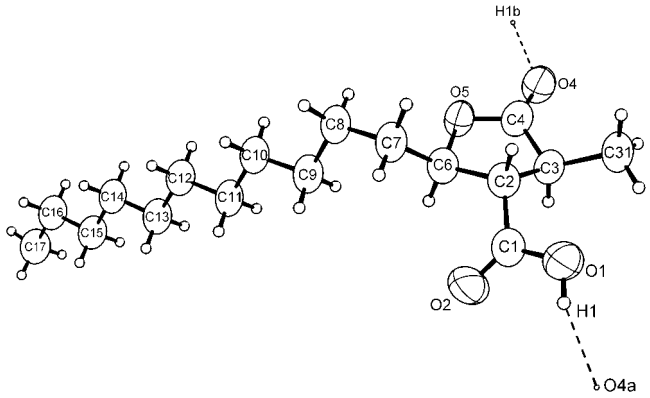
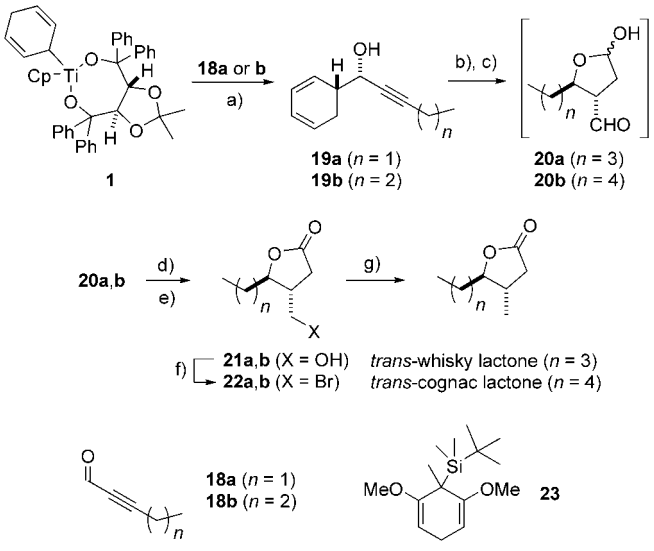


Figure 2. X-ray structure of nephrosteranic acid.



Scheme 5. Synthesis of *trans*-whisky lactone and *trans*-cognac lactone: a) THF/Et_2O, −100 to −110 °C; b) O_3, Me_2S, CH_2Cl_2, −78 °C; c) H_2, Pd/C, EtOH; d) CrO_3/H_2SO_4, acetone, room temperature; e) BH_3·SMe_2, THF, 0 °C; f) CBr_4, PPh_3, CH_2Cl_2, room temperature; g) **23**, AIBN, hexane, 80 °C. AIBN = azobisisobutyronitrile.

duced tin hydride substitute **23**[13] gave (+)-*trans*-whisky lactone (74%; e.r. = 97:3, as determined by chiral GC).

The homologous *trans*-cognac lactone was prepared by using the same reaction sequence. Reaction of **1** with aldehyde **18b** gave diene **19b** (57%, *syn*:*anti* > 99:1; e.r. not determined). Ozonolysis, hydrogenation, Jones oxidation, and reduction by treatment with BH_3·SMe_2 afforded alcohol **21b** in 21.5% overall yield (steps b–e). The Appel reaction (→ **22b**, 67%) and dehalogenation (95%) led to *trans*-cognac lactone (e.r. = 97.5:2.5, chiral GC).

Conclusion

We have reported the first examples of stereoselective cyclohexadienyl transfer to aldehydes from 3-metalated 1,4-cyclohexadienes. Cyclohexadienyl transfer from 3-siylated and 3-stannylated 1,4-cyclohexadienes to aldehydes in the presence of Lewis acids could not be performed with high selectivity. Cyclohexadienyl Ti coumpounds underwent the same reaction with excellent diastereoselectivity. Moreover, the use of chiral cyclohexadienyl Ti TADDOLate **1** allows differentiation between the two enantiotopic double bonds of the corresponding cyclohexadiene. Excellent diastereo- and enantioselectivities were obtained upon reaction of **1** with aromatic aldehydes. Lower but still satisfactory selectivities were obtained with aliphatic aldehydes. Compound **1** reacted with alkynals with good enantioselectivities. Alkynals can be used as surrogates for aliphatic aldehydes.

We have shown that bench-stable dimer **11**, which is readily obtained after workup of the cyclohexadienyl transfer, can be reused. This is an important result since stoichiometric amounts of Ti complex are needed for the desymmetrization reactions. The reactivation of **11** can be monitored by ^{1}H NMR spectroscopy. We believe that this protocol can also be used for the parent Duthaler allylation.

Functionalized 1,3-cyclohexadienes are very useful building blocks for the preparation of biologically important γ-butyrolactones. (+)-Nephrosteranic acid, (+)-*trans*-whisky lactone, and (+)-*trans*-cognac lactone were successfully prepared by our new method. These functionalized 1,3-cyclohexadienes can be used as substrates in Diels–Alder reactions for the preparation of complex rigid compounds. Such reactions are currently being studied in our laboratory.

Experimental Section

General: All reactions involving air- or moisture-sensitive reagents or intermediates were carried out in heat-gun-dried glassware under an argon atmosphere. THF was freshly distilled from potassium under argon. Diethylether (Et_2O) was freshly distilled from K/Na under argon. Dichloromethane (CH_2Cl_2) was freshly distilled from phosphorus(v)oxide (P_2O_5). Triethylamine (Et_3N) was distilled from CaH_2 and stored under argon. TMEDA was distilled from Na and stored under argon over activated 4-Å molecular sieves. All other solvents and reagents were purified according to standard procedures or were used as received from Aldrich or Fluka. ^{1}H and ^{13}C NMR spectroscopy: Bruker AMX 500, AMX 400, AC 300, or ARX 200 spectrometer; chemical shifts, δ, were measured in ppm relative to $CHCl_3$ (7.26 ppm), which was used as an external standard. Polarimetry: optical rotations were measured on a Perkin Elmer 241 po-

larimeter. TLC: Merck silica gel 60 F_{254} plates; detection with UV light or by dipping into a solution of $KMnO_4$ (1.5 g in 400 mL H_2O, 5 g $NaHCO_3$) or a solution of $Ce(SO_4)_2{\cdot}H_2O$ (10 g), phosphormolybdic acid hydrate (25 g), and conc. H_2SO_4 (60 mL) in H_2O (940 mL), followed by heating. Flash column chromatography (FC): Merck or Fluka silica gel 60 (40–63 μm) at approximately 0.4 bar. GC: Hewlett Packard 5890 chromatograph with a Supelco β-DEX 120 (whisky and cognac lactone) or Supelco γ-DEX 120 column (all other compounds). Temperature programme (unless otherwise stated) for γ-DEX: 5 min at 125 °C (T_0), then a temperature gradient: rate, 1.3 °C min^{-1}; final temperature, 200 °C (T_E). Temperature programme for β-DEX: 130 °C (T_0), no temperature gradient. HPLC: Gynkotek UVD160S instrument, High Precision Pump Model 480, Chiracel OD column, eluent: 2% *i*PrOH in *n*hexanes (1 mL min^{-1}). Retention times recorded when HPLC or GC analysis was used for the determination of enantiomer ratios are given below with the details of the relevant experiment. Gynkotek Software (Version 5.50) was used for data analysis. Melting points: Büchi 510 apparatus, uncorrected. IR spectroscopy: Perkin Elmer 782 or Bruker IFS-200 spectrophotometer. MS: VG Tribid, Varian CH7 instruments (EI); IonSpec Ultima, Finnigan MAT TSQ 700, or Finnigan MAT 95S spectrometer (ESI); m/*z* (percentage of basis peak) recorded.

General procedure 1 (GP 1): Preparation of cyclohexadienyllithium: *s*BuLi (1.08 equiv, 1.3–1.46 M in hexanes) and TMEDA (1.08 equiv) were added to a solution of 1,4-cyclohexadiene (1.0 equiv) in THF (ca. 0.2 M) cooled to −78 °C. The resulting yellow solution was stirred for 60–90 min at this temperature and was then used for transmetalation reactions.

General procedure 2 (GP 2): Allylation with titanate 1: A suspension of $CpTiCl_3$ (2.1 equiv) in dry diethylether (0.1 M) was treated with TADDOL (2.1 equiv) at room temperature under argon, with all moisture excluded. The reaction mixture was stirred for 1 min. A solution of NEt_3 (4.6 equiv) in diethylether (0.5 M) was added over a period of 15 min at room temperature and the formation of a white solid was observed. The resulting suspension was stirred at room temperature overnight. Moisture and oxygen were excluded whilst the precipitate was separated from the liquid phase and the solid was then washed twice with dry ether. Solvent was removed in vacuo until a concentration of approximately 0.2 M was reached. The resulting solution was cooled to between −100 and −110 °C. A solution of cyclohexadienyllithium (2.0 equiv) prepared according to GP 1 was added slowly enough to keep the temperature below −100 °C. Once all the cyclohexadienyllithium solution had been added, the brown reaction mixture containing **1** was stirred for 15 min at −100 to −110 °C. An aldehyde (1.0 equiv) was slowly added and the temperature was maintained at −100 to −110 °C. After 3 h at this temperature the reaction mixture was treated with water (10 mL). Methyl *t*butyl ether (MTBE; 20 mL) was added and the reaction mixture was allowed to warm to room temperature. The phases were separated and the aqueous layer was extracted twice with MTBE. The combined organic layers were washed with brine and dried ($MgSO_4$). The solvents were removed in vacuo and the alcohols **2** were purified by FC.

General procedure 3 (GP 3): Allylation with silane 3: Silane **3** (1.0–1.3 equiv) was added to a solution of an aldehyde (0.1–0.2 M) in CH_2Cl_2 at −78 °C. The resulting solution was stirred for 5 min and a Lewis acid was added. After a given reaction time, the reaction was terminated by the addition of KF (10% aq. soln.) or NH_4Cl (sat. aq.) solution. CH_2Cl_2 was added and the phases were separated. The aqueous layer was extracted twice with MTBE. The combined organic layers were washed with NH_4Cl (aq. sat.) and NaCl (aq. sat.) solutions. The resulting mixture was dried ($MgSO_4$) and the solvents were removed in vacuo. The alcohols **2** were purified by FC.

General procedure 4 (GP 4): Allylation with stannane 4: Stannane **4** (1.0–1.3 equiv) was added to a solution of an aldehyde (0.1–0.2 M) in CH_2Cl_2 at −78 °C. The resulting solution was stirred for 5 min and $BF_3{\cdot}OEt_2$ (1.0–1.3 equiv) was added. After 1 h at −78 °C, KF (10% aq. soln.) was added. A white precipitate was removed by filtration 5 min later and CH_2Cl_2 was added. The phases were separated and the aqueous layer was extracted twice with MTBE. The combined organic layers were washed with NH_4Cl (aq. sat.) and NaCl (aq. sat.) solutions. The resulting mixture was dried ($MgSO_4$) and the solvents were removed in vacuo. The alcohols **2** were purified by FC.

General procedure 5 (GP 5): Allylation with titanate 6: Titanium(IV) isopropoxide (Ti(O-*i*Pr)$_4$; 1.3 equiv) was added to a solution of cyclohexadienyllithium (1.2 equiv, 0.2 M in THF, prepared according to GP 1) at −78 °C. The resulting brown mixture was stirred for 10 min at this temperature. An aldehyde (1.0 equiv) was then added. The brown reaction mixture was stirred for 1 h at −78 °C and turned yellow. Water and MTBE were added and a white precipitate formed. The mixture was stirred for 15 min at room temperature before the phases were separated. The aqueous layer was extracted twice with MTBE, washed (NaCl, aq. sat.), and dried ($MgSO_4$). The solvents were removed in vacuo. The alcohols **2** were purified by FC.

General procedure 6 (GP 6): Reaction of dimer 11 with various electrophiles: The electrophile (2.0 mmol) was added to a solution of dimer **11** (1170 mg, 1.0 mmol) in Et_2O (10 mL) and THF (2 mL) under argon at room temperature. The reaction mixture was stirred for 1–18 h then cooled to −110 °C. A solution of cyclohexadienyllithium (1.90 mmol, prepared according to GP 1) was slowly added and the temperature was kept below −100 °C. The resulting brown solution was stirred for 20–60 min at −110 °C. Benzaldehyde (101 mg, 0.95 mmol) was added. After 3 h at −100 to −110 °C the reaction mixture was treated with water (10 mL). MTBE (20 mL) was added and the reaction mixture was allowed to warm to room temperature. The phases were separated and the aqueous layer was extracted twice with MTBE. The combined organic layers were washed with brine and dried ($MgSO_4$). The solvents were removed in vacuo. Alcohol **2d** was purified by FC.

2,5-Cyclohexadienyl(trimethyl)silane (3): Trimethylchlorosilane (9.09 mL, 47 mmol) was added to a solution of cyclohexadienyllithium (43 mmol, prepared according to GP 1). The yellow reaction mixture decolorized. The mixture was allowed to warm to room temperature and was then stirred for 1 h. Water (15 mL) and Et_2O (50 mL) were added and the phases were separated. The aqueous layer was extracted twice with Et_2O (2 × 20 mL). The combined organic phases were washed with saturated NH_4Cl and NaCl solutions (25 mL each) and dried ($MgSO_4$). The solvents were removed in vacuo. Distillation (69 °C, 34 mbar) of the residue yielded silane **3** (5.62 g, 88%) as a clear, colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.73–5.64 (m, 2H; CH_2CH), 5.58–5.50 (m, 2H; SiCHC*H*), 2.74–2.64 (m, 2H; CH_2CH), 2.28–2.16 (m, 1H; CHSi), 0.03 ppm (s, 6H; $Si(CH_3)_2$). The spectral data are in accordance with the literature values.[26]

2,5-Cyclohexadienyl(tributyl)stannane (4): Tributyltin chloride (4.47 mL, 16.5 mmol) was added to a solution of cyclohexadienyllithium (15 mmol, prepared according to GP 1) and the yellow reaction mixture decolorized. The mixture was allowed to warm to room temperature and was stirred for 1 h. Water (15 mL) and Et_2O (50 mL) were added and the phases were separated. The aqueous layer was extracted twice with Et_2O (× 20 mL) then the combined organic phases were washed with saturated NH_4Cl and NaCl solutions (25 mL each) and dried ($MgSO_4$). The solvents were removed in vacuo. FC (P/MTBE 50:1) yielded **4** (5.46 g, 99%) as a colorless clear liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.82–5.64 (m, 2H; CH_2CH), 5.40–5.28 (m, 2H; SnCHC*H*), 3.05–2.48 (m, 3H; CHSn), 1.59–1.19 (m, 18H; $Sn((CH_2)_3CH_3)_3$), 0.96–0.76 ppm (m, 9H; CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 128.7, 119.0, 29.2, 27.5, 26.4, 13.7, 10.1, 9.5 ppm. ESI-MS: 369 (12, $[M]^+$), 323 (100), 291 (40), 267 (58), 235 (8), 211 (25), 179 (6), 102 (16).

***rac*-1-Cyclohexa-2,4-dien-1-yl-propan-1-ol (2a)**: Homoallylic alcohol **2a** was obtained from silane **3** (0.76 g, 5.0 mmol), $TiCl_4$ (0.95 g, 5.0 mmol), and propanal (0.36 mL, 5.0 mmol) by applying GP 3. FC (P/MTBE 2.5:1) yielded **2a** (247 mg, 36%) as a colorless oil. d.r. (*syn*:*anti*) = 1.6:1, determined by GC analysis (T_0 = 100 °C, rate: 0.3 °C min^{-1}); retention times: major diastereoisomer: 23.53 min (both enantiomers), minor diastereoisomer: enantiomer 1: 24.11 min, enantiomer 2: 24.53 min. IR (neat): $\tilde{\nu}$ = 3375(s), 3037(s), 2962(s), 2934(s), 2876(s), 1462(m), 1429(w), 1410(w), 1376(w), 1109(m), 1065(m), 1037(m), 968(s), 919(m), 686(s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.04–5.95 (m, 1H; vinyl H), 5.91–5.74 (m, 2H; vinyl H), 5.69–5.63 (m, 1H; vinyl H), 3.60–3.53 (m, 1H; C*H*OH, *syn* isomer), 3.53–3.45 (m, 1H; C*H*OH, *anti* isomer), 2.43–2.17 (m, 2H; $CHCH_2$), 1.64–1.39 (m, 3H; OH, CH_2CH$_3$), 0.96 ppm (*t*, *J* = 7.5 Hz, 3H; CH_3). ^{13}C NMR (75 Hz, $CDCl_3$, *syn* isomer): δ = 127.5 (CH), 126.1 (CH), 125.3 (CH), 123.6 (CH), 74.6 (CH), 38.4 (CH), 26.9 (CH_2), 23.1 (CH_2), 10.1 ppm (CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, *anti* isomer): δ = 126.3 (CH), 125.6 (CH), 125.4 (CH), 123.9 (CH), 76.4 (CH), 34.9 (CH), 27.0 (CH_2),

25.7 (CH_2), 10.2 ppm (CH_3). MS (EI): 138 (1, $[M]^+$), 107 (4), 91 (8), 80 (100), 79 (56), 59 (20), 41 (7); elemental analysis (%) calcd for $C_9H_{14}O$ (138.21): C 78.21, H 10.21; found: C 78.24, H 10.21.

Homoallylic alcohol **2a** was obtained from stannane **4** (738 mg, 2.0 mmol), $BF_3{\cdot}OEt_2$ (0.25 mL, 2.0 mmol), and propanal (0.14 mL, 2.0 mmol) by applying GP 4. FC (P/MTBE 2.5:1) yielded **2a** (207 mg, 75%) as a colorless oil. d.r. (*syn*:*anti*) = 1.7:1, determined by ^{1}H NMR spectroscopy.

GP 4 was used to obtain homoallylic alcohol **2a** from stannane **4** (738 mg, 2.0 mmol), $AlCl_3$ (264 mg, 2.0 mmol), and propanal (0.14 mL, 2.0 mmol). FC (P/MTBE 2.5:1) yielded **2a** (69 mg, 25%) as a colorless oil. d.r. (*syn*:*anti*) = 2.5:1, determined by ^{1}H NMR spectroscopy.

GP 5 was used to obtain homoallylic alcohol **2a** from cyclohexadienyllithium (2.4 mmol, prepared according to GP 1), titanium(IV) isopropoxide (738 mg, 2.6 mmol), and propanal (116 mg, 2.0 mmol). FC (P/MTBE 2.5:1) yielded **2a** (251 mg, 91%) as a colorless oil. d.r. (*syn*:*anti*) = 11.0:1, determined by ^{1}H NMR spectroscopy.

(1*R*)-1-[(1*R*)-Cyclohexa-2,4-dien-1-yl]propan-1-ol (2a): GP 2 was used to obtain homoallylic alcohol **2a** from $CpTiCl_3$ (976 mg, 4.45 mmol), TADDOL (2.08 g, 4.45 mmol), NEt_3 (990 mg, 1.30 mL, 9.79 mmol), cyclohexadienyllithium (4.20 mmol, prepared according to GP 1), and propanal (122 mg, 2.1 mmol). FC (P/MTBE 10:1) yielded **2a** (116 mg, 40%) as a colorless oil. d.r. (*syn*:*anti*) > 99:1, determined by GC analysis; retention times: only diastereoisomer: 27.43 min. GC and NMR analysis showed that 11% of the product consisted of isomeric cyclohexa-2,5-dienylpropan-1-ol (**5a**; retention time: 28.36 min).

The enantiomeric ratio was determined after oxidation of **2a** to 1-phenyl-1-propanol: **2a** (33 mg, 0.21 mmol) was dissolved in dry methanol (1 mL). $Cu(OAc)_2$ (13 mg, 0.072 mmol) and $Pd(OAc)_2$ (13 mg, 0.058 mmol) were added to the solution at room temperature. Moisture was excluded and the reaction mixture was stirred overnight under atmospheric conditions. The solvent was removed in vacuo and CH_2Cl_2 (5 mL) was added. The suspension was filtered through a short silica pad and the solvent was again removed in vacuo. FC (P/MTBE 10:1) yielded an analytically pure sample for GC analysis. Enantiomeric ratio = 93:7 (GC analysis: T_0 = 100 °C, rate: 0.3 °C min^{-1}; retention times: enantiomer 1: 35.66 min, enantiomer 2: 36.34 min). The *R* enantiomer eluted first and was the major enantiomer. The retention times were confirmed after comparison with an authentic sample (Aldrich) of the *R* enantiomer.

***rac*-1-Cyclohexa-2,4-dien-1-yl-2-methylpropan-1-ol (2b)**: GP 3 was used to obtain homoallylic alcohol **2b** from silane **3** (304 mg, 2.0 mmol), $TiCl_4$ (0.22 mL, 2.0 mmol), and isobutyraldehyde (0.18 mL, 2.0 mmol). FC (P/MTBE 2.5:1) yielded **2b** (106 mg, 35%) as a colorless oil. d.r. (*syn*:*anti*) = 1.6:1, determined by ^{1}H NMR spectroscopy; IR (neat): $\tilde{\nu}$ = 3436(m), 3037(m), 2960(m), 2872(m), 1468(m), 1386(w), 1131(w), 1007(m), 685(m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.04–5.93 (m, 1H; vinyl H), 5.91–5.75 (m, 2H; vinyl H), 5.67–5.53 (m, 1H; vinyl H), 3.38 (*t*, *J* = 5.7 Hz, 1H; C*H*OH, *syn* isomer), 3.22 (*t*, *J* = 5.7 Hz, 1H; C*H*OH, *anti* isomer), 2.59–2.08 (m, 2H; $CHCH_2$), 1.86–1.69 (m, 1H; $CH(CH_3)_2$), 1.54 (brs, 1H; ROH), 1.03–0.79 ppm (m, 6H; $CH(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$, *syn* isomer): δ = 127.7 (CH), 126.1 (CH), 125.5 (CH), 123.6 (CH), 77.7 (CH), 36.0 (CH), 29.9 (CH), 22.8 (CH_2), 16.8 ppm (CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, *anti* isomer): δ = 126.4 (CH), 126.3 (CH), 125.6 (CH), 123.9 (CH), 78.0 (CH), 35.9 (CH), 30.2 (CH), 26.4 (CH_2), 16.8 ppm (CH_3). MS (EI): 152 (7, $[M]^+$), 150 (5, $[M-H_2]^+$), 107 (59), 80 (100), 79 (80), 78 (27), 73 (26), 55 (13), 43 (21). HRMS ($[M]^+$): calcd for $C_{10}H_{16}O$: 152.1201; found: 152.1197.

GP 4 was used to obtain homoallylic alcohol **2b** from stannane **4** (738 mg, 2.0 mmol), $BF_3{\cdot}OEt_2$ (0.25 mL, 2.0 mmol), and isobutyraldehyde (0.18 mL, 2.0 mmol). FC (P/MTBE 10:1) yielded **2b** (138 mg, 45%) as a colorless oil. d.r. (*syn*:*anti*) = 1.6:1, determined by ^{1}H NMR spectroscopy.

GP 5 was used to obtain homoallylic alcohol **2b** from cyclohexadienyllithium (2.4 mmol, prepared according to GP 1), titanium(IV) isopropoxide (738 mg, 2.6 mmol), and isobutyraldehyde (144 mg, 2.0 mmol). FC (P/MTBE 10:1) yielded **2b** (276 mg, 91%) as a colorless oil. d.r. (*syn*:*anti*) = 2.9:1, determined by ^{1}H NMR spectroscopy.

***rac*-1-Cyclohexa-2,4-dien-1-yl-2,2-dimethylpropan-1-ol (2c)**: GP 3 was used to obtain homoallylic alcohol **2c** from silane **3** (304 mg, 2.0 mmol), $TiCl_4$ (0.22 mL, 2.0 mmol), and pivalaldehyde (0.22 mL, 2.0 mmol). FC (P/MTBE 10:1) yielded **2c** (19 mg, 11%) as a colorless oil. IR (neat): $\tilde{\nu}$ = 3462(m), 3038(m), 2954(s), 2869(s), 1480(m), 1396(m), 1364(m), 1097(m), 1011(m), 923(w), 704(m), 648(w) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.04–5.91 (m, 1H; vinyl H), 5.91–5.73 (m, 2H; vinyl H), 5.64–5.53 (m, 1H; vinyl H), 3.40 (brs, 1H; C*H*OH, *anti* isomer), 3.19–3.12 (m, 1H; C*H*OH, *syn* isomer), 2.75–2.60 (m, 1H; CH_2CH), 2.51–2.20 (m, 2H; CH_2CH), 1.75 (brd, *J* = 4.2 Hz, 1H; O*H*), 0.94 ppm (s, 9H; $C(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 127.0 (CH), 126.3 (CH), 126.1 (CH), 123.9 (CH), 83.5 (CH), 35.9 (C), 34.4 (CH), 30.1 (CH_2), 26.6 ppm (CH_3). MS (EI): 164 (5, $[M-H_2]^+$), 138 (7), 125 (13), 107 (46), 95 (49), 91 (23), 87 (51), 80 (87) 79 (98), 57 (100), 43 (28), 41 (48). HRMS ($[M-H_2]^+$): calcd for $C_{11}H_{16}O$: 164.1202; found: 164.1195.

GP 5 was used to obtain homoallylic alcohol **2c** from cyclohexadienyl lilthium (2.4 mmol, prepared according to GP 1), titanium(IV) isopropoxide (738 mg, 2.6 mmol), and pivalaldehyde (168 mg, 2.0 mmol). FC (P/MTBE 10:1) yielded **2c** (285 mg, 87%) as a colorless oil. d.r. (*syn*:*anti*) = 6.5:1, determined by ^{1}H NMR spectroscopy.

***rac*-1-Cyclohexa-2,4-dien-1-yl-(phenyl)methanol (2d)**: GP 3 was used to obtain homoallylic alcohol **2d** from silane **3** (304 mg, 2.0 mmol), $TiCl_4$ (0.22 mL, 2.0 mmol), and benzaldehyde (0.20 mL, 2.0 mmol). The reaction was stopped after 5 min by addition of NH_4Cl (sat. aq.). FC (P/MTBE 10:1) yielded **2d** (115 mg, 31%) as a colorless solid. d.r. (*syn*:*anti*) = 1.6:1, determined by ^{1}H NMR spectroscopy. M.p.: 26–28 °C. IR (nujol): $\tilde{\nu}$ = 3385(w), 2925(s), 1456(s), 1377(m), 1151(w), 1016(m), 970(m), 758(m), 701(m), 680(m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.25 (m, 5H; Ph-H), 5.99–5.87 (m, 2H; vinyl H), 5.84–5.75 (m, 1H; vinyl H), 5.43–5.33 (m, 1H; vinyl H), 4.66 (d, *J* = 7.6 Hz, 1H; C*H*OH), 2.71–2.68 (m, 1H; $CHCH_2$), 2.60–2.22 (m, 2H; $CHCH_2$), 2.12–1.92 ppm (m, 1H; OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.9 (C), 128.4 (CH), 128.3 (CH), 127.6 (CH), 127.0 (CH), 126.7 (CH), 126.4 (CH), 126.0 (CH), 125.6 (CH), 123.8 (CH), 75.6 (CH), 40.3 (CH), 24.1 ppm (CH_2). MS (EI): 184 (5, $[M-H_2]^+$), 108 (85), 107 (100), 80 (87), 79 (97), 78 (19), 77 (37). HRMS ($[M-H_2]^+$): calcd for $C_{13}H_{12}O$: 184.0888; found: 184.0886; elemental analysis (%) calcd for $C_{13}H_{14}O$ (186.25): C 83.83, H 7.58; found: C 83.53, H 7.71.

GP 4 was used to obtain homoallylic alcohol **2d** from stannane **4** (738 mg, 2.0 mmol), $BF_3{\cdot}OEt_2$ (0.25 mL, 2.0 mmol), and benzaldehyde (0.20 mL, 2.0 mmol). FC (P/MTBE 10:1) yielded **2d** (430 mg, 77%) as a colorless solid. d.r. (*syn*:*anti*) = 1:3, determined by ^{1}H NMR spectroscopy.

GP 5 was used to obtain homoallylic alcohol **2d** from cyclohexadienyllithium (12 mmol, prepared according to GP 1), titanium(IV) isopropoxide (3.69 g, 13 mmol), and benzaldehyde (1.06 g, 10.0 mmol). FC (P/MTBE 10:1) yielded **2d** (1.85 g, 99%) as a colorless solid. d.r. (*syn*:*anti*) = 9.0:1, determined by GC analysis; retention times: major diastereoisomer: enantiomer 1: 51.00 min, enantiomer 2: 51.28 min; minor diastereoisomer: enantiomer 1: 52.13 min, enantiomer 2: 52.34 min.

(*S*)-(1*R*)-Cyclohexa-2,4-dien-1-yl-(phenyl)methanol (2d): GP 2 was used to obtain homoallylic alcohol **2d** from $CpTiCl_3$ (584 mg, 2.67 mmol), TADDOL (1.25 g, 2.67 mmol), NEt_3 (594 mg, 0.78 mL, 5.87 mmol), cyclohexadienyllithium (2.52 mmol, prepared according to GP 1), and benzaldehyde (134 mg, 1.26 mmol). FC (P/MTBE 10:1) yielded **2d** (206 mg, 83%) as a colorless solid. $[\alpha]_{25}^{D}$ = +160.9° (*c* = 1.01 in $CHCl_3$). d.r. (*syn*:*anti*) > 99:1; e.r. = 98:2, determined by GC analysis.

Reactions involving dimer 11: Homoallylic alcohol **2d** was obtained by using GP 6 with TMSCl (317 mg, 2.0 mmol). The reaction mixture was stirred for 18 h before the transmetalation step and 20 min before the aldehyde was added. FC (P/MTBE 10:1) yielded **2d** (60 mg, 32%) as a colorless solid. d.r. (*syn*:*anti*) > 99:1; e.r. = 98:2, determined by GC analysis.

Homoallylic alcohol **2d** was obtained by using GP 6 with TMSI (400 mg, 2.0 mmol). The reaction mixture was stirred for 1 h before the transmetalation step and 1 h before the aldehyde was added. FC (P/MTBE 10:1) yielded **2d** (123 mg, 70%) as a colorless solid. d.r. (*syn*:*anti*) > 99:1; e.r. = 94:6, determined by GC analysis.

Homoallylic alcohol **2d** was obtained by using GP 6 with TMSOTf (444 mg, 2.0 mmol). The reaction mixture was stirred for 1 h before the transmetalation step and 1 h before the aldehyde was added. FC (P/MTBE 10:1) yielded **2d** (125 mg, 71%) as a colorless solid. d.r. (*syn*:*anti*) > 99:1; e.r. = 97:3, determined by GC analysis.

***rac*-1-Cyclohexa-2,4-dien-1-yl-dodecan-1-ol (2e)**: GP 5 was used to obtain homoallylic alcohol **2e** from cyclohexadienyllithium (6.0 mmol, prepared according to GP 1), titanium(IV) isopropoxide (1.85 g,

6.5 mmol), and dodecanal (920 mg, 5 mmol). FC (P/MTBE 10:1) yielded **2e** (1.27 g, 96 %) as a colorless oil. d.r. (*syn*:*anti*) = 13.3:1, determined by GC analysis; retention times: major diastereoisomer: 88.68 min; minor diastereoisomer: 88.90 min. IR (nujol): $\tilde{\nu}$ = 3355(w), 2959(s), 1463(s), 1376(m), 1303(w), 1065(w), 970(w), 721(m), 686(w) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.98–5.93 (m, 1H; vinyl H), 5.89–5.72 (m, 2H; vinyl H), 5.66–5.60 (m, 1H; vinyl H), 3.67–3.51 (m; C*H*OH), 2.42–2.15 (m, 3H), 1.61–1.10 (m, 20H), 0.87 ppm (t, J = 6.6 Hz, 3H; CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 127.6 (CH), 126.2 (CH), 125.5 (CH), 123.7 (CH), 73.5 (CH), 38.9 (CH), 34.2 (CH_2), 31.9 (CH_2), 29.7–29.6 (5× CH_2), 29.3 (CH_2), 26.0 (CH_2), 23.1 (CH_2), 22.7 (CH_2), 14.1 ppm (CH_3). MS (EI): 262 (2, $[M-H_2]^+$), 108 (85), 111 (15), 97 (29), 83 (33), 80 (100), 69 (12), 57 (22), 43 (14). HRMS ($[M-H_2]^+$): calcd for $C_{18}H_{30}O$: 262.2297; found: 262.2292; elemental analysis (%) calcd for $C_{18}H_{32}O$ (264.45): C 81.75, H 12.20; found: C 81.80, H 12.07.

(1*R*)-1-[(1*R*)-Cyclohexa-2,4-dien-1-yl]dodecan-1-ol (2e): GP 2 was used to obtain homoallylic alcohol **2e** from $CpTiCl_3$ (2.53 g, 11.55 mmol), TADDOL (5.40 g, 11.55 mmol), NEt_3 (3.37 mL, 25.41 mmol), cyclohexadienyllithium (11.0 mmol, prepared according to GP 1), and dodecanal (1.01 g, 5.5 mmol). FC (P/MTBE 10:1) yielded **2e** (1.14 g, 79 %) as a colorless oil. d.r. (*syn*:*anti*) > 99:1, determined by GC analysis; retention times: only diastereoisomer: 88.63 min. GC and NMR analysis showed 12 % of the product to consist of isomeric 1-cyclohexa-2,5-dien-1-yl-dodecan-1-ol **(5e)**.

***rac*-Cyclohexa-2,4-dien-1-yl(cyclohexyl)methanol (2f)**: GP 5 was used to obtain homoallylic alcohol **2f** from cyclohexadienyllithium (6.0 mmol, prepared according to GP 1), titanium(IV) isopropoxide (1.85 g, 6.5 mmol), and dodecanal (920 mg, 5 mmol). FC (P/MTBE 10:1) yielded **2f** (226 mg, 59 %) as a colorless oil. d.r. (*syn*:*anti*) = 2.7:1, determined by GC analysis; retention times: major diastereoisomer: enantiomer 1: 42.58 min, enantiomer 2: 42.80 min; minor diastereoisomer: 43.22 min (both enantiomers). IR (nujol): $\tilde{\nu}$ = 3380(br m), 3035(m), 2924(s), 2852(s), 1449(m), 1300(w), 1107(w), 1086(w), 972(w), 704(m), 688(s), 640(m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 6.04–5.56 (m, 4H; vinyl H), 3.50–3.30 (m, 1H; C*H*OH, *syn* isomer), 3.27–3.18 (m, 1H; C*H*OH, *anti* isomer), 2.70–2.07 (m, 3H), 1.92–0.82 ppm (m, 12H). ^{13}C NMR (50 MHz, $CDCl_3$, *syn* isomer): δ = 127.4 (CH), 125.7 (CH), 125.1 (CH), 123.3 (CH), 75.8 (CH), 39.1 (CH), 34.8 (CH), 29.2 (CH_2), 27.1 (CH_2), 25.9 (CH_2), 25.7 (CH_2), 21.9 ppm (CH_2). ^{13}C NMR (50 MHz, $CDCl_3$, *anti* isomer): δ = 127.4 (CH), 125.6 (CH), 125.0 (CH), 122.9 (CH), 75.8 (CH), 39.1 (CH), 34.7 (CH), 29.1 (CH_2), 26.9 (CH_2), 25.8 (CH_2), 25.4 (CH_2), 21.9 ppm (CH_2). MS (EI): 192 (< 1, $[M]^+$), 190 (< 1, $[M-H_2]^+$), 107 (19), 95 (80), 80 (100). HRMS ($[M]^+$): calcd for $C_{13}H_{20}O$: 192.1514; found: 192.1519.

***rac*-Cyclohexa-2,4-dien-1-yl-(4-methylphenyl)-methanol (2g)**: GP 5 was used to obtain homoallylic alcohol **2g** from cyclohexadienyllithium (2.4 mmol, prepared according to GP 1), titanium(IV) isopropoxide (738 mg, 2.6 mmol), and 4-methylbenzaldehyde (240 mg, 2.0 mmol). FC (P/MTBE 10:1) yielded **2g** (394 mg, 98 %) as a colorless oil. d.r. (*syn*:*anti*) = 14.4:1, determined by GC analysis; retention times: major diastereoisomer: enantiomer 1: 54.04 min, enantiomer 2: 54.29 min; minor diastereoisomer: enantiomer 1: 55.02 min, enantiomer 2: 55.27 min. IR (neat): $\tilde{\nu}$ = 3388(br s), 3036(s), 2920(m), 2864(m), 1514(m), 1427(m), 1409(m), 1373(m), 1048(m), 1016(m), 821(m), 761(m), 722(m), 681(s), 565(m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.23–7.15 (m, 4H; Ar–H), 5.93–5.87 (m, 2H; vinyl H), 5.83–5.78 (m, 1H; vinyl H), 5.39–5.34 (m, 1H; vinyl H), 4.62–4.60 (m; C*H*OH), 2.69–2.58 (m, 1H; CH_2CH), 2.49–2.26 (m, 2H; CH_2), 2.35 (s, 3H; CH_3); 1.92 ppm (s, 1H; OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.0 (C), 137.2 (C), 129.0 (2×CH), 127.1 (CH), 126.6 (2×CH), 126.0 (CH), 125.4 (CH), 123.8 (CH), 75.4 (CH), 40.3 (CH), 24.2 (CH_2), 21.1 ppm (CH_3). MS (EI): 198 (< 1, $[M-H_2]^+$), 182 (< 1), 167 (2), 121 (100), 93 (58), 91 (21), 80 (26), 77 (30). HRMS ($[M-H_2]^+$): calcd for $C_{14}H_{14}O$: 198.1045; found: 198.1049; elemental analysis (%) calcd for $C_{14}H_{16}O$ (200.28): C 83.96, H 8.05; found: C 83.57, H 8.20.

(*S*)-(1*R*)-Cyclohexa-2,4-dien-1-yl-(4-methylphenyl)methanol (2g): GP 2 was used to obtain homoallylic alcohol **2g** from $CpTiCl_3$ (508 mg, 2.32 mmol), TADDOL (1.08 g, 2.32 mmol), NEt_3 (0.68 mL, 5.87 mmol), cyclohexadienyllithium (2.21 mmol, prepared according to GP 1), and 4-methylbenzaldehyde (133 mg, 1.11 mmol). FC (P/MTBE 10:1) yielded **2g** (182 mg, 82 %) as a colorless oil. d.r. (*syn*:*anti*) > 99:1; e.r. = 95:5, determined by GC analysis: retention times: major diastereoisomer: enantiomer 1: 54.04 min, enantiomer 2: 54.29 min; minor diastereoisomer: enantiomer 1: 55.02 min, enantiomer 2: 55.27 min). $[\alpha]_{25}^{D} = +137.2°$ (c = 1.42 in $CHCl_3$).

***rac*-Cyclohexa-2,4-dien-1-yl-(4-methoxyphenyl)-methanol (2h)**: GP 5 was used to obtain homoallylic alcohol **2h** from cyclohexadienyllithium (2.4 mmol, prepared according to GP 1), titanium(IV) isopropoxide (738 mg, 2.6 mmol), and 4-methoxybenzaldehyde (272 mg, 2.0 mmol). FC (P/MTBE 10:1) yielded **2h** (428 mg, 99 %) as a colorless solid. d.r. (*syn*:*anti*) = 32:1, determined by GC analysis; retention times: major diastereoisomer: enantiomer 1: 70.54 min, enantiomer 2: 70.84 min; minor diastereoisomer: enantiomer 1: 71.56 min, enantiomer 2: 71.80 min. M.p.: 48 °C. IR (neat): $\tilde{\nu}$ = 3360(w), 2924(s), 1611(m), 1584(m), 1515(m), 1463(s), 1376(m), 1254(m), 1176(w), 1112(w), 1033(m), 970(w), 831(m), 682(m), 568(m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.28–7.23 (m, 1H; Ar–H), 7.26–7.23 (m, 2H; Ar–H), 6.90–6.86 (m, 2H; Ar–H), 5.97–5.75 (m, 3H; vinyl H), 5.39–5.31 (m, 1H; vinyl H), 4.60 (dd, 1H; J_1 = 7.5, J_2 = 2.8 Hz; C*H*OH), 4.57 (s, 3H; CH_3), 2.70–2.24 (m, 3H), 1.81 ppm (d, 1H, J = 3.0 Hz; OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.2 (C), 127.9 (CH), 127.1 (2×CH), 125.9 (CH), 125.4 (CH), 124.4 (C), 123.9 (CH), 113.7 (2× CH), 75.2 (CH), 55.3 (CH_3), 40.4 (CH), 24.4 ppm (CH_2). MS (EI): 198 (4, $[M-H_2O]^+$), 137 (100), 132 (27), 109 (19), 79 (5). HRMS ($[M-H_2O]^+$): calcd for $C_{14}H_{14}O$: 198.1045; found: 198.1043.

(*S*)-(1*R*)-Cyclohexa-2,4-dien-1-yl-(4-methoxyphenyl)methanol (2h): GP 2 was used to obtain homoallylic alcohol **2h** from $CpTiCl_3$ (570 mg, 2.60 mmol), TADDOL (1.22 g, 2.60 mmol), NEt_3 (578 mg, 0.76 mL, 5.72 mmol), cyclohexadienyllithium (2.48 mmol, prepared according to GP 1), and 4-methoxybenzaldehyde (1.24 mg, 1.24 mmol). FC (P/MTBE 10:1) yielded **2h** (168 mg, 0.78 mmol, 63 %) as a colorless solid. d.r. (*syn*:*anti*) > 99:1, determined by GC analysis; retention times: only diastereoisomer: 72.01 min; e.r. = 95:5, determined by HPLC analysis; retention times: enantiomer 1: 25.93 min, enantiomer 2: 27.10 min. $[\alpha]_{25}^{D} = +102.5°$ (c = 1.00 in $CHCl_3$).

***rac*-(4-Bromophenyl)-[cyclohexa-2,4-dien-1-yl]methanol (2i)**: GP 5 was used to obtain homoallylic alcohol **2i** from cyclohexadienyllithium (2.4 mmol, prepared according to GP 1), titanium(IV) isopropoxide (738 mg, 2.6 mmol), and 4-bromobenzaldehyde (370 mg, 2.0 mmol). FC (P/MTBE 10:1) yielded **2i** (509 mg, 96 %) as a colorless oil. d.r. (*syn*:*anti*) = 2.5:1, determined by GC analysis; retention times: major diastereoisomer: enantiomer 1: 80.15 min, enantiomer 2: 80.58 min; minor diastereoisomer: enantiomer 1: 81.04 min, enantiomer 2: 82.29 min. IR (neat): $\tilde{\nu}$ = 3391(br s), 3037(m), 1591(m), 1486(s), 1407(m), 1199(m), 1071(s), 1009(s), 821(s), 720(m), 638(s) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.49–7.45 (m, 2H; Ar–H), 7.23–7.19 (m, 2H; Ar–H), 6.01–5.75 (m, 3H; vinyl H), 5.40–5.33 (m, 1H; vinyl H), 4.62 (dd, 1H, J_1 = 7.0, J_2 = 3.0 Hz; C*H*OH), 2.66–2.18 (m, 3H), 1.92 ppm (d, 1H, J = 3.0 Hz; OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.9 (C), 131.3 (2×CH), 128.4 (2×CH), 128.1 (CH), 126.5 (CH), 125.8 (CH), 123.8 (CH), 121.3 (C), 74.8 (CH), 40.2 (CH), 23.9 ppm (CH_2). MS (ESI): 529 ($[2M+H]^+$) (20), 295 (20), 270 (60), 169 (43), 163 (80), 131 (100), 99 (57), 71 (30).

(*S*)-(4-Bromophenyl)-[(1*R*)-cyclohexa-2,4-dien-1-yl]methanol (2i): GP 2 was used to obtain homoallylic alcohol **2i** from $CpTiCl_3$ (495 mg, 2.26 mmol), TADDOL (1.05 g, 2.26 mmol), NEt_3 (0.66 mL, 4.96 mmol), cyclohexadienyllithium (2.13 mmol, prepared according to GP 1), and 4-bromobenzaldehyde (197 mg, 1.07 mmol). FC (P/MTBE 10:1) yielded **2i** (265 mg, 1.00 mmol, 94 %) as a colorless oil. d.r. (*syn*:*anti*) > 99:1; e.r. = 97:3, determined by GC analysis; retention times: major diastereoisomer: enantiomer 1: 80.15 min, enantiomer 2: 80.58 min; minor diastereoisomer: enantiomer 1: 81.04 min, enantiomer 2: 82.29 min). $[\alpha]_{25}^{D} = +126.0°$ (c = 1.24 in $CHCl_3$).

***rac*-Cyclohexa-2,4-dien-1-yl-(3-methoxyphenyl)methanol (2k)**: GP 5 was used to obtain homoallylic alcohol **2k** from cyclohexadienyllithium (2.4 mmol, prepared according to GP 1), titanium(IV) isopropoxide (738 mg, 2.6 mmol), and 3-methoxybenzaldehyde (272 mg, 2.0 mmol). FC (P/MTBE 10:1) yielded **2k** (426 mg, 98 %) as a colorless solid. d.r. (*syn*:*anti*) = 11.9:1, determined by HPLC analysis; retention times: major diastereoisomer: enantiomer 1: 26.71 min, enantiomer 2: 36.94 min; minor diastereoisomer: enantiomer 1: 26.71 min, enantiomer 2: 40.79 min. M.p.: 64 °C. IR (neat): $\tilde{\nu}$ = 3422(br s), 3037(s), 2834(m), 1601(s), 1487(s), 1455(m), 1435(m), 1260(s), 1151(m), 1047(s), 875(w), 781(m), 704(m),

684(m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.28–7.23$ (m, 1H; Ar–H), 6.91–6.80 (m, 3H; Ar–H), 6.05–5.70 (m, 3H; vinyl H), 5.41–5.37 (m, 1H; vinyl H), 4.62–4.59 (m, 1H; C*H*OH), 3.80 (s, 3H; CH_3), 2.67–2.57 (m, 1H; C*H*CH_2), 2.48–2.24 (m, 2H; CH_2), 2.10–2.01 ppm (m, 1H; OH). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 159.6$ (C), 144.6 (C), 129.3 (CH), 127.0 (CH), 126.0 (CH), 125.5 (CH), 123.8 (CH), 119.0 (CH), 113.0 (CH), 112.2 (CH), 75.5 (CH), 55.2 (CH_3), 40.3 (CH), 24.1 ppm (CH_2). MS (EI): 216 (<1, $[M]^+$), 198 (<1, $[M-H_2O]^+$), 137 (100), 109 (95), 94 (23), 80 (56), 77 (28). HRMS ($[M]^+$): calcd for $C_{14}H_{16}O_2$: 216.1150; found: 216.1143.

***rac*-Cyclohexa-2,4-dien-1-yl(4-nitrophenyl)methanol (2j)**: GP 5 was used to obtain homoallylic alcohol **2j** from cyclohexadienyllithium (2.4 mmol, prepared according to GP 1), titanium(IV) isopropoxide (738 mg, 2.6 mmol), and 4-nitrobenzaldehyde (302 mg, 2.0 mmol). FC (P/MTBE 10:1) yielded **2j** (106 mg, 23%) as a yellow oil. d.r. (*syn*:*anti*) = 1.9:1, determined by GC analysis, rate = 5 °C min^{-1}; retention times: major diastereoisomer: enantiomer 1: 105.60 min, enantiomer 2: 106.63 min; minor diastereoisomer: enantiomer 1: 101.49 min, enantiomer 2: 102.47 min. IR (neat): $\tilde{\nu} = 3410$(brs), 3039(m), 2869(m), 1704(m), 1604(w), 1520(m), 1348(m), 1198(m), 1108(m), 1073(m), 1031(m), 1013(m), 857(s), 823(m), 752(m), 701(s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.24–8.19$ (m, 2H; Ar–H), 7.53–7.50 (m, 2H; Ar–H), 6.10–5.71 (m, 4H; vinyl H), 4.83–4.76 (m, 1H; C*H*OH), 2.73–2.12 ppm (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 150.3$ (C), 147.3 (C), 127.1 (CH), 126.4 (2×CH), 125.7 (CH), 125.0 (CH), 124.1 (CH), 123.7 (2×CH), 74.3 (CH), 40.2 (CH), 23.4 ppm (CH_2). MS (EI): 151 (44), 136 (5), 106 (10), 91 (12), 77 (25), 73 (100), 57 (20), 43 (15).

(*S*)-(1*R*)-Cyclohexa-2,4-dien-1-yl-(3-methoxyphenyl)methanol (2k): GP 2 was used to obtain homoallylic alcohol **2k** from $CpTiCl_3$ (578 mg, 2.63 mmol), TADDOL (1.23 g, 2.63 mmol), NEt_3 (0.77 mL, 5.90 mmol), cyclohexadienyllithium (2.50 mmol, prepared according to GP 1), and 3-methoxybenzaldehyde (170 mg, 1.25 mmol). FC (P/MTBE 10:1) yielded **2k** (156 mg, 0.73 mmol, 58%) as a colorless solid. d.r. (*syn*:*anti*) > 99:1; e.r. = 97:3, determined by HPLC analysis; retention times: major diastereoisomer: enantiomer 1: 26.71 min, enantiomer 2: 36.94 min; minor diastereoisomer: enantiomer 1: 26.71 min, enantiomer 2: 40.79 min. $[\alpha]_{25}^{D} = +134.4°$ ($c = 1.08$ in $CHCl_3$).

***rac*-Cyclohexa-2,4-dien-1-yl-(2-methoxyphenyl)methanol (2l)**: GP 5 was used to obtain homoallylic alcohol **2l** from cyclohexadienyllithium (2.4 mmol, prepared according to GP 1), titanium(IV) isopropoxide (738 mg, 2.6 mmol), and 2-methoxybenzaldehyde (272 mg, 2.0 mmol). FC (P/MTBE 10:1) yielded **2l** (415 mg, 96%). d.r. (*syn*:*anti*) = 39:1, determined by GC analysis; retention times: major diastereoisomer: enantiomer 1: 61.77 min, enantiomer 2: 61.97 min; minor diastereoisomer: enantiomer 1: 63.04 min, enantiomer 2: 63.26 min). IR (neat): $\tilde{\nu} = 2923$(s), 2853(m), 1601(w), 1459(m), 1377(m), 1300(w), 1238(w), 1119(w), 1020(w), 750(w), 724(w) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.31–7.25$ (m, 2H; Ar–H), 7.01–6.90 (m, 2H; Ar–H), 5.97–5.82 (m, 3H; vinyl H), 5.43–5.39 (m, 1H; vinyl H), 4.82–4.72 (m, 1H; C*H*OH), 3.88 (s, 3H; CH_3), 2.89–2.70 (m, 2H), 2.56–2.44 (m, 1H), 2.39–2.28 ppm (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 156.7$ (C), 130.3 (C), 128.7 (CH), 128.4 (CH), 127.7 (CH), 126.2 (CH), 125.0 (CH), 123.8 (CH), 120.5 (CH), 110.5 (CH), 73.3 (CH), 55.2 (CH_3), 38.5 (CH), 24.2 ppm (CH_2). MS (EI): 216 (<1, $[M]^+$), 198 (2, $[M-H_2O]^+$), 137 (100), 107 (44), 91 (12). HRMS ($[M]^+$): calcd for $C_{14}H_{16}O_2$: 216.1150; found: 216.1150.

(*S*)-(1*R*)-Cyclohexa-2,4-dien-1-yl-(2-methoxyphenyl)methanol (2l): GP 2 was used to obtain homoallylic alcohol **2l** from $CpTiCl_3$ (670 mg, 3.05 mmol), TADDOL (1.42 g, 3.05 mmol), NEt_3 (0.89 mL, 6.71 mmol), cyclohexadienyllithium (2.90 mmol, prepared according to GP 1), and 2-methoxybenzaldehyde (165 mg, 1.21 mmol). FC (P/MTBE 10:1) yielded **2l** (159 mg, 61%) as a colorless oil. d.r. (*syn*:*anti*) > 99:1; e.r. > 99:1, determined by GC analysis; retention times: major diastereoisomer: enantiomer 1: 61.77 min, enantiomer 2: 61.97 min; minor diastereoisomer: enantiomer 1: 63.04 min, enantiomer 2: 63.26 min. $[\alpha]_{25}^{D} = +124.0°$ ($c = 1.09$ in $CHCl_3$).

***rac*-Cyclohexa-2,4-dien-1-yl-(2-methylphenyl)methanol (2m)**: GP 5 was used to obtain homoallylic alcohol **2m** from cyclohexadienyllithium (2.4 mmol, prepared according to GP 1), titanium(IV) isopropoxide (738 mg, 2.6 mmol), and 2-methylbenzaldehyde (240 mg, 2.0 mmol). FC (P/MTBE 10:1) yielded **2m** (392 mg, 98%) as a colorless solid. d.r. (*syn*:*anti*) = 21:1, determined by GC analysis; retention times: major diastereoisomer: enantiomer 1: 55.02 min, enantiomer 2: 55.20 min; minor diastereoisomer: 56.70 min (both enantiomers). M.p.: 48–50 °C. IR (nujol): $\tilde{\nu} = 3267$(brs), 3926(s), 1462(s), 1377(m), 1239(m), 1185(w), 1053(w), 1009(w), 758(w), 726(w), 638(w) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.50–7.45 (m, 1H; Ar–H), 7.27–7.12 (m, 3H; Ar–H), 5.94–5.81 (m, 3H; vinyl H), 5.35–5.30 (m, 1H; vinyl H), 4.98–4.94 (m, 1H; C*H*OH), 2.69–2.47 (m, 1H), 2.39–2.28 (m, 2H), 2.31 (s, 3H; CH_3), 1.98–1.78 ppm (m, 1H; OH). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 141.1$ (C), 135.2 (C), 130.3 (CH), 127.3 (CH), 126.8 (CH), 126.2 (CH), 126.1 (CH), 126.0 (CH), 125.7 (CH), 123.8 (CH), 71.0 (CH), 39.5 (CH_3), 24.3 (CH_2), 19.4 ppm (CH_3). MS (EI): 182 (<1, $[M-H_2O]^+$), 121 (100), 93 (44), 80 ppm (38). HRMS ($[M-H_2O]^+$): calcd for $C_{14}H_{14}$: 182.1096; found: 182.1092; elemental analysis (%) calcd for $C_{14}H_{16}O$ (200.28): C 83.96, H 8.05; found: C 83.59, H 8.25.

(*S*)-(1*R*)-Cyclohexa-2,4-dien-1-yl-(2-methylphenyl)methanol (2m): GP 2 was used to obtain homoallylic alcohol **2m** from $CpTiCl_3$ (554 mg, 2.53 mmol), TADDOL (1.18 g, 2.53 mmol), NEt_3 (0.74 mL, 5.55 mmol), cyclohexadienyllithium (2.39 mmol, prepared according to GP 1), and 2-methylbenzaldehyde (143 mg, 1.20 mmol). FC (P/MTBE 10:1) yielded **2m** (135 mg, 56%) as a colorless solid. d.r. (*syn*:*anti*) > 99:1; e.r. = 96:4, determined by GC analysis; retention times: major diastereoisomer: enantiomer 1: 55.02 min, enantiomer 2: 55.20 min; minor diastereoisomer: 56.70 min (both enantiomers). $[\alpha]_{25}^{D} = +152.5°$ ($c = 1.01$ in $CHCl_3$).

***rac*-(2-Bromophenyl)-[cyclohexa-2,4-dien-1-yl]methanol (2n)**: GP 5 was used to obtain homoallylic alcohol **2n** from cyclohexadienyllithium (2.4 mmol, prepared according to GP 1), titanium(IV) isopropoxide (738 mg, 2.6 mmol), and 2-bromobenzaldehyde (370 mg, 2.0 mmol). FC (P/MTBE 10:1) yielded **2n** (519 mg, 98%) as a colorless oil. d.r. (*syn*:*anti*) = 2.8:1, determined by GC analysis; retention times: major diastereoisomer: 67.86 min (both enantiomers); minor diastereoisomer: 68.98 min (both enantiomers). IR (neat): $\tilde{\nu} = 3397$(brs), 3037(s), 2934(w), 1567(s), 1468(s), 1409(w), 1195(m), 1122(w), 1094(m), 1017(s), 753(s), 725(m), 684(s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.54–7.51$ (m, 2H; Ar–H), 7.36–7.31 (m, 1H; Ar–H), 7.16–7.11 (m, 1H; Ar–H), 6.08–5.75 (m, 3H; vinyl H), 5.54–5.49 (m, 1H; vinyl H), 5.15–5.01 (m, 1H; C*H*OH), 2.89–2.75 (m, 2H), 2.46–2.12 ppm (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 141.2$ (C), 132.7 (CH), 128.9 (CH), 128.5 (CH), 127.4 (CH), 126.6 (CH), 126.3 (CH), 125.2 (CH), 123.7 (CH), 122.6 (C), 74.3 (CH), 38.5 (CH), 23.1 ppm (CH_2). MS (ESI): 303 ($[M+K]^+$) (5), 289 (12), 270 (20), 242 (50), 231 (17), 195 (18), 186 (25), 169 (35), 163 (73), 142 (60), 131 (100), 99 (62), 71 (42). HRMS: ($[M+K]^+$) calcd for $C_{13}H_{13}BrKO$: 302.9787; found: 302.9795.

(*S*)-(2-Bromophenyl)-[(1*R*)-cyclohexa-2,4-dien-1-yl]methanol (2n): GP 2 was used to obtain homoallylic alcohol **2n** from $CpTiCl_3$ (495 mg, 2.26 mmol), TADDOL (1.05 g, 2.26 mmol), NEt_3 (0.66 mL, 4.96 mmol), cyclohexadienyllithium (2.13 mmol, prepared according to GP 1), and 2-bromobenzaldehyde (197 mg, 1.07 mmol). FC (P/MTBE 10:1) yielded **2n** (261 mg, 92%) as a colorless oil. $[\alpha]_{25}^{D} = +74.8°$ ($c = 0.81$ in $CHCl_3$).

To determine the enantiomeric ratio, **2n** (100 mg, 0.38 mmol) was dissolved in THF (10 mL) and cooled to −78 °C. *t*BuLi (0.64 mL, 1.78 M in hexane, 1.14 mmol, 3 equiv) was added slowly and the reaction mixture was stirred for two hours at −78 °C. Water (3 mL) was added carefully and the reaction mixture was allowed to warm to room temperature. MTBE (10 mL) was added and the phases were separated. The aqueous phase was extracted with MTBE (3×10 mL) and the combined organic phases were washed with brine and dried over $MgSO_4$. The solvents were removed by evaporation in vacuo. FC (P/MTBE 10:1) gave **2d** (36 mg, 50%). GC analysis of this sample indicated the presence of one single enantiomer (see above for GC retention times of **2d**).

***rac*-Cyclohexa-2,4-dien-1-yl-(2-furyl)methanol (2o)**: GP 5 was used to obtain homoallylic alcohol **2o** from cyclohexadienyllithium (2.4 mmol, prepared according to GP 1), titanium(IV) isopropoxide (738 mg, 2.6 mmol), and furfural (192 mg, 2.0 mmol). FC (P/MTBE 10:1) yielded **2o** (323 mg, 94%) as a yellow oil. d.r. (*syn*:*anti*) = 13.2:1, determined by GC analysis; retention times: major diastereoisomer: 31.59 min (both enantiomers); minor diastereoisomer: 31.96 min (both enantiomers). IR (neat): $\tilde{\nu} = 3403$(brs), 3037(s), 2923(w), 1671(w), 1503(m), 1393(w), 1309(w), 1227(w), 1148(m), 1010(s), 739(m), 678(m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.38$ (s, 1H; Ar–H), 6.34–6.33 (m, 1H; Ar–H),

6.26–6.24 (m, 1H; Ar–H), 6.05–5.71 (m, 3H; vinyl H), 5.48–5.43 (m, 1H; vinyl H), 4.63–4.61 (m, 1H; C*H*OH), 2.85–2.73 (m, 1H), 2.47–2.30 (m, 2H), 2.14–1.96 ppm (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.4 (C), 142.9 (CH), 126.2 (CH), 125.7 (CH), 125.5 (CH), 123.9 (CH), 110.2 (CH), 107.3 (CH), 69.0 (CH), 38.0 (CH), 24.2 ppm (CH_2). MS (EI): 174 ($[M-H_2]^+$) (<1), 97 (100), 80 (17), 41 (12). HRMS ($[M-H_2]^+$): calcd for $C_{11}H_{10}O_2$: 174.0681; found: 174.0676.

(*S*)-(1*R*)-Cyclohexa-2,4-dien-1-yl-(2-furyl)methanol (2o): GP 2 was used to obtain homoallylic alcohol **2o** from $CpTiCl_3$ (558 mg, 2.54 mmol), TADDOL (1.19 g, 2.54 mmol), NEt_3 (0.74 mL, 5.59 mmol), cyclohexadienyllithium (2.42 mmol, prepared according to GP 1), and furfural (116 mg, 1.21 mmol). FC (P/MTBE 10:1) yielded **2o** (153 mg, 72%) as a pale yellow oil. d.r. (*syn*:*anti*) = 98:2, determined by GC analysis; retention times: major diastereoisomer: 32.27 min; minor diastereoisomer: 33.18 min; e.r. = 93:7, determined by HPLC analysis; retention times: major diastereoisomer: enantiomer 1: 14.30 min, enantiomer 2: 16.66 min. $[\alpha]_{25}^{D} = +190.6°$ (c = 1.04 in $CHCl_3$).

***rac*-Cyclohexa-2,4-dien-1-yl-(1-naphthyl)methanol (2p)**: GP 5 was used to obtain homoallylic alcohol **2p** from cyclohexadienyllithium (2.4 mmol, prepared according to GP 1), titanium(IV) isopropoxide (738 mg, 2.6 mmol), and 1-naphthaldehyde (312 mg, 2.0 mmol). FC (P/MTBE 10:1) yielded **2p** (428 mg, 99%) as a colorless oil. d.r. (*syn*:*anti*) = 2.0:1, determined by HPLC analysis; retention times: major diastereoisomer: enantiomer 1: 24.02 min, enantiomer 2: 70.58 min; minor diastereoisomer: enantiomer 1: 25.23 min, enantiomer 2: 83.94 min. IR (neat): $\tilde{\nu}$ = 3409(br s), 3038(s), 2974(w), 2938(m), 1690(m), 1597(m), 1511(m), 1367(s), 1200(m), 1167(m), 1075(m), 996(m), 848(m), 780(m), 683(s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11–8.06 (m, 1H; Ar–H), 7.91–7.87 (m, 2H; Ar–H), 7.66–7.61 (m, 1H; Ar–H), 7.52–7.46 (m, 3H; Ar–H), 6.09–5.71 (m, 3H; vinyl H), 5.48–5.43 (m, 2H; vinyl H, C*H*OH), 3.01–2.87 (m, 1H), 2.59–2.43 (m, 1H), 2.32–2.10 ppm (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.3 (C), 133.8 (C), 130.7 (C), 128.9 (CH), 128.1 (CH), 127.3 (CH), 126.6 (CH), 125.8 (CH), 125.6 (CH), 125.4 (CH), 125.2 (CH), 124.1 (CH), 123.7 (CH), 123.3 (CH), 72.1 (CH), 39.6 (CH), 23.9 ppm (CH_2). MS (EI): 236 ($[M]^+$) (<1), 218 (2), 158 (50), 133 (16), 129 (100), 78 (13), 75 (45). HRMS: ($[M]^+$) calcd for $C_{17}H_{16}O$: 236.1201; found: 236.1199.

(*S*)-(1*R*)-Cyclohexa-2,4-dien-1-yl-(1-naphthyl)methanol (2p): GP 2 was used to obtain homoallylic alcohol **2p** from $CpTiCl_3$ (567 mg, 2.59 mmol), TADDOL (1.21 g, 2.59 mmol), NEt_3 (0.76 mL, 5.70 mmol), cyclohexadienyllithium (2.47 mmol, prepared according to GP 1), and 1-naphtaldehyde (204 mg, 1.24 mmol). FC (P/MTBE 10:1) yielded **2p** (281 mg, 96%) as a colorless oil. d.r. (*syn*:*anti*) > 99:1; e.r. > 99:1, determined by HPLC analysis; retention times: major diastereoisomer: enantiomer 1: 24.02 min, enantiomer 2: 70.58 min; minor diastereoisomer: enantiomer 1: 25.23 min, enantiomer 2: 83.94 min. $[\alpha]_{25}^{D} = +91.3°$ (c = 1.00 in $CHCl_3$).

***rac*-Cyclohexa-2,4-dien-1-yl-(2-naphthyl)methanol (2q)**: GP 5 was used to obtain homoallylic alcohol **2q** from cyclohexadienyllithium (2.4 mmol, prepared according to GP 1), titanium(IV) isopropoxide (738 mg, 2.6 mmol), and 2-naphthaldehyde (312 mg, 2.0 mmol). FC (P/MTBE 10:1) yielded **2q** (428 mgm 99%) as a colorless solid. d.r. (*syn*:*anti*) = 9.4:1, determined by HPLC analysis; retention times: major diastereoisomer: enantiomer 1: 37.38 min, enantiomer 2: 48.24 min; minor diastereoisomer: enantiomer 1: 40.89 min, enantiomer 2: 53.75 min. M.p.: 95–97 °C. IR (nujol): $\tilde{\nu}$ = 3325(br s), 3033(w), 2926(s), 2859(s), 1464(m), 1376(m), 1341(m), 1150(m), 1028(m), 972(m), 948(m), 857(m), 824(m), 787(m), 741(m), 682(s), 598(w), 479(m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81–7.77 (m, 4H; Ar–H), 7.50–7.44 (m, 3H; Ar–H), 6.08–5.70 (m, 3H; vinyl H), 5.42–5. 37 (m, 1H; vinyl H), 4.82–4.76 (m, 1H; C*H*OH), 2.80–2.70 (m, 1H), 2.55–2.44 (m, 1H), 2.38–2.26 (m, 2H), 2.08–2.03 ppm (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.3 (C), 133.1 (C), 133.0 (C), 128.1 (CH), 127.9 (CH), 127.6 (CH), 126.9 (CH), 126.0 (CH), 125.8 (CH), 125.6 (CH), 125.5 (CH), 125.4 (CH), 124.5 (CH), 123.8 (CH), 75.6 (CH), 40.2 (CH), 24.1 ppm (CH_2). MS (EI): 236 ($[M]^+$) (<1), 218 (3), 157 (100), 129 (93), 106 (7), 80 (17). HRMS: ($[M]^+$) calcd for $C_{17}H_{16}O$: 236.1201; found: 236.1203; elemental analysis (%) calcd for $C_{17}H_{16}O$ (236.31): C 86.40, H 6.82; found: C 86.47, H 6.75.

(*S*)-(1*R*)-Cyclohexa-2,4-dien-1-yl-(2-naphthyl)methanol (2q): GP 2 was used to obtain homoallylic alcohol **2q** from $CpTiCl_3$ (544 mg, 2.48 mmol), TADDOL (1.16 g, 2.48 mmol), NEt_3 (0.72 mL, 5.45 mmol), cyclohexadienyllithium (2.36 mmol, prepared according to GP 1), and 2-naphtaldehyde (188 mg, 1.18 mmol). FC (P/MTBE 10:1) yielded **4j** (226 mg, 1.19 mmol, 81%) as a colorless solid. d.r. (*syn*:*anti*) > 99:1; e.r. = 90:10, determined by HPLC analysis; retention times: major diastereoisomer: enantiomer 1: 37.38 min, enantiomer 2: 48.24 min; minor diastereoisomer: enantiomer 1: 40.89 min, enantiomer 2: 53.75 min. $[\alpha]_{25}^{D} = +162.8°$ (c = 1.18 in $CHCl_3$).

***rac*-(2*E*)-1-[Cyclohexa-2,4-dien-1-yl]-3-phenylprop-2-en-1-ol (2r)**: GP 5 was used to obtain homoallylic alcohol **2r** from cyclohexadienyllithium (2.4 mmol, prepared according to GP 1), titanium(IV) isopropoxide (738 mg, 2.6 mmol), and cinnamaldehyde (264 mg, 2.0 mmol). FC (P/MTBE 10:1) yielded **2r** (377 mg, 89%) as a colorless solid. d.r. (*syn*:*anti*) = 2.7:1, determined by HPLC analysis; retention times: major diastereoisomer: enantiomer 1: 34.20 min, enantiomer 2: 53.59 min; minor diastereoisomer: enantiomer 1: 34.20 min, enantiomer 2: 60.15 min. M.p.: 47 °C. IR (nujol): $\tilde{\nu}$ = 3396(br m), 3036(w), 2925(s), 2857(s), 1493(m), 1450(s), 1375(m), 1329(m), 1149(m), 1078(w), 1008(w), 968(m), 748(m), 683(s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.22 (m, 5H; Ar–H), 6.61 (d, 1H, J = 15.9 Hz; PhC*H*=CH), 6.24 (dd, 1H, J_1 = 15.9, J_2 = 6.8 Hz; PhCH=C*H*), 6.06–5.69 (m, 4H; vinyl H), 4.31–4.27 (m, 1H; C*H*OH), 2.61–2.50 (m, 1H), 2.38–2.17 (m, 2H), 1.69 ppm (m, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.7 (C), 131.7 (CH), 130.6 (CH), 128.6 (CH), 127.7 (CH), 126.5 (CH), 126.1 (CH), 125.6 (CH), 123.8 (CH), 75.6 (CH), 39.3 (CH), 25.3 ppm (CH_2). MS (ESI): 315 (100), 289 (36), 250 ($[M-H+K]^+$) (30), 240 (10), 227 (10), 195 (13), 186 (52), 132 (10), 116 (100). HRMS: ($[M+Na]^+$) calcd for $C_{15}H_{16}ONa$: 235.1099; found: 235.1094.

(1*R*,2*E*)-1-[(1*R*)-Cyclohexa-2,4-dien-1-yl]-3-phenylprop-2-en-1-ol (2r): GP 2 was used to obtain homoallylic alcohol **2r** from $CpTiCl_3$ (544 mg, 2.48 mmol), TADDOL (1.16 g, 2.48 mmol), NEt_3 (0.72 mL, 5.45 mmol), cyclohexadienyllithium (189 mg, 2.36 mmol, prepared according to GP 1), and cinnamaldehyde (156 mg, 1.18 mmol). FC (P/MTBE 10:1) yielded **2r** (232 mg, 93%) as a colorless solid. d.r. (*syn*:*anti*) > 99:1; e.r. = 90:10, determined by HPLC analysis; retention times: major diastereoisomer: enantiomer 1: 34.20 min, enantiomer 2: 53.59 min; minor diastereoisomer: enantiomer 1: 34.20 min, enantiomer 2: 60.15 min. $[\alpha]_{25}^{D} = +229.9°$ (c = 1.08 in $CHCl_3$).

***rac*-1-[Cyclohexa-2,4-dien-1-yl]-3-phenylprop-2-yn-1-ol (2s)**: GP 5 was used to obtian homoallylic alcohol **2s** from cyclohexadienyllithium (2.4 mmol, prepared according to GP 1), titanium(IV) isopropoxide (738 mg, 2.6 mmol), and phenylpropargyl aldehyde (260 mg, 2.0 mmol). FC (P/MTBE 10:1) yielded **2s** (391 mg, 93%) as a yellow oil. d.r. (*syn*:*anti*) = 1.9:1, determined by HPLC analysis; retention times: major diastereoisomer: enantiomer 1: 25.26 min, enantiomer 2: 69.03 min; minor diastereoisomer: enantiomer 1: 27.68 min, enantiomer 2: 53.06 min. IR (neat): $\tilde{\nu}$ = 3363(br s), 3038(s), 2867(m), 2231(w), 1597(m), 1490(s), 1442(w), 1429(w), 1409(w), 1371(w), 1328(w), 1070(m), 1036(s), 999(w), 972(m), 757(s), 690(s), 573(w), 525(w), 504(w) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.31 (m, 5H; Ar–H), 6.03–5.85 (m, 4H; vinyl H), 4.62–4.52 (m, 1H; C*H*OH), 2.79–2.61 (m, 1H), 2.53–2.31 (m, 2H), 2.11 ppm (br s, 1H; OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 131.7 (CH), 128.4 (CH), 128.3 (CH), 125.9 (CH), 125.6 (CH), 126.5 (CH), 123.8 (CH), 122.5 (C), 88.9 (C), 86.3 (C), 65.9 (CH), 40.1 (CH), 25.2 ppm (CH_2). MS (EI): 210 ($[M]^+$; 2), 208 ($[M-H_2]^+$; 2), 131 (100), 114 (10), 103 (17), 79 (40). HRMS: ($[M]^+$) calcd for $C_{15}H_{14}O$: 210.1045; found: 210.1041.

(1*S*)-1-[(1*R*)-Cyclohexa-2,4-dien-1-yl]-3-phenylprop-2-yn-1-ol (2s): GP 2 was used to obtain homoallylic alcohol **2s** from $CpTiCl_3$ (504 mg, 2.30 mmol), TADDOL (1.08 g, 2.30 mmol), NEt_3 (0.67 mL, 5.05 mmol), cyclohexadienyllithium (2.19 mmol, prepared according to GP 1), and phenylpropargyl aldehyde (143 mg, 1.10 mmol). FC (P/MTBE 10:1) yielded **2s** (198 mg, 86%) as a yellow oil. d.r. (*syn*:*anti*) > 99:1; e.r. = 99:1, determined by HPLC analysis; retention times: major diastereoisomer: enantiomer 1: 25.26 min, enantiomer 2: 69.03 min; minor diastereoisomer: enantiomer 1: 27.68 min, enantiomer 2: 53.06 min. $[\alpha]_{25}^{D} = +219.9°$ (c = 1.12 in $CHCl_3$).

***rac*-1-[Cyclohexa-2,4-dien-1-yl]dodec-2-yn-1-ol (2t)**: GP 5 was used to obtain homoallylic alcohol **2t** from cyclohexadienyllithium (2.4 mmol, prepared according to GP 1), titanium(IV) isopropoxide (738 mg, 2.6 mmol), and dodec-2-yn-1-al (**15**; 360 mg, 2.0 mmol). FC (P/MTBE 10:1) yielded **2t** (480 mg, 92%) as a colorless oil. d.r. (*syn*:*anti*) = 1.9:1,

determined by HPLC analysis; retention times: major diastereoisomer: enantiomer 1: 28.73 min, enantiomer 2: 39.34 min; minor diastereoisomer: enantiomer 1: 25.00 min, enantiomer 2: 34.52 min. IR (neat): $\tilde{\nu}$ = 3379(w), 3038(m), 2855(m), 2229(w), 1674(w), 1465(s), 1377(m), 1140(w), 1016(m), 970(w), 683(w) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.02–5.96 (m, 1H; vinyl H), 5.91–5.74 (m, 3H; vinyl H), 4.36–4.24 (m, 1H; C*H*OH), 2.61–2.46 (m, 1H), 2.43–2.28 (m, 2H), 2.20 (dt, J_1 = 6.9, J_2 = 2.0 Hz, 2H; C≡CCH_2), 1.87 (br s, 1H; OH), 1.54–1.45 (m, 2H), 1.42–1.18 (m, 12H), 0.87 ppm (*t*, *J* = 6.6 Hz, 3H; CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 126.4 (CH), 125.7 (CH), 125.5 (CH), 123.9 (CH), 87.0 (C), 80.2 (C), 65.7 (CH), 40.4 (CH), 31.9 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.8 (CH_2), 28.6 (CH_2), 25.2 (CH_2), 22.6 (CH_2), 18.7 (CH_2), 14.1 ppm (CH_3). MS (EI): 258 (1, $[M-H_2]^+$), 105 (2), 95 (4), 83 (7), 80 (57), 79 (48), 78 (38), 70 (100), 55 (8). HRMS: ($[M-H_2]^+$) calcd for $C_{18}H_{26}O$: 258.1984; found: 258.1980.

(1*S*)-1-[(1*R*)-Cyclohexa-2,4-dien-1-yl]dodec-2-yn-1-ol (2t): GP 2 was used to obtain homoallylic alcohol **2t** from $CpTiCl_3$ (715 mg, 3.26 mmol), TADDOL (1.53 g, 3.26 mmol), NEt_3 (1.00 mL, 7.18 mmol), cyclohexadienyllithium (3.10 mmol, prepared according to GP 1), and dodec-2-yn-1-al (**15**; 279 mg, 1.55 mmol). FC (P/MTBE 10:1) yielded **2t** (334 mg, 83%) as a colorless oil. d.r. (*syn*:*anti*) > 99:1; e.r. = 98.5:1.5, determined by HPLC analysis; retention times: major diastereoisomer: enantiomer 1: 28.73 min, enantiomer 2: 39.34 min; minor diastereoisomer: enantiomer 1: 25.00 min, enantiomer 2: 34.52 min.

***rac*-1-[Cyclohexa-2,4-dien-1-yl]hexan-1-ol (2u)**: GP 5 was used to obtain homoallylic alcohol **2u** from cyclohexadienyllithium (24 mmol, prepared according to GP 1), titanium(IV) isopropoxide (7.38 g, 26 mmol), and hexanal (2.00 g, 20 mmol). FC (P/MTBE 7:1) yielded **2u** (3.63 g, 96%) as a colorless oil. d.r. (*syn*:*anti*) = 28:1, determined by GC analysis; retention times: major diastereoisomer: enantiomer 1: 44.64 min, enantiomer 2: 44.88 min; minor diastereoisomer: 45.28 min, both enantiomers. IR (neat): $\tilde{\nu}$ = 3374(br s), 2930(s), 2859(m), 1677(w), 1456(m), 1379(w), 1057(m), 729(w), 700(w) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.99–5.95 (m, 1H; vinyl H), 5.87–5.80 (m, 2H; vinyl H), 5.67–5.62 (m, 1H; vinyl H), 3.69–3.61 (m, 1H; C*H*OH), 2.37–2.24 (m, 3H), 1.50–1.30 (m, 8H; CH_2), 0.89 ppm (t, 3H, *J* = 6.6 Hz; CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 127.6 (CH), 126.1 (CH), 125.4 (CH), 123.7 (CH), 73.5 (CH), 38.9 (CH), 34.2 (CH_2), 31.9 (CH_2), 25.6 (CH_2), 23.1 (CH_2), 22.6 (CH_2), 14.0 ppm (CH_3). MS (EI): 180 (4, $[M]^+$), 178 (1, $[M-H_2]^+$), 107 (78), 94 (26), 93 (28), 81 (58), 78 (100), 77 (47), 68 (13), 61 (27), 56 (15). HRMS: ($[M]^+$) calcd for $C_{12}H_{20}O$: 180.1514; found: 180.1523.

(1*R*)-1-[(1*R*)-cyclohexa-2,4-dien-1-yl]hexan-1-ol (2u): GP 2 was used to obtain homoallylic alcohol **2u** from $CpTiCl_3$ (812 mg, 3.70 mmol), TADDOL (1.73 g, 3.70 mmol), NEt_3 (1.08 mL, 8.10 mmol), cyclohexadienyllithium (3.50 mmol, prepared according to GP 1), and hexanal (176 mg, 1.76 mmol). FC (P/MTBE 10:1) yielded **2u** (156 mg, 49%) as a colorless oil. d.r. (*syn*:*anti*) > 99:1; e.r. = 92:8, determined by GC analysis; retention times: major diastereoisomer: enantiomer 1: 44.64 min, enantiomer 2: 44.88 min; minor diastereoisomer: 45.28 min, both enantiomers. GC and NMR analysis showed that 12% of the product consisted of isomeric [cyclohexa-2,5-dien-1-yl]-hexan-1-ol (**5u**; retention time: 45.90 min).

Synthesis of (2*R*,3*S*,4*S*)-(+)-2-undecyl-4-methyl-5-oxo-tetrahydrofuran-3-carboxylic acid (nephrosteranic acid):

*(2R,3S)-(+)-2-undecyl-5-oxo-tetrahydrofuran-3-carboxylic acid (**17**)*: A solution of **2t** (1.00 g, 3.85 mmol, 1.0 equiv) in dry CH_2Cl_2 (150 mL) was cooled to −78 °C and ozone was bubbled through the solution until a blue color appeared (ca. 30 min). Oxygen was then bubbled through the solution until the blue color disappeared (ca. 10 min). Dimethylsulfide (1.20 g, 19.25 mmol, 5.0 equiv) was added. The reaction mixture was stirred for 10 minutes at −78 °C and was then allowed to warm to 0 °C and stirred overnight at this temperature. The solvents were removed in vacuo. MTBE (50 mL) and water (30 mL) were added. The phases were separated and the organic layer was washed with water (25 mL). The combined aqueous phases were extracted with MTBE (2 × 100 mL). The combined organic phases were dried ($MgSO_4$) and the solvents were removed in vacuo.

The collected material (1.18 g) was dissolved in EtOH (100 mL). A catalytic amount (ca. 30 mg) of Pd/C was added to the solution. The suspension was stirred overnight under a hydrogen atmosphere at ambient pressure. The suspension was passed over a short celite pad and the solvent was removed in vacuo. The crude product **16** (1.48 g) was used without further purification in the next step.

Crude lactol **16** (336 mg, 1.24 mmol) was dissolved in acetone (20 mL) and cooled to 0 °C. Freshly prepared Jones reagent (2.49 g CrO_3, 1.8 mL H_2SO_4, 3.6 mL H_2O; 20.0 equiv) was cooled to 0 °C and was added dropwise to the reaction mixture. The mixture was stirred for 3 h at 0 °C then *i*PrOH was added carefully to the brownish solution to destroy excess reagent. CH_2Cl_2 (150 mL) and water (50 mL) were added to the dark green reaction mixture and the phases were separated. The aqueous layer was extracted four times with CH_2Cl_2 (4 × 70 mL). The combined organic layers were washed four times with water and brine and then dried ($MgSO_4$). The solvents were removed by evaporation in vacuo. FC (CH_2Cl_2/MeOH 10:1) and recrystallization (hexane/*i*PrOH 98:2) gave lactone **17** as a white solid (75 mg, 21% over all steps). ^1H NMR (500 MHz, $CDCl_3$): δ = 4.62 (dt, 1H, J_1 = 7.5, J_2 = 4.5 Hz), 3.11–3.06 (m, 1H), 2.94 (dd, 1H, J_1 = 17.9, J_2 = 8.5 Hz), 2.81 (dd, 1H, J_1 = 17.9, J_2 = 9.6 Hz), 1.84–1.70 (m, 1H), 1.66–1.37 (m, 2H), 1.37–1.20 (m, 17H), 0.88 ppm (t, 3H, *J* = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.3 (C), 174.3 (C), 81.8 (CH), 45.5 (CH), 35.4 (CH), 34.0 (CH), 31.9 (CH), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 25.2 (CH_2), 22.7 (CH_2), 14.1 ppm (CH_3). MS (EI): 284 ($[M]^+$, 9), 266 (100), 248 (24), 239 (33), 238 (70) 225 (52), 223 (11), 206 (15), 192 (11), 183 (12), 167 (23), 154 (25), 145 (23), 140 (41), 129 (38), 118 (73), 112 (22), 100 (41), 83 (31), 56 (20). HRMS: ($[M]^+$) calcd for $C_{16}H_{28}O_4$: 284.1988; found: 284.1982.

(2R,3S,4S)-(+)-2-Undecyl-4-methyl-5-oxo-tetrahydrofuran-3-carboxylic acid (nephrosteranic acid): NaHMDS (1.0 M in THF, 0.154 mL, 0.154 mmol, 3.6 equiv) was added to a solution of **17** (20 mg, 0.07 mmol) in THF (1.0 mL) at −78 °C over 15 min. After 1 h at −78 °C, MeI (0.042 mL, 0.67 mmol) was added. The mixture was stirred at −78 °C for 2 h then the temperature was allowed to rise to −20 °C overnight. 2 N HCl (0.75 mL) was added and the mixture was allowed to warm to room temperature and was then extracted with EtOAc (3 × 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. FC ($CHCl_3$/MeOH 10:1) and recrystallization (hexane/*i*PrOH 98:2) gave nephrosteranic acid (18.7 mg, 89%) as a white crystalline solid. Crystals suitable for x-ray analysis were obtained from a solution of nephrosteranic acid in CH_2Cl_2 laminated with hexane. M.p.: 97 °C. $[\alpha]_{25}^{D} = +27.3°$ (*c* = 0.97 in $CHCl_3$), ref. [22a]: $[\alpha]_{25}^{D} = +27.2°$ (*c* = 1.45 in $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 4.48 (dt, 1H, J_1 = 8.8, J_2 = 3.8 Hz), 2.98 (dq, 1H, J_1 = 11.4, J_2 = 6.9 Hz), 2.69 (dd, 1H, J_1 = 9.7, J_2 = 10.9 Hz), 1.86–1.79 (m, 1H; Ar−H), 1.74–1.67 (m, 1H), 1.56–1.48 (m, 1H), 1.43–1.22 (m, 17H), 1.36 (d, 3H, *J* = 6.9 Hz), 0.88 ppm (t, 3H, *J* = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.6 (C), 175.6 (C), 79.4 (CH), 53.9 (CH), 39.8 (CH), 34.9 (CH), 31.9 (CH), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 25.3 (CH_2), 22.7 (CH_2), 14.5 (CH_3), 14.1 ppm (CH_3).

Synthesis of (4*S*,5*R*)-5-butyl-4-methyldihydrofuran-2(3H)-one (*trans*-whisky lactone):

*(1S)-1-[(1R)-Cyclohexa-2,4-dien-1-yl]pent-2-yn-1-ol (**19a**)*: GP 2 was used to obtain homoallylic alcohol **19a** from $CpTiCl_3$ (1098 mg, 5.00 mmol), TADDOL (2.34 g, 5.00 mmol), NEt_3 (1.53 mL, 11.01 mmol), cyclohexadienyllithium (4.75 mmol, prepared according to GP 1), and pent-2-yn-1-al (**18a**; 195 mg, 2.38 mmol). FC (first FC: P/MTBE 10:1, second FC: P/acetone 8:1) yielded **19a** (334 mg, 66%) as a colorless oil. The diastereomeric and the enantiomeric ratios could not be determined. IR (neat): $\tilde{\nu}$ = 3378(s), 3038(w), 2976(m), 2878(m), 2231(w), 1668(w), 1454(m), 1318(m), 1141(w), 1017(s), 686(m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.03–5.94 (m, 1H; vinyl H), 5.92–5.75 (m, 3H; vinyl H), 4.35–4.25 (m, 1H; C*H*OH), 2.60–2.43 (m, 1H), 2.42–2.18 (m, 4H), 1.87 (br s, 1H; OH), 1.18–1.11 ppm (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 126.3 (CH), 125.8 (CH), 125.5 (CH), 124.0 (CH), 88.2 (C), 79.5 (C), 64.4 (CH), 40.4 (CH), 25.2 (CH_2), 13.8 (CH_3), 12.8 ppm (CH_2). MS (EI): 160 (4, $[M-H_2]^+$), 83 (47), 80 (46), 79 (100), 77 (20), 55 (43). HRMS: ($[M-H_2]^+$) calcd for $C_{11}H_{12}O$: 160.0888; found: 160.0892.

*(4R,5R)-5-butyl-4-(hydroxymethyl)dihydrofuran-2(3H)-one (**21a**)*: A solution of **19a** (843 mg, 5.20 mmol, 1.0 equiv) in dry CH_2Cl_2 (60 mL) was cooled to −78 °C and ozone was bubbled through the solution until a blue color could be observed (ca. 45 min). Oxygen was bubbled through the solution until the blue color disappeared (ca. 15 min). Dimethylsul-

fide (1.61 g, 26.02 mmol, 5.0 equiv) was added. The reaction mixture was stirred for 10 minutes at −78 °C and was then allowed to warm to 0 °C, and was stirred overnight at this temperature. The solvents were removed in vacuo. Et_2O (20 mL), acetone (20 mL), and water (10 mL) were added. The phases were separated and the organic layer was washed with water (10 mL). The combined aqueous phases were extracted with MTBE (3×20 mL). The combined organic phases were dried ($MgSO_4$) and the solvents were removed in vacuo.

The collected material (864 mg) was dissolved in EtOH (60 mL). A catalytic amount of Pd/C (ca. 20 mg) was added to the solution. The suspension was stirred overnight under a hydrogen atmosphere at ambient pressure and temperature and was then passed over a short celite pad. The solvent was removed in vacuo. The crude lactol **20a** (804 mg) obtained by this method was used without further purification in the next step.

Lactol **20a** (1.19 g, 6.91 mmol) was dissolved in acetone (200 mL) and cooled to 0 °C. Freshly prepared Jones reagent (6.90 g CrO_3, 4.90 mL H_2SO_4, 9.80 mL H_2O; 10.0 equiv) was cooled to 0 °C and added dropwise to the reaction mixture. The mixture was stirred for 2.25 h at 0 °C, and then *i*PrOH was added carefully to the brownish solution to destroy excess reagent. CH_2Cl_2 (100 mL) and water (50 mL) were added to the reaction mixture and the phases were separated. The aqueous layer was extracted four times with CH_2Cl_2 (4×50 mL). The combined organic layers were dried ($MgSO_4$). After evaporation of the solvents in vacuo, the lactone acid (1.18 g) corresponding to lactol **20a** was obtained as a yellow oil. This crude product was used without further purification in the next step.

A procedure described by Mori et al.[27] was applied. Crude lactone acid (266 mg, 1.43 mmol, 1.0 equiv) was dissolved in THF (10 mL) and cooled to 0 °C. $BH_3{\cdot}SMe_2$ (10.0 M in THF, 0.18 mL, 1.79 mmol, 1.25 equiv) was added and the mixture was stirred for 3.5 h at this temperature. The reaction was stopped by the addition of MeOH (ca. 5 mL) and the solvents were removed in vacuo. The residue was dissolved in MeOH (10 mL) and the solution was evaporated in vacuo. This procedure was repeated. The residue was purified by FC (PE/EtOAc 1:1) and the product **21a** was obtained as a colorless oil (38 mg, 0.22 mmol, 13% over all steps). IR (neat): $\tilde{\nu}$ = 3443(br s), 2934(s), 2872(m), 1771(s), 1467(w), 1195(s), 1119(m), 1078(w), 982(m), 733(m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.36 (dt, 1H, J = 7.4, 5.4 Hz; OCH), 3.69 (d, 2H, J = 5.8 Hz; OCH_2), 2.65 (dd, 1H, J_1 = 17.5, J_2 = 8.7 Hz; O=CCH_a), 2.44 (dd, 1H, J_1 = 17.6, J_2 = 7.0 Hz; O=CCH_b), 2.40–2.34 (m, 1H; CH), 1.80–1.30 (m, 7H; CH_2, OH), 0.91 ppm (t, 3H, J = 7.2 Hz; CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.5 (C), 82.8 (CH), 63.0 (CH_2), 42.5 (CH), 34.9 (CH_2), 31.4 (CH_2), 27.5 (CH_2), 22.4 (CH_2), 13.9 ppm (CH_3). MS (ESI): 539 (100, $[3M+Na]^+$), 367 (95, $[3M+Na]^+$), 227 (55), 185 (55). HRMS (ESI): calcd for $C_{27}H_{48}O_9Na$ ($[3M+Na]^+$): 539.3196; found: 539.3227; calcd for $C_{18}H_{32}O_6Na$ ($[2M+Na]^+$): 367.2097; found: 367.2064.

*(4S,5R)-4-(Bromomethyl)-5-butyldihydrofuran-2(3H)-one (**22a**)*: A procedure described by Montforts et al.[28] was used. Alcohol **21a** (132 mg, 776 μmol, 1.0 equiv) and CBr_4 (721 mg, 2.17 mmol, 2.8 equiv) were dissolved in CH_2Cl_2 (70 mL) and cooled to 0 °C. After 10 min, PPh_3 (1.14 g, 4.35 mmol, 5.6 equiv) was added and the ice bath was removed. The reaction mixture turned dark red and was stirred overnight. The mixture was successively washed with water, HCl (1 M in H_2O), and a saturated aqueous $NaHCO_3$ solution (10 mL each). The phases were separated and the organic phase dried ($MgSO_4$). The solvent was removed in vacuo. The residue was purified by chromatography (P/MTBE 2:1) and **22a** (144 mg, 615 μmol, 79%) was obtained as a colorless oil. IR (neat): $\tilde{\nu}$ = 2957(s), 2933(s), 2872(m), 1776(s), 1466(w), 1257(m), 1208(m), 1179(s), 1125(w), 995(m), 636(m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.32 (dt, 1H, J_1 = 7.4, J_2 = 5.4 Hz; OCH), 3.49 (dd, 1H, J_1 = 10.6, J_2 = 5.6 Hz; $BrCH_a$), 3.42 (dd, 1H, J_1 = 10.7, J_2 = 6.1 Hz; $BrCH_b$), 2.75 (dd, 1H, J_1 = 17.2, J_2 = 8.2 Hz; O=CCH_a), 2.61–2.53 (m, 1H; CH), 2.51 (dd, 1H, J_1 = 17.1, J_2 = 7.0 Hz; O=CCH_b), 1.75–1.63 (m, 2H; CH_2), 1.54–1.31 (m, 4H; CH_2), 0.92 ppm (t, 3H, J = 6.9 Hz; CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.9 (C), 83.6 (CH), 42.4 (CH), 34.5 (CH_2), 34.0 (CH), 33.6 (CH_2), 27.4 (CH_2), 22.3 (CH_2), 13.8 ppm (CH_3). MS (ESI): 491 (25, $[2M+Na]^+$), 291 (100), 257 (45, $[M+Na]^+$), 227 (100), 171 (30, $[M-Br]^+$). HRMS (ESI): calcd for $C_9H_{15}O_2BrNa$ ($[M+Na]^+$): 257.0153; found: 257.0152.

(4S,5R)-5-Butyl-4-methyldihydrofuran-2(3H)-one (trans-whisky lactone): A procedure described by Studer et al.[13] was used. Bromide **22a** (45 mg, 191 μmol, 1.0 equiv), AIBN (9.5 mg, 58 μmol, 0.33 equiv), and diene **23** (102.5 mg, 382 μmol, 2.0 equiv) were dissolved in hexane (1.0 mL) and heated to 80 °C in a sealed tube. The reaction mixture was stirred overnight at 80 °C. The solvent was removed in vacuo. *trans*-Whiskylactone was isolated by FC (P/MTBE 4:1) as a colorless oil (22 mg, 141 μmol, 74%). d.r. (*syn*:*anti*) > 99:1; e.r. = 97:3, determined by GC analysis; retention times: major diastereoisomer: enantiomer 1: 25.27 min, enantiomer 2: 25.80 min; minor diastereoisomer: enantiomer 1: 32.89 min, enantiomer 2: 33.35 min. IR (neat): $\tilde{\nu}$ = 2959(m), 2934(m), 2873(w), 1781(s), 1667(m), 1460(w), 1212(m), 1172(m), 985(m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.01 (dt, 1H, J_1 = 7.7, J_2 = 4.0 Hz; OCH), 2.70–2.60 (m, 1H), 2.25–2.14 (m, 2H), 1.72–1.30 (m, 6H), 1.12 (d, 3H, J = 6.4 Hz; CH_3), 0.91 ppm (t, 3H, J = 6.4 Hz; CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.5 (C), 87.4 (CH), 37.1 (CH_2), 36.0 (CH), 33.7 (CH), 27.8 (CH_2), 22.4 (CH_2), 17.5 (CH_3), 13.8 ppm (CH_3). MS (ESI): 335 (35, $[2M+Na]^+$), 211 (100), 179 (40, $[M+Na]^+$), 157 (20, $[M+H]^+$). HRMS (ESI): calcd for $C_9H_{16}O_2Na$ ($[M+Na]^+$): 179.1048; found: 179.1031.

All data are in accordance with the values reported in the literature.[22a]

Synthesis of (4*S*,5*R*)-4-methyl-5-pentyldihydrofuran-2(3H)-one (*trans*-cognac lactone):

*(1S)-1-[(1R)-Cyclohexa-2,4-dien-1-yl]hex-2-yn-1-ol (**19b**)*: GP 2 was used to obtain homoallylic alcohol **19b** from $CpTiCl_3$ (2.19 g, 10.00 mmol), TADDOL (4.68 g, 10.00 mmol), NEt_3 (3.07 mL, 22.00 mmol), cyclohexadienyllithium (9.50 mmol, prepared according to GP 1), and hex-2-yn-1-al (**18b**; 456 mg, 4.75 mmol). FC (P/MTBE 10:1) yielded **19b** (480 mg, 57%) as a colorless oil. The diastereomeric and the enantiomeric ratios were not determined. IR (neat): $\tilde{\nu}$ = 3386(br s), 3039(w), 2963(m), 2872(m), 2231(w), 1457(w), 1430(m), 1380(m), 1034(s), 1007(m), 684(s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.03–5.95 (m, 1H; vinyl H), 5.91–5.74 (m, 3H; vinyl H), 4.33–4.28 (m, 1H; C*H*OH), 2.61–2.46 (m, 1H), 2.42–2.25 (m, 4H), 2.19 (dt, 2H, J_1 = 7.0, $^5J_2$ = 2.0 Hz; CCH_2), 1.96 (br s, 1H; OH), 1.51 (sex, 2H, J = 7.2 Hz; C$H_2$$CH_3$), 0.97 ppm (t, 3H, J = 7.5 Hz; CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 126.4 (CH), 125.7 (CH), 125.4 (CH), 123.9 (CH), 86.7 (C), 80.4 (C), 64.4 (CH), 40.4 (CH), 25.2 (CH_2), 22.0 (CH_2), 20.7 (CH_2), 13.4 ppm (CH_3). MS (EI): 174 (3, $[M-H_2]^+$), 97 (20), 95 (18), 83 (11), 80 (44), 79 (100), 77 (20), 70 (52), 55 (15), 43 (15), 41 (26). HRMS: ($[M-H_2]^+$) calcd for $C_{12}H_{14}O$: 174.1045; found: 174.1038.

*(4R,5R)-4-(Hydroxymethyl)-5-pentyldihydrofuran-2(3H)-one (**21b**)*: A solution of **19b** (1.42 g, 8.07 mmol, 1.0 equiv) in dry CH_2Cl_2 (80 mL) was cooled to −78 °C and ozone was bubbled through the solution until a blue color could be observed (ca. 45 min). Oxygen was bubbled through the solution until the blue color disappeared (ca. 15 min). Dimethylsulfide (2.72 g, 43.9 mmol, 5.0 equiv) was added. The reaction mixture was stirred for 10 minutes at −78 °C and was then allowed to warm to 0 °C and was stirred overnight at this temperature. The solvents were removed in vacuo. Et_2O (30 mL), acetone (40 mL), and water (20 mL) were added and the phases separated. The organic layer was washed with water (20 mL). The combined aqueous phases were extracted with MTBE (3× 40 mL). The combined organic phases were dried ($MgSO_4$) and the solvents were removed in vacuo.

A sample of the collected material (1.27 g of 1.52 g) was dissolved in EtOH (100 mL). A catalytic amount (ca. 30 mg) of Pd/C was added to the solution. The suspension was stirred vigorously for 60 h in an autoclave under hydrogen at a pressure of 20 bar and at ambient temperature. The suspension was passed over a short celite pad and the solvent was removed in vacuo. The crude lactol **20b** (1.53 g) was used without further purification in the next step.

Crude lactol **20b** (744 mg, 4.00 mmol) was dissolved in acetone (60 mL) and was cooled to 0 °C. Freshly prepared Jones reagent (4.00 g CrO_3, 3.60 mL H_2SO_4, 7.20 mL H_2O; 10.0 equiv) was cooled to 0 °C and added dropwise to the reaction mixture. The mixture was stirred for 2.25 h at 0 °C, then *i*PrOH was added carefully to the brownish solution to destroy excess reagent. CH_2Cl_2 (50 mL) and water (20 mL) were added to the reaction mixture and the phases were separated. The aqueous layer was extracted four times with CH_2Cl_2 (4×50 mL). The combined organic layers were dried ($MgSO_4$) and the solvents were removed by evaporation in vacuo to give a yellow oil. FC ($CHCl_3$/MeOH/HOAc 70:10:1) yielded (2*R*,3*S*)-5-oxo-2-pentyltetrahydrofuran-3-carboxylic acid (346 mg, 43%). Analysis of the product provided data identical to those reported in the

literature.[29] A procedure described by Mori et al.[27] was then applied. The obtained carboxylic acid (30 mg, 150 μmol, 1.0 equiv) was dissolved in THF (1 mL) and cooled to 0 °C. $BH_3{\cdot}SMe_2$ (10.0 M in THF, 19 μL, 190 μmol, 1.25 equiv) was added and the mixture was stirred for 3 h at this temperature. The reaction was terminated by the addition of MeOH (1 mL) and the solvents were removed in vacuo. The residue was dissolved in MeOH (5 mL) and the solvent was evaporated in vacuo. This procedure was repeated. The residue was purified by FC (PE/EtOAc 1:1) and **21b** was obtained as a colorless oil (14 mg, 75 μmol, 21.5% over all steps). IR (neat): $\tilde{\nu}$ = 3441(br s), 2933(s), 2872(s), 1770(s), 1467(m), 1202(s), 1118(m), 1077(w), 994(m), 948(w) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 4.36 (dt, 1H, J = 7.6, J = 5.5 Hz; OCH), 3.68 (d, 2H, J = 5.5 Hz; OCH_2), 2.64 (dd, 1H, J_1 = 17.6, J_2 = 8.9 Hz; O=CCH_a), 2.44 (dd, 1H, J_1 = 17.7, J_2 = 8.5 Hz; O=CCH_b), 2.39–2.34 (m, 1H; CH), 2.00 (br s, 1H; OH), 1.71–1.61 (m, 2H; CH_2), 1.55–1.26 (m, 6H; CH_2), 0.89 ppm (t, 3H, J = 6.9 Hz; CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.7 (C), 83.0 (CH), 62.9 (CH_2), 42.5 (CH), 35.2 (CH_2), 31.5 (CH_2), 31.4 (CH_2), 27.5 (CH_2), 22.4 (CH_2), 13.9 ppm (CH_3). MS (ESI): 581 (80, $[3M+Na]^+$), 395 (100, $[2M+Na]^+$), 241 (75), 225 (55, $[M+K]^+$), 209 (35, $[M+Na]^+$), 187 (15, $[M+H]^+$). HRMS (ESI): calcd for $C_{20}H_{36}O_6Na$ ($[2M+Na]^+$): 395.2410 found: 395.2426.

*(4S,5R)-4-(Bromomethyl)-5-pentyldihydrofuran-2(3H)-one (**22b**)*: A procedure described by Montforts et al.[28] was used. Alcohol **21b** (76 mg, 409 μmol, 1.0 equiv) and CBr_4 (379 mg, 1.14 mmol, 2.8 equiv) were dissolved in CH_2Cl_2 (30 mL) and cooled to 0 °C. After 10 min, PPh_3 (600 mg, 2.29 mmol, 5.6 equiv) was added and the ice bath was removed. The reaction mixture turned dark red and was stirred overnight. The mixture was successively washed with water, HCl (1 M in H_2O), and a saturated aqueous solution of $NaHCO_3$ (5 mL each). The phases were separated and the organic phase was dried ($MgSO_4$). The solvent was removed in vacuo. The residue was adsorbed on silica gel and was purified by FC (P/MTBE 2:1). **22b** (68 mg, 273 μmol, 67%) was obtained as a colorless oil. IR (neat): $\tilde{\nu}$ = 2931(m), 2860(m), 1777(s), 1465(w), 1258(m), 1177(s), 1108(m), 999(m), 617(m) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 4.31 (m, 1H; OCH), 3.47 (dd, 1H, J_1 = 10.7, J_2 = 5.8 Hz; $BrCH_a$), 3.41 (dd, 1H, J_1 = 10.5, J_2 = 6.2 Hz; $BrCH_b$), 2.75 (dd, 1H, J_1 = 17.4, J_2 = 8.5 Hz; O=CCH_a), 2.61–2.53 (m, 1H; CH), 2.50 (dd, 1H; J_1 = 17.4, J_2 = 7.1 Hz; O=CCH_b), 1.73–1.62 (m, 2H; CH_2), 1.54–1.27 (m, 6H; CH_2), 0.93–0.88 ppm (m, 3H; CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.9 (C), 83.7 (CH), 42.4 (CH), 34.9 (CH_2), 34.0 (CH), 33.6 (CH_2), 31.4 (CH_2), 25.0 (CH_2), 22.4 (CH_2), 13.9 ppm (CH_3). MS (ESI): 521 (100, $[2M+Na]^+$), 303 (100), 289 (65, $[M+K]^+$), 273 (25, $[M+Na]^+$), 249 (55, $[M+H]^+$), 223 (100), 201 (72). HRMS (ESI): calcd for $C_{10}H_{17}O_2BrNa$ ($[M+Na]^+$): 271.0310; found: 271.0307.

(4S,5R)-4-methyl-5-pentyldihydrofuran-2(3H)-one (trans-cognac lactone): A procedure described by Studer et al.[13] was used. Bromide **22b** (34 mg, 136 μmol, 1.0 equiv), AIBN (7.5 mg, 46 μmol, 0.33 equiv), and diene **23** (73 mg, 273 μmol, 2.0 equiv) were dissolved in hexane (1.5 mL) and heated to 80 °C in a sealed tube. The reaction mixture was stirred overnight at 80 °C. The solvent was removed in vacuo. FC (P/MTBE 4:1) gave *trans*-cognaclactone as a colorless oil (22 mg, 130 μmol, 95%). d.r. (*syn*:*anti*) > 99:1; e.r. = 97.5:2.5, determined by GC analysis; retention times: minor diastereoisomer: enantiomer 1: 21.78 min, enantiomer 2: 22.40 min; major diastereoisomer: enantiomer 1: 35.52 min, enantiomer 2: 36.54 min). IR (neat): $\tilde{\nu}$ = 2958(m), 2933(m), 2861(w), 1779(s), 1669(m), 1458(w), 1210(m), 1169(m), 1107(s), 1003(w), 938(m) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 4.01 (dt, 1H, J_1 = 7.7, J_2 = 3.9 Hz; OCH), 2.73–2.63 (m, 1H; O=CCH_a), 2.28–2.15 (m, 2H, CH; O=CCH_b); 1.72–1.27 (m, 8H; CH_2), 1.14 (d, 3H, J = 6.5 Hz; CH_3), 0.89 ppm (t, 3H, J = 6.4 Hz; CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.9 (C), 87.5 (CH), 37.1 (CH_2), 36.1 (CH), 34.0 (CH_2), 31.6 (CH_2), 25.4 (CH_2), 22.5 (CH_2), 17.5 (CH_3), 13.6 ppm (CH_3). MS (ESI): 376 (80, $[2M+Na]^+$), 307 (35), 225 (90, $[M+Na+MeOH]^+$), 193 (100, $[M+Na]^+$), 171 (20, $[M+H]^+$), 153 (30). HRMS (ESI): calcd for $C_{11}H_{22}O_3Na$ ($[M+MeOH+Na]^+$): 225.1467; found: 225.1460; calcd for $C_{10}H_{19}O_2$ ($[M+H]^+$): 171.1386; found: 171.1299; calcd for $C_{10}H_{18}O_2Na$ ($[M+Na]^+$): 193.1205; found: 193.1187.

All data are in accordance with those given in the literature.[22a]

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