DOI: 10.1002/adsc.201000384

Efficient Enantioselective Syntheses of Sertraline, 2-Epicatalponol and Catalponol from Tetralin-1,4-dione

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Received: May 16, 2010; Published online: September 8, 2010

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201000384.

Abstract: Tetralin-1,4-dione, the stable tautomer of dihydroxynaphthalene, was reduced with catecholborane in the presence of 3,3-diphenyl-1-butyltetrahydro-3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole as catalyst to give enantiomerically highly enriched 4-hydroxy-1-tetralone (99% *ee*) in an efficient one-pot procedure. The *R*-enantiomer provided a rapid access to sertraline while the *S*-enantiomer was converted into 2-epicatalponol and catalponol. A more selective enantioselective route to the antithermitic catalponol made use of the planar chiral tricarbonylchromium complex of hydroxytetralone. Its precursor chromium(tricarbonyl)[η^6-(1-4,4a,8a)-tetralin-5,8-dione] was obtained *via* direct complexation of 1,4-dihydroxynaphthalene using chromium(tricarbonyl)-tris(ammonia) and boron trifluoride etherate as source of the chromium(tricarbonyl) fragment. Enolate prenylation was best carried out in the presence of a tetraamine ligand. Complete inversion of the stereogenic center bearing the prenyl group of the initially obtained tetralone complex was achieved *via* enolate formation followed by protonation.

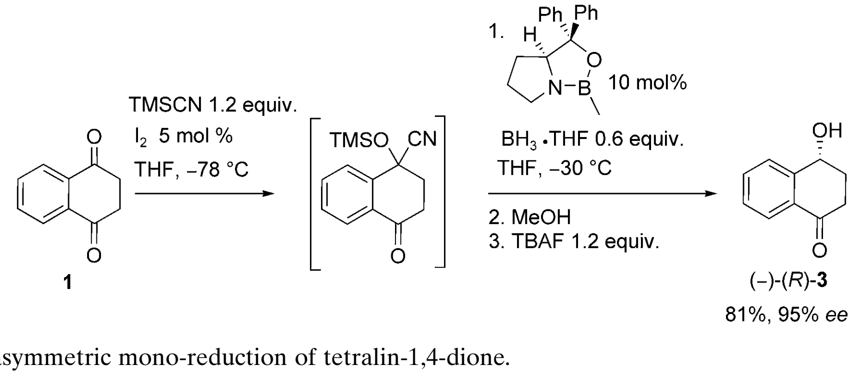
Keywords: arene complexes; asymmetric reduction; chromium tricarbonyl; prenylation; tautomerism

Introduction

Tetralin-1,4-dione (**1**) is readily obtained by tautomerization of 1,4-dihydroxynaphthalene (**2**) in trifluoroacetic acid.[1] In the solid as well as in solution in the absence of acid or base, **1** and **2** do not interconvert unless heated at >100 °C. Dione **1** can be reduced with fair to excellent selectivity to give either the *cis*-diol or the *trans*-diol preferentially depending on the reducing agent.[2] Of special interest to the study described in this paper is the finding that a two-step, one-pot enantioselective mono-reduction of **1** to give (−)-(*R*)-**3** can be achieved (Scheme 1).[2,3]

4-Hydroxy-1-tetralone (*rac*-**3**) is a naturally occurring compound isolated from *Ampelocera edentula* with activity against cutaneous Leishmaniasis.[4]

In this article we report on (i) the application of highly enantiomerically enriched (*R*)-**3** to a formal,



Scheme 1. Two-step, asymmetric mono-reduction of tetralin-1,4-dione.

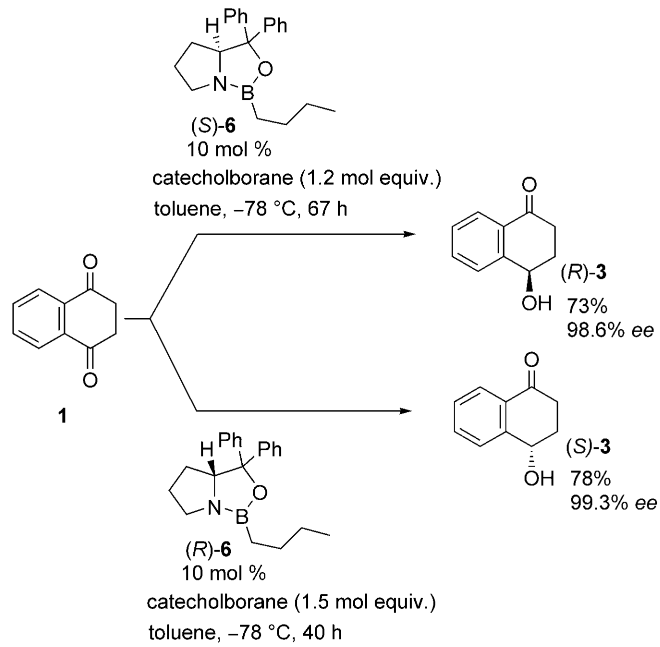
efficient synthesis of sertraline; (ii) a new one-step enantioselective catalytic reduction of **1** to **3**; (iii) the application of (*S*)-**3** to a synthesis of catalponol and 2-epicatalponol; (iv) an improved synthesis of the chromium tricarbonyl complex of **1** and its enantioselective mono-reduction; and (v) an enantioselective synthesis of catalponol *via* desymmetrization of a $[Cr(arene)(CO)_3]$ complex.

Results and Discussion

The antidepressant sertraline [(+)-*cis*-(1*S*,4*S*)-4-(3,4-dichlorophenyl)-(1-4)-tetrahydronaphthalene-1-amine] is a popular target of asymmetric synthesis.[5,6] The route reported by Lautens and Rovis involves the key intermediate (*R*)-**5**.[6h] This was synthesized *via* a six-step sequence from oxabenzonorbornadiene. Although the reported synthesis was efficient, the ready access of (*R*)-**3** suggested to us that the route to (*R*)-**5** and hence to sertraline may be shortened considerably. The realization of this project is shown in Scheme 2.[7]

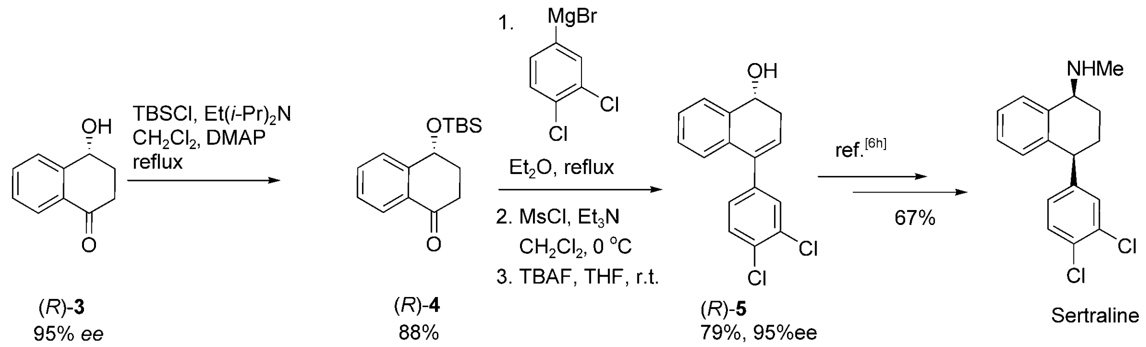
In the course of these studies we reinvestigated the mono-reduction of dione **1**. We were pleased to find that by switching from borane to catecholborane and using (*S*)-**6** as catalyst, the transformation of **1** to (*R*)-**3** could be carried out in toluene in good yield with high asymmetric induction (Scheme 3). Hence passing *via* the cyanohydrin intermediate (Scheme 1) is not required and this shortens further the access to highly enantioenriched 4-hydroxy-1-tetralone. Its enantiomer was also synthesized *via* this route and a further improvement was realized by increasing the quantity of catecholborane from 1.2 to 1.5 mol equivalents (Scheme 3).

Shortly before submission of this manuscript an article appeared reporting access to (*R*)-**3** *via* (1*R*,4*R*)-tetralindiol[1a,2] and Ru-catalyzed transfer-dehydrogenation.[8] The authors showed that the oxidation of the first alcohol function was faster than that of the second, and this provided a different access to (*R*)-**3** which was then transformed into a sertraline precursor.[8] While this is elegant and of interest, our new one-step asymmetric mono-reduction of **1** (Scheme 3) is more efficient and operationally simpler than the two-step double reduction/mono-oxidation sequence.



Scheme 3. One-step enantioselective mono-reduction of tetralin-1,4-dione (**1**).

Several natural products contain the 4-hydroxy-1-tetralone unit (Figure 1). Examples include catalponol,[9] epicatalponol,[9] isocatalponol,[10] junglanoside A,[11] and isoshinanolone.[12] The rapid access to both enantiomers of highly enantioenriched **3** opens the way to efficient syntheses of these products. In this paper we will focus attention on catalponol. Catalponol [(2*R*,4*S*)-4-hydroxy-2-(3-methylbut-2-enyl)tetralin-1-one][9] was isolated from the wood of *Catalpa ovata*.[9d–g] Its correct structure as shown in Figure 1 was established by Inoue et al.[9c] and its antithermitic activity was documented by McDaniel.[9b] Catalponol is also reported to enhance dopamine biosynthesis and



Scheme 2. Synthesis of sertraline intermediate (*R*)-**5**.

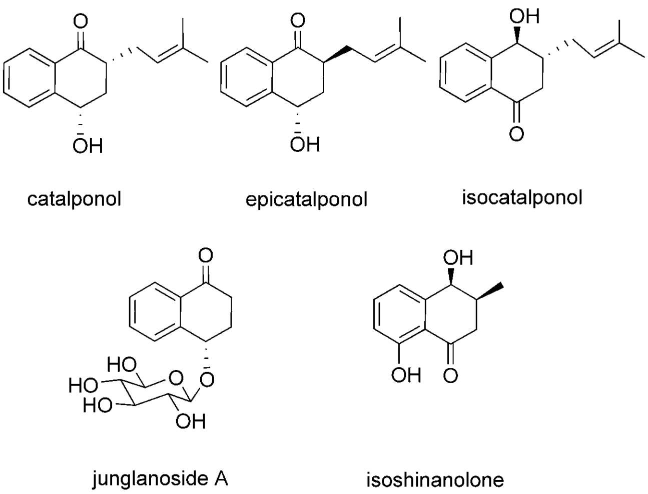
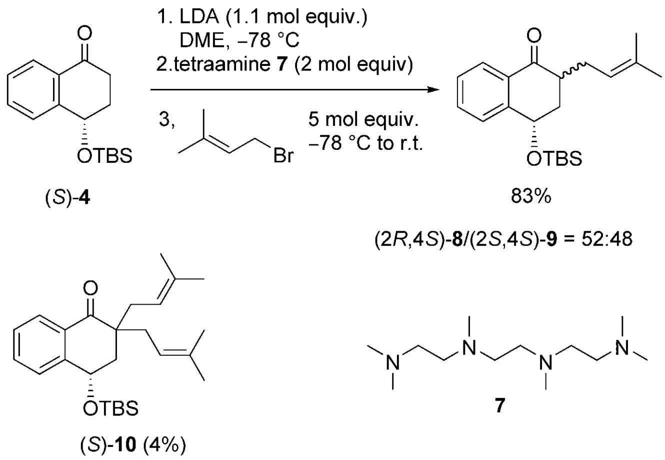


Figure 1. Natural products with a 4-hydroxy-1-tetralone motif.



Scheme 4. *alpha*-Prenylation of (*S*)-**4**.

to protect against L-DOPA-induced cytotoxicity in PC12 cells.[13] To the best of our knowledge, the synthesis of catalponol has not been reported.

With (+)-(*S*)-**3** in hand, the synthesis of catalponol requires alcohol protection, prenylation α to the ketone and removal of the protecting group.

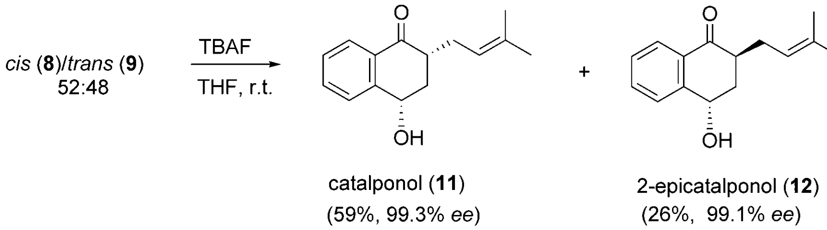
Initial attempts at mono-prenylation of (*S*)-**4** (LDA/THF/prenyl bromide) were plagued by low yields of the sought after monoprenylated products **8** and **9**, competitive bis-prenylation and partial recovery of starting material. Similar findings have been reported by Koga and co-workers in the allylation of tetralone.[14] Taking our cue from their work by switching to DME as solvent and adding the tetradentate amine **7** to the Li-enolate before the addition of prenyl bromide gave an 83% yield of a 52:48 mixture of the *cis* and *trans* diastereoisomers (**8** and **9**, respectively), together with 4% of diprenylated compound **10** and 9% of recovered **4** (Scheme 4).

Not unexpectedly, the pseudoequatorial OTBS group at the C-4 stereogenic center did not result in significant diastereoselection of the enolate prenylation. Nevertheless, after treating the mixture of diastereoisomers **8** and **9** with TBAF, chromatographic separation allowed the isolation of catalponol and 2-epicatalponol. (Scheme 5). The ratio of **11**/**12** is different from that of the precursors **8**/**9** raising the possibility of isomerization during desilylation.

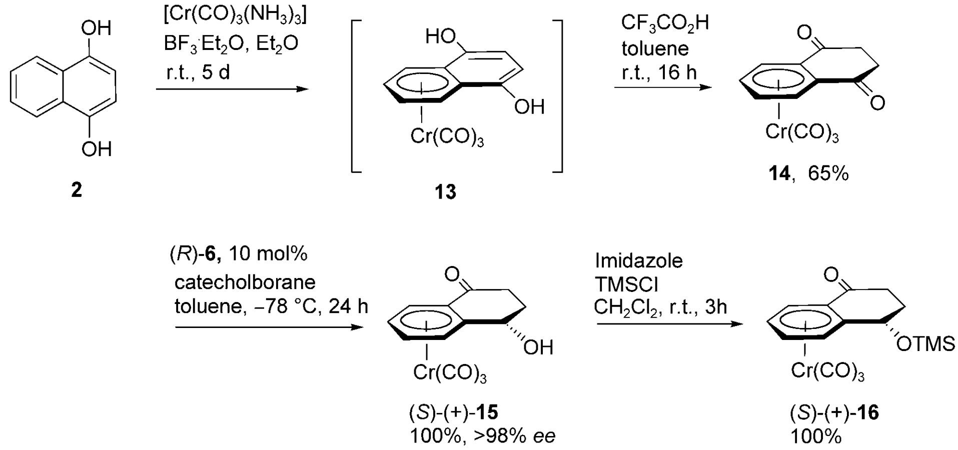
While this demonstrated the feasibility of the route starting from tetralin-1,4-dione, we felt that catalponol could be obtained with a higher selectivity than that shown in Scheme 4. Turning to chiral enolates or enamines would have been a likely successful route to achieve this goal.

We chose instead a different approach, one that builds on our long-standing interest in asymmetric synthesis using [Cr(arene)$(CO)_3$] complexes.[16] Transition metal π-complexes of arenes with different substituents in the *ortho-* or *meta*-positions are chiral. This and the fact that additions to [Cr(arene)$(CO)_3$] complexes occur predominantly *exo* to the metal then offer opportunities in asymmetric synthesis.

For the problem at hand, a rapid access to [$Cr(CO)_3$(tetralin-5,8-dione)] (**14**) is important. The two published methods for the synthesis of its precursor **13** both start with the readily available 1,4-dihydroxynaphthalene (**2**) and both use a protection/complexation/deprotection sequence.[1a,15] We have demonstrated earlier that **13** readily tautomerizes to the dione **14**.[1a,15b] While this last part of the sequence is efficient, the protection/deprotection sequence is not very economical but appeared necessary.



Scheme 5. Catalponol and 2-epicatalponol.

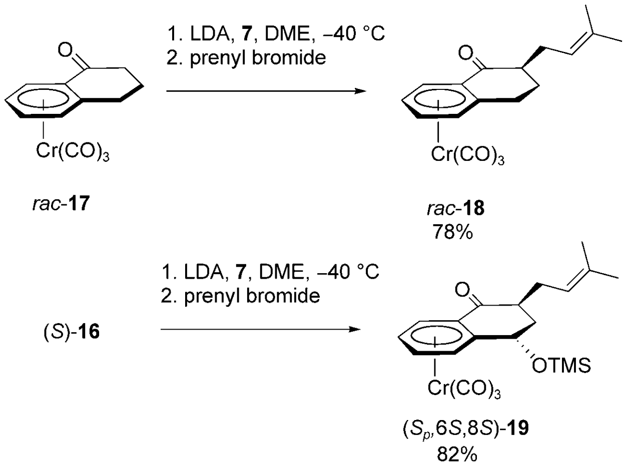


Scheme 6. New access to **14** and its asymmetric mono-reduction and silylation.

We now report that 1,4-dihydroxynaphthalene (**2**) can be complexed directly to give, after tautomerization, the tetralindione complex **14**. Enantioselective reduction of **14** afforded the requisite complex **15** which was silylated to give **16** (Scheme 6).

Optimized conditions of enolate formation and prenylation were first established for [Cr(CO)$_3$(tetralin)] (*rac*-**17**) (Scheme 7) using *in-situ* IR spectroscopy (see supporting information) to yield *rac*-**18** as a single diastereoisomer. As noted above for **4**, prenylation is best carried out in the presence of tetraamine **7**.

When applied to the catalponol precursor (*S*)-**16**, the Cr(CO)$_3$ complex of the TMS ether of epicatalponol was formed selectively. It is well established in reactions of arene tricarbonylchromium complexes that nucleophilic and electrophilic reagents approach the complexed arene on the face opposite to the metal[16,17] The structural assignment of **19** rests on the precedence of diastereoselective methylation of the enolate of complex **17**,[18] on NOESY measurements [C-6-H-C-8-H coupling in (6*S*,8*S*)-**20**, but not in (6*R*,8*S*)-**19**], and on comparison of spectral data of compounds obtained after desilylation/decomplexation with those of **11** and **12**. On treating *rac*-**18** with Na$_2$CO$_3$ in MeOH at 0°C, epimerization occured to give, after 15 h, an equilibrium mixture of *exo*-prenyl/*endo*-prenyl product in a 1:4 ratio. The same ratio was observed by Jaouen and Meyer for the methyltetralone complex.[18]



Scheme 7. Prenylation of *rac*-[Cr(CO)$_3$(tetralone)] (*rac*-**17**) and of (*S*)-**16**.

In order to obtain the *endo* complex (*Sp*,6*R*,8*S*)-**20** selectively we took recourse to enolate formation and *exo*-protonation with citric acid at −40°C. As shown in Scheme 8, this was successful. Ether hydrolysis and decomplexation then delivered enantiomerically pure catalponol.

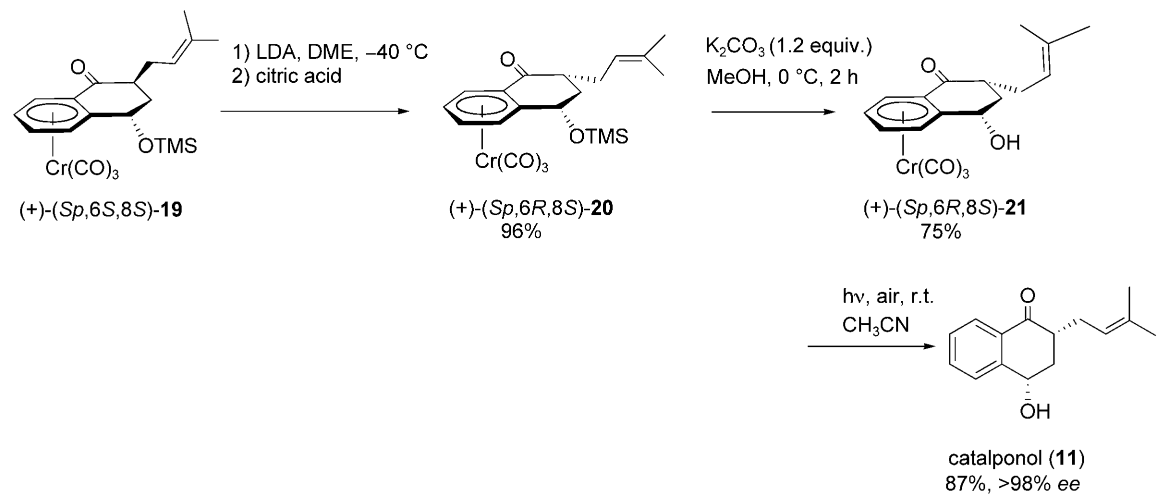
Conclusions

In conclusion, the efficient enantioselective mono-reduction of tetralin-1,4-dione, the stable tautomer of 1,4-dihydroxynaphthalene, provides access to a highly useful chiral building block. This is shown here in the rapid syntheses of the three title products. Reactions of the corresponding Cr(CO)$_3$ complex demonstrate the power of complexation to access selectively and at will one or the other highly enantioenriched diastereoisomeric product.

Experimental Section

General

Reactions and manipulations involving organometallics or moisture-sensitive compounds were carried out under an atmosphere of N$_2$ in dry glassware. Solvents were degassed and dried by filtration on Al$_2$O$_3$ (Solvtek©) or distillation from Na/benzophenone ketyl. Chemicals were obtained from Aldrich, Acros, and Strem and used as received unless



Scheme 8. Inversion of configuration at C-6 in **19**, desilylation and decomplexation to give catalponol.

noted. All chromium complexes were kept away from light. Reactions were followed by analytical TLC [Al-sheet, silica gel 60 F_{254} (Merck)]/UV. Yields given are of material purified by crystallization or flash column chromatography (f.c) [Aldrich silica gel 60 Å (230–400 mesh)]. ^{1}H and ^{13}C NMR (room temperature) were recorded on Brucker AMX-500, AMX-400, or AMX-300. Chemical shifts are given in ppm, int *d*-lock. Coupling constants *J* are given in Hertz. Multiplicities are indicated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m). IR spectra were taken on a Perkin–Elmer Spectrum 100/Golden Gate accessory. HR-MS were obtained with a QSTAR Pulsar (AB/MDS Sciex). For HPLC, Agilent 1100/Chiracel-OD-H or OJ-H columns were used. Optical rotations (20 °C) were measured on a JACSO P-1030 polarimeter with a quartz cell (l = 10 cm), λ = 589 nm. Melting points were determined on a Büchi 510. 1,4-Naphthoquinone was purified by recrystallization. 1,4-dihydroxynaphthalene (**2**),[19] tetralin-1,4-dione (**1**),[2] (*S*)- and (*R*)-3,3-diphenyl-1-butyltetrahydro-3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole [(*R*)-**6**], its (*S*)-antipode[20], $[Cr(CO)_3(NH_3)_3]$[21], and $[Cr(CO)_3$(tetralone)$]$[22] were synthesized according to the cited literature procedures. 1,1,4,10,10-Hexamethyltriethylenetetramine was filtered on Al_2O_3 and prenyl bromide was dried over CaH_2 and distilled prior to use.

(4*S*)-4-Hydroxy-1-tetralone [(*S*)-(3)]

Under N_2, a Schlenk tube was charged with tetralin-1,4-dione (**1**) (561 mg, 3.50 mmol) and dry toluene (15 mL). The solution was cooled to −78 °C before adding a solution of (*R*)-3,3-diphenyl-1-butyl tetrahydro-3*H*-pyrrolo[1,2-*c*]-[1,3,2]oxazaborole (3.5 mL, 0.1 M in toluene, 0.35 mmol). Catecholborane (5.3 mL, 1 M in toluene, 5.3 mmol) was added after 2 h *via* a syringe over 15 min. After stirring at −78 °C for 40 h the reaction mixture was quenched with MeOH (4 mL) and diluted with AcOEt. Volatiles were removed under reduced pressure and the residue was purified by f.c. on silica gel (eluent: pentane/Et_2O = 1/1) to afford (*S*)-(**3**) as a liquid; yield: 443 mg (78%); 99.3% *ee* determined by HPLC analysis (Chiralcel OJ, hexane/*i*-PrOH = 99/1, gradient to 90/10 over 60 min, 1 mL min^{-1}, 254 nm): t_R = 40.1 min [minor, (*R*)-**3**], 42.0 min [major, (*S*)-**3**]; $[\alpha]_D^{23}$: +23.2 (*c* 1.01, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 7.8 Hz, 1 H), 7.56–7.44 (m, 2 H), 7.30 (t, *J* = 7.1 Hz, 1 H), 4.89–4.81 (m, 1 H), 4.01 (bs, 1 H), 2.85–2.73 (m, 1 H), 2.53–2.40 (m, 1 H), 2.32–2.21 (m, 1 H), 2.12–1.99 (m, 1 H).

(4*R*)-4-(*tert*-Butyldimethylsilyloxy)-1-tetralone [(*R*)-4]

A two-neck round-bottomed flask equipped with a condenser was charged under N_2 with (*R*)-4-hydroxy-1-tetralone [(*R*)-**3**][2] (400 mg, 2.49 mmol, 95% *ee*), CH_2Cl_2 (18 mL), (*i*-Pr)$_2$EtN (2.17 mL, 12.45 mmol), DMAP (60 mg, 0.50 mmol) and TBSCl (1.495 g, 9.96 mmol). The clear solution was refluxed for 60 h, quenched with H_2O (20 mL) and stirred at room temperature for 3 h. The reaction mixture was extracted with CH_2Cl_2 (3×) and the combined organic layers dried with Na_2SO_4. Evaporation of the solvent under reduced pressure and purification of the residue by f.c. (Et_2O/pentane 1:15) gave 4-(*tert*-butyldimethylsiloxy)-1-tetralone [(*R*)-**4**] as a white solid; yield: 605 mg (88%); $[\alpha]_D^{20}$: +2 (*c* 1.12 CH_2Cl_2). Spectral data agreed with literature values.[23]

(+)-(1*R*)-4-(3,4-Dichlorophenyl)-1,2-dihydronaphthalen-1-ol [(*R*)-5]

A two-neck round-bottomed flask equipped with condenser was charged under N_2 with Mg (50 mg, 2.06 mmol), a crystal of I_2 and Et_2O (1.6 mL). A solution of 4-bromo-1,2-dichlorobenzene (264 µL, 2.06 mmol) in 2.5 mL of Et_2O was added dropwise under stirring over 5 min while heating gently to maintain reflux. This suspension was further refluxed during 1 h to give a clear solution. Then, a solution of (*R*)-**4** (285 mg, 1.03 mmol, 95% *ee*) in Et_2O (2.5 mL) was added dropwise and the mixture was refluxed for 19 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with Et_2O (3×). The combined organic phases were dried over Na_2SO_4 and volatiles were removed under reduced pressure. The crude product was dissolved in CH_2Cl_2 (8.6 mL, 0 °C) under N_2. A solution of Et_3N (724 µL, 5.16 mmol) in CH_2Cl_2 (8.6 mL, 0 °C) and a solution of MsCl (319 µL, 4.12 mmol) in CH_2Cl_2 (8.6 mL, 0 °C) were added sequentially. After further stirring at 0°C for 2 h and at room temperature, for 2 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with Et_2O (3×). The organic phases were combined, dried with Na_2SO_4 and the solvent evaporated under reduced pressure. This residue was dissolved in THF (10 mL) and a solution of TBAF (1 M in THF, 1.55 mL, 1.55 mmol) was added at room temperature. The mixture was stirred for 1 h, diluted with Et_2O, washed with saturated aqueous $NaHCO_3$ and extracted with Et_2O (3×). The organic phases were combined, dried with $MgSO_4$ and evaporated under reduced pressure. Purification by f.c. (AcOEt/pentane 1:4) furnished (*R*)-**5** as a white solid; yield: 237 mg (79%); 95% *ee*; mp 107–109 °C (CH_2Cl_2/cyclohexane); $[\alpha]_D^{20}$: +35 (*c* 0.47, CH_2Cl_2). Spectral data agreed with literature values.[6h] R_F = 0.30 (Et_2O/pentane, 1: 4); IR (neat): ν = 3346, 3060, 2928, 2857, 2824, 1547, 1468, 1380, 1333, 1198, 1131, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.28 (m, 3 H), 7.12 (td, *J* = 7.3 and 1.3 Hz, 1 H), 7.07 (td, *J* = 7.5 and 1.4 Hz, 1 H), 7.01 (dd, *J* = 8.2 and 0.0 Hz, 1 H), 6.86 (d, *J* = 7.5 Hz, 1 H), 5.83 (t, *J* = 4.5 Hz, 1 H), 4.65 (t, *J* = 5.9 Hz, 1 H), 2.52–2.47 (m, 2 H), 1.99 (broad s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.4, 137.8, 137.7, 133.0, 132.7, 131.7, 130.9, 130.6, 128.5, 128.47, 128.43, 127.0, 125.9, 125.6, 68.0, 33.0; HR-MS (EI): *m/z* = 272.0156, calcd. for $C_{16}H_{10}OCl_2$ $[M-H_2O]^+$: 272.0159; HPLC (Chiralcel OJ, F = 1 mL·min^{-1}, hexane/*i*-PrOH = 99:1 gradient to 90/10 over 60 min, λ = 254 nm): t_R = 30.3 min [(4*R*)-enantiomer] and 33.6 min [(4*S*)-enantiomer].

(2*R*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-2-(3′-methylbut-2′-en-1-yl)-1,2,3,4-tetrahydronaphthalene-1-one (8)
(2*S*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-2-(3′-methylbut-2′-en-1-yl)-1,2,3,4-tetrahydronaphthalene-1-one (9)
(4*S*)-4-(*tert*-Butyldimethylsilyloxy)-2,2-bis(3′-methylbut-2′-en-1-yl)-1,2,3,4-tetrahydronaphthalene-1-one (10)

Under an atmosphere of N_2, a solution of *n*-BuLi (0.609 mL, 1.6 M in hexane, 1.10 mmol) was added to a stirred solution of diisopropylamine (170 μL, 1.21 mmol) in DME (5 mL) at −78 °C (dry ice/EtOH). After 1 h, a solution of (*S*)-**4** (276 mg, 1.00 mmol) in DME (5 mL) was added dropwise *via* a syringe over 5 min at −78 °C. Tetraamine **7** (0.550 mL, 2.02 mmol) was then added in one portion and the mixture was stirred for 2 h. After this time, prenyl bromide (620 μL, 95%, 5.06 mmol) was added in one portion and the reaction mixture was brought from −78 °C to room temperature over the course of a 15 h period. The resulting mixture was diluted with CH_2Cl_2, filtered, concentrated, and the residue was purified by f.c. on silica gel (eluent: pentane/Et_2O first 50/1 then 10/1) to afford a 1.08:1 mixture of diastereoisomers **8** and **9** (yield: 286 mg, 83%, determined by ^1H NMR) and **10** (yield: 15 mg, 4%).

8 and 9: IR (neat): ν = 2929, 1686, 1601, 1455, 1362, 1253, 1131, 1077 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 7.6 Hz, **8** and **9** together, 2 H), 7.63–7.51 (m, **8** and **9** together, 3 H), 7.42–7.33 (m, **8** and **9** together, 3 H), 5.20–5.12 (m, **8** and **9** together, 2 H), 4.99 (dd, *J* = 11.1, 4.5 Hz, **8**, 1 H), 4.96 (dd, *J* = 5.8, 3.3 Hz, **9**, 1 H), 3.10–3.00 (m, **9**, 1 H), 2.74–2.64 (m, **8**, 1 H), 2.64–2.55 (m, **9**, 1 H), 2.55–2.46 (m, **8**, 1 H), 2.39–2.18 (m, **8** and **9** together, 4 H), 2.09 (ddd, *J* = 13.1, 9.7, 3.4 Hz, **9**, 1 H), 1.88 (q, *J* = 12.5 Hz, **8**, 1 H), 1.72 (s, **8** and **9** together, 6 H), 1.65 (s, **8**, 3 H), 1.63 (s, **9**, 3 H), 1.00 (s, **8**, 9 H), 0.89 (s, **9**, 9 H), 0.23 (s, **8**, 3 H), 0.19 (s, **8**, 3 H), 0.17 (s, **9**, 3 H), 0.10 (s, **9**, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.6, 198.4, 147.3, 144.6, 133.7, 133.5, 133.4, 133.3, 131.12, 131.06, 127.9, 127.2, 127.1, 126.9, 125.6, 121.7, 121.2, 69.2, 67.0, 46.4, 42.8, 38.7, 36.3, 28.0, 27.8, 25.8, 25.7, 25.6, 18.1, 17.9, 17.78, 17.76, −4.3, −4.7, −4.9; MS (ESI): *m/z* (%) = 345 ($[M+H]^+$), 367 ($[M+Na]^+$); HR-MS (ESI): *m/z* = 367.2073, calcd. for $C_{21}H_{32}O_2NaSi$ ($[M+Na]^+$): 367.2063.

(*S*)-10: IR (neat): ν = 2929, 1683, 1601, 1453, 1377, 1255, 1132, 1079 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 7.8 Hz, 1 H), 7.62–7.55 (m, 2 H), 7.41–7.33 (m, 1 H), 5.26–5.18 (m, 1 H), 5.11–5.01 (m, 2 H), 2.57 (dd, *J* = 14.3, 6.2 Hz, 1 H), 2.35 (dd, *J* = 14.9, 7.8 Hz, 1 H), 2.29–2.06 (m, 4 H), 1.74 (s, 3 H), 1.64 (s, 3 H), 1.62 (s, 3 H), 1.60 (s, 3 H), 1.00 (s, 9 H), 0.23 (s, 3 H), 0.18 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.9, 146.4, 134.8, 134.2, 133.4, 130.6, 127.6, 127.4, 125.9, 119.9, 118.9, 66.0, 50.1, 40.4, 34.9, 34.4, 26.1, 25.9, 25.8, 18.1, 18.0, 17.9, −4.3, −4.9; MS (ESI): *m/z* (%) = 413 ($[M+H]^+$), 435 ($[M+Na]^+$); HR-MS (ESI): *m/z* = 413.2876, calcd. for $C_{26}H_{41}O_2Si$ ($[M+H]^+$): 413.2870.

Catalponol (11) and 2-Epicatalponol (12)

To a solution of a mixture of **8** and **9** (1.08:1) (278 mg, 0.81 mmol) in dry THF (17 mL) was added TBAF (1.7 mL, 1.0 M in toluene, 1.70 mmol) under N_2 at room temperature. The reaction mixture was stirred for 15 min, then concentrated and the residue was purified by f.c. on silica gel (eluent: pentane/Et_2O = 2/1) to afford first 39 mg of catalponol and then 123 mg of a mixture of catalponol and 2-epicatalponol. This 123 mg mixture was chromatgraphed on silica gel (eluent: pentane/Et_2O = 4/1) for the second time to afford another 70 mg of catalponol and 48 mg of 2-epicatalponol.

Catalponol (11): liquid, yield: 109 mg (59%); 99.3% *ee* determined by HPLC analysis (Chiralcel OJ, hexane/*i*-PrOH = 99/1, gradient to 90/10 over 60 min, 1 mL·min^{-1}, 254 nm): t_R = 30.4 min (major), 32.6 min (minor); $[\alpha]_D^{23}$: +10.6 (*c* 1.2, MeOH); IR (neat): ν = 3432, 2916, 1679, 1601, 1454, 1336, 1271, 1220, 1074, 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 7.6 Hz, 1 H), 7.72 (d, *J* = 7.8 Hz, 1 H), 7.59 (t, *J* = 7.5 Hz, 1 H), 7.39 (t, *J* = 7.6 Hz, 1 H), 5.18–5.11 (m, 1 H), 5.00 (dd, *J* = 11.2, 3.9 Hz, 1 H), 2.75–2.66 (m, 1 H), 2.56–2.46 (m, 2 H), 2.34 (bs, 1 H), 2.34–2.21 (m, 1 H), 1.79 (q, *J* = 13.0, 1 H), 1.71 (s, 3 H), 1.64 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.7, 146.5, 134.0, 133.7, 131.1, 127.8, 127.1, 125.7, 121.2, 68.4, 46.5, 38.6, 27.9, 25.9, 17.9; MS (ESI): *m/z* (%) = 231 ($[M+H]^+$), 253 ($[M+Na]^+$); HR-MS (ESI): *m/z* = 253.1189, calcd. for $C_{15}H_{18}O_2Na$ ($[M+Na]^+$): 253.1199; HPLC (Chiracel OJ-H, F = 1 mL·min^{-1}, hexane/*i*-PrOH: 99:1 to 90:10 gradient over 60 min, λ = 254 nm): t_R = 28.0 min (2*S*,4*R*)-4-hydroxy-2-prenyl-3,4-dihydronaphthalenone) and t_R = 29.9 min (2*R*,4*S*)-4-hydroxy-2-prenyl-3,4-dihydronaphthalenone (**11**), $[\alpha]_D^{34}$: +11° (*c* 1.2, MeOH, > 98% *ee*). Ref.[9d] $[\alpha]_D^{34}$: +11° (*c* 1.2, MeOH).

2-Epicatalponol (12): liquid; yield: 48 mg (26%); 99.1% *ee* determined by HPLC analysis (Chiralcel OJ, hexane/*i*-PrOH = 99/1, gradient to 90/10 over 60 min, 1 mL·min^{-1}, 254 nm): t_R = 28.8 min (minor), 32.4 min (major); IR (neat):

$\nu = 3421, 2919, 1674, 1600, 1454, 1377, 1332, 1277, 1227, 1049\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.03$ (dd, $J = 7.8$, 1.3 Hz, 1H), 7.62–7.54 (m, 1H), 7.49–7.39 (m, 2H), 5.21–5.12 (m, 1H), 5.04–4.96 (m, 1H), 3.06–2.97 (m, 1H), 2.65–2.55 (m, 1H), 2.36–2.22 (m, 2H), 2.15 (ddd, $J = 13.9$, 10.6, 3.3 Hz, 1H), 2.03 (d, $J = 3.8$ Hz, 1H), 1.71 (s, 3H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 199.5$, 143.6, 133.92, 133.86, 131.3, 128.8, 128.3, 127.4, 121.3, 66.7, 42.4, 35.7, 28.0, 25.8, 17.9; MS (ESI): *m/z* (%) = 231 ($[M+H]^+$).

{$Cr(CO)_3$[η^6(1-4,4a,6a)tetralin-5,8-dione]} (14)[1a,2]

A Carius tube was charged with 1,4-dihydroxynaphthalene (687 mg, 4.29 mmol), $Cr(CO)_3(NH)_3$[19] (536 mg, 2.86 mmol), Et_2O (30 mL) and $BF_3{\cdot}Et_2O$ (2.17 mL, 17.16 mmol). The yellow suspension was stirred at room temperature under N_2 for 5d. The contents were cooled with an ice/NaCl bath and Et_2O (40 mL) was added followed by aqueous saturated $NaHCO_3$ (160 mL). The organic layer was transferred *via* canula to another Schlenk tube containing $MgSO_4$ and the aqueous layer was extracted three times with small portions of Et_2O (30 mL). The combined organic layers were filtered and then all volatiles were removed under vacuum. The orange residue was taken up in toluene (42 mL) and CF_3COOH (440 µL, 5.72 mmol). The suspension was degassed three times by freeze-pump-thaw cycles and stirred at room temperature for 14 h. A colour change from orange to dark red was observed. The reaction mixture was then cooled to 0 °C, filtered *via* canula to a Schlenk tube and all volatiles were removed under vacuum. The crude product was recrystallized, under N_2, from boiling, *i*-Pr_2O (30 mL) to give **14** as a deep red solid; yield: 554 mg (65%).

[(+)-(S_p,8*S*)-$Cr(CO)_3$(η^6-8-hydroxy-5-tetralone)] [(S_p,8*S*)-15][2]

A dry Schlenk tube charged with **14** (300 mg, 1.01 mmol) and dry toluene (5 mL) was cooled to −78 °C. To the stirred solution was added (*R*)-3,3-diphenyl-1-butyltetrahydro-3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole[18] (1.0 mL, 0.1 M in toluene, 0.10 mmol) dropwise. After 40 min of stirring at −78 °C, a solution of catecholborane (1.5 mL, 1 M in toluene, 1.52 mmol) was added during 20 min. After stirring for 24 h at −78 °C, the red solution turned to orange. The mixture was then quenched with saturated aqueous $NaHCO_3$ (10 mL) and the separated org. phase was washed with saturated aqueous $NaHCO_3$ (3×10 mL). After extraction with Et_2O (30 mL), the combined organic layers were dried over $MgSO_4$ and all volatiles were removed under reduced pressure. This residue was purified by f.c. (eluent: Et_2O) to give (*S*)-**15** as an orange solid; yield: 297 mg (>99%), >98% *ee*; mp 184 °C (dec. under N_2) (hexane/*i*-PrOH). IR (CH_2Cl_2): $\nu = 3602, 3063, 2929, 1981, 1914, 1688, 1523, 1454, 1421, 1326\ cm^{-1}$; ^1H NMR (400 MHz, C_6D_6): $\delta = 5.70$ (d, $J = 6.6$ Hz, 1H), 5.00 (d, $J = 6.8$ Hz, 1H), 4.56 (t, $J = 6.8$ Hz, 1H), 4.28 (t, $J = 6.1$ Hz, 1H), 3.90–3.80 (m, 1H), 2.21–2.16 (m, 1H), 1.63–1.23 (m, 4H); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 231.6$, 193.8, 128.0, 100.4, 93.4, 92.9, 90.3, 87.0, 65.9, 35.9, 31.8; HR-MS (EI): *m/z* = 299.0009, calcd. for $C_{13}H_{11}O_5Cr$ $[M+H]^+$: 299.0006; HPLC (Chiracel OD-H, F = 1 mL·min^{-1}, hexane/*i*-PrOH: 90/10 iso over 60 min, λ = 254 nm): $t_R = 24.6$ min. (−)-(8*R*)-**15** and $t_R = 28.8$ min. (+)-(8S)-**15**; anal. calcd. for $C_{13}H_{10}O_5Cr$: C 52.36%, H 3.38%; found: C 52.56%, H 3.35%; $[\alpha]_D^{20}$: +684 (*c* 0.2, CH_2Cl_2).

[(+)-(*Sp*,8*S*)-$Cr(CO)_3$(η^6-8-trimethylsilyloxy-5-tetralone)] [(*Sp*,8*S*)-16]

A Schlenk tube was charged with (8*S*)-**15** (620 mg, 2.08 mmol), imidazole (424.82 mg, 6.24 mmol) and CH_2Cl_2 (23 mL). TMSCl (0.55 mL, 4.16 mmol) was added to this solution and the mixture was stirred for 3 h under N_2. The reaction was then quenched with saturated aqueous NH_4Cl (30 mL) and the mixture extracted with CH_2Cl_2 (3×30 mL). The organic layers were washed with brine (30 mL) and then dried over anhydrous $MgSO_4$. The solvent was evaporated under vacuum and the residue was purified by f.c. over SiO_2 (eluent: Et_2O) to give (8*S*)-**16** as an orange solid; yield: 771 mg (>99%); >98% *ee*; mp 96–98 °C. IR (CH_2Cl_2): $\nu = 1981, 1912, 1685\ cm^{-1}$; ^1H NMR (400 MHz, C_6D_6): δ = 5.74 (dd, $J = 0.8$ and 6.8 Hz, 1H), 5.05 (d, $J = 6.6$ Hz, 1H), 4.64 (t, $J = 6.6$ Hz, 1H), 4.37 (t, $J = 6.8$ Hz, 1H), 4.10 (dd, $J = 4.8$ and 10.9 Hz, 1H), 2.29–2.23 (m, 1H), 1.85–1.48 (m, 3H), 0.05 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ = 231.5, 193.9 , 119.3, 93.4, 92.7, 90.2, 89.2, 86.9, 66.7, 35.7, 32.2, 0.1; HR-MS (ESI): *m/z* = 371.0399, calcd. for $C_{16}H_{19}CrO_5Si$ $[M+H]^+$: 371.0401; HPLC (Chiracel OD-H, F = 1 mL·min^{-1}, hexane/*i*-PrOH: 90/10 iso over 60 min, λ = 254 nm): $t_R = 11.5$ min (8*R*)-**16** and $t_R = 23.9$ min (8*S*)-**16**; anal. calcd. for $C_{16}H_{18}Cr_1O_5Si$: C 51.88%, H 4.90%;found; C 51.97%, H 4.97%; $[\alpha]_D^{20}$: +729 (*c* 0.2, CH_2Cl_2).

[*rac*-$Cr(CO)_3$(η^6-6-(3′-methylbut-2′-enyl)-5-tetralone] [*rac*-(18)]

To a cooled solution of (±)-[$Cr(CO)_3$(η^6-tetralone)] (**17**) (197.5 mg, 0.7 mmol) in dry and degassed DME (8.5 mL) was added dropwise at −40 °C a freshly prepared solution of LDA (1 mL, 1 M in DME, 1 mmol), followed by addition of 1,1,4,10,10-hexamethyltriethylenetetramine (484 µL, 2.1 mmol). The orange solution turned first yellow and then red. Freshly distilled prenyl bromide (0.7 mL, 5.6 mmol) was then slowly injected to the mixture. After 2 h of stirring at −40 °C, the reaction was quenched with 30 mL of aqueous citric acid (40%) and extracted three times with CH_2Cl_2 (3×30 mL). The organic extracts were washed with saturated aqueous $NaHCO_3$ (30 mL), and with brine (30 mL). Organic layers were dried over anhydrous $MgSO_4$ and filtered. The filtrate was evaporated under vacuum and the residue was purified by f.c. (Et_2O/pentane: 1/1) to give (±)-[$Cr(CO)_3$(η^6-6-prenyl-5-tetralone)] (**18**); yield: 190 mg (78%). IR (methylcyclohexane): $\nu = 1987, 1930, 1914, 1694\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): δ = 6.21 (d, $J = 6.7$ Hz, 1H), 5.64 (t, $J = 6.2$ Hz, 1H), 5.23 (t, $J = 6.4$ Hz, 1H), 5.13 (m, 1H), 3.00–2.90 (m, 1H), 2.81–2.71 (m, 1H), 2.65–2.43 (m, 2H), 2.26–2.14 (m, 2H), 1.91–1.82 (m, 1H), 1.72 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (400 MHz, C_6D_6): δ = 231.6, 121.6, 94.3, 91.4, 89.9, 89.5, 79.5, 47.6, 41.8, 28.5, 28.0, 26.8, 26.0.

[(+)-(S_p,6*S*,8*S*)-$Cr(CO)_3$(η^6-6-(3′-methylbut-2′-enyl)-8-trimethylsilyloxy-5-tetralone] [(S_p,6*S*,8*S*)-(19)]

To a cooled solution of (8*S*)-**16** (680 mg, 1.84 mmol) in dry and degassed DME (24 mL) was added dropwise at −40 °C a freshly prepared solution of LDA (2.6 mL, 1 M in DME, 2.6 mmol), followed by addition of 1,1,4,10,10-hexamethyltriethylenetetramine (1.55 mL, 5.5 mmol). The orange solution turned first yellow and then orange. Freshly distilled prenyl bromide (1.2 mL, 9.2 mmol) was then slowly injected into the mixture. After 2 h of stirring at −40 °C more prenyl bromide (0.5 mL, 3.7 mmol) was added to the now red reaction mixture. The reaction was monitored by TLC (Et_2O/pentane: 1:1). After 4 h at −40 °C, the reaction was quenched with 30 mL of aqueous citric acid (40%) and extracted with CH_2Cl_2 (3×30 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (30 mL), and with brine (30 mL). The organic phase was dried over anhydrous $MgSO_4$ and filtered. The filtrate was evaporated under vacuum and the residue was purified by f.c. over SiO_2 (Et_2O/pentane: 1/1) to give (S_p,6*S*,8*S*)-**19** as an orange oil; yield:; 662 mg (82%); >98% *ee*. IR (CH_2Cl_2): ν=3685, 2952, 2927, 2855, 1980, 1911, 1681, 1605, 1456 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): δ=5.82 (d, *J*=6 Hz, 1 H), 5.10 (d, *J*=6.8 Hz, 1 H), 4.90 (m, 1 H), 4.64 (t, *J*=6 Hz, 1 H), 4.57 (dd, *J*=4.8, 10.4 Hz, 1 H), 4.38 (t, *J*=6.4 Hz, 1 H), 2.60–1.80 (m, 5 H), 1.60 (s, 3 H), 1.40 (s, 3 H), 0.09 (s, 9 H); ^{13}C NMR (100 MHz, C_6D_6): δ=231.5, 196.7, 134.2, 121.8, 119.1, 92.9, 92.8, 90.4, 89.4, 87.3, 63.4, 44.8, 35.4, 29.3, 25.8, 17.9, 0.1; HR-MS (ESI): *m/z*=439.1007, calcd. for $C_{21}H_{27}O_5Si$ Cr $[M+H]^+$: 439.1027; anal. calcd. for $C_{21}H_{26}Cr_1O_5Si$: C 57.52%, H 5.98%; found: C 57.15%, H 5.95%; $[\alpha]_D^{20}$: +329 (*c* 0.2, CH_2Cl_2).

{(+)-(S_p,6*R*,8*S*)-$Cr(CO)_3$[η^6-6-(3′-methylbut-2′-enyl)-8-trimethylsilyloxy-5-tetralone]} [(S_p,6*R*,8*S*)-(20)]

To a cooled solution of (S_p,6*S*,8*S*)-**19** (660 mg, 1.51 mmol) in DME (20 mL) was added dropwise at −40 °C a freshly prepared solution of LDA (2.2 mL, 1 M in DME, 2.2 mmol). The orange mixture was stirred at −40 °C for 1 h. Then a solution of citric acid (1 mL, 1 M in distilled water) was added slowly at −40 °C. The mixture was allowed to warm up to room temperature. After 30 min, distilled water (10 mL) was added and the mixture was extracted three times with Et_2O (3×30 mL). The organic extracts were washed with saturated aqueous $NaHCO_3$ (40 mL), and with brine (40 mL). The organic phase was dried over anhydrous $MgSO_4$. Solvents were removed under reduced pressure and the crude product was purified by f.c. over SiO_2 (Et_2O/pentane: 1/2) to give (S_p,6*R*,8*S*)-**20** as an orange oil; yield: 636 mg (96%); >98% *ee*. ^{1}H NMR (400 MHz, C_6D_6): δ=5.80 (d, *J*=6.4 Hz, 1 H), 5.25 (t, *J*=7.6 Hz, 1 H), 5.10 (d, *J*=6.8 Hz, 1 H), 4.68–4.64 (m, 1 H), 4.38–4.35 (m, 1 H), 4.30–4.20 (dd, *J*=4.8 and 10.9 Hz, 1 H), 2.60–2.50 (m, 2 H), 2.10–1.92 (m, 2 H), 1.88–1.84 (m, 1 H), 1.70 (s, 3 H), 1.52 (s, 3 H), 0.10 (s, 9 H); HPLC (Chiracel OD-H, F=1 mL·min^{-1}, hexane/*i*-PrOH: 90/10 iso over 60 min, λ=254 nm): t_R=8.2 min. (S_p,6*R*,8*S*)-**20**; $[\alpha]_D^{20}$: +360 (*c* 0.2, CH_2Cl_2).

[(S_p)-$Cr(CO)_3$(Catalponol)] [(S_p)-(21)]

To a solution of (S_p,6*R*,8*S*)-**20** (614 mg, 1.4 mmol) in dry and degassed MeOH (15 mL) at 0 °C was added K_2CO_3 (235 mg, 1.7 mmol) under N_2. After 2 h of stirring at 0 °C, the mixture was quenched with distilled water (10 mL) and the extracted with Et_2O (3×30 mL). The combined organic layers were washed with brine (40 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by f.c. over SiO_2 with pentane/ether (1: 4) afforded (S_p)-**21** as a red solid; yield: 385 mg (75%); 98% *ee*; mp 113–114 °C; IR (CH_2Cl_2): ν=1980, 1915, 1683, 1605 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): δ=5.75 (d, *J*=5.8 Hz, 1 H), 5.17 (t, *J*=7.6 Hz, 1 H), 5.10 (d, *J*=6.6 Hz, 1 H), 4.58 (t, *J*=6 Hz, 1 H), 4.29 (t, *J*=5.8 Hz, 1 H), 4.00 (m, 1 H), 2.50 (m, 2 H), 1.71 (s, 3 H), 1.60 (m, 1 H), 1.51 (s, 3 H); ^{13}C NMR (100 MHz, C_6D_6): δ=231.7, 195.7, 134.5, 128.3, 121.0, 119.3, 93.4, 90.5, 90.3, 86.8, 65.9, 46.0, 37.0, 28.3, 26.0, 17.9; HPLC (Chiracel OD-H, F=1 mL·min^{-1}, hexane/*i*-PrOH: 90/10 iso over 60 min, λ=254 nm): t_R=18.4 min **21**; anal. calcd. for $C_{18}H_{18}CrO_5$: C 59.02%, H 4.95%; found: C 58.75%, H 4.72%; $[\alpha]_D^{20}$: +523 (*c* 0.5, CH_2Cl_2).

Catalponol (11)

A 250-mL round-bottom flask was charged with (S_p,6*R*,8*S*)-**21** (366 mg, 1 mmol) and CH_3CN (150 mL) and was exposed to sunlight and air. Decomplexation was monitored by TLC (ether/pentane: 1:2). After 1 h, solvent was removed under reduced pressure and the residue was dissolved in ether and filtered over celite. F.c. of the crude product over SiO_2 (ether/pentane: 1:8) afforded catalponol as a colourless oil; yield: 200.4 mg (87%); >98% *ee*. Data see above.

Acknowledgements

We thank Prof. Alexandre Alexakis and Dr. S. Belot for a gift of (R)-(+)-α,α-diphenyl-2-pyrrolidinemethanol. Financial support of this project by the University of Geneva and by the Swiss National Science Foundation (project 200020 119947) is gratefully acknowledged.

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