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Stereoselective synthesis of cyclohexa-2,4-dien-1-ones and cyclohex-2-en-1-ones from phenols

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Abstract—A convenient synthetic method for the synthesis of substituted cyclohex-2-en-1-ones by the direct alkylation of phenols has been developed. Furthermore, enantiomerically enriched 2,6-dimethyl-6-(3-methylbut-2-enyl)-cyclohexa-2,4-dienone was prepared by the deprotonation of 2,6-dimethylphenol with a sparteine–lithium complex followed by alkylation with 1-chloro-3-methylbut-2-ene. 2,6-Dimethyl-6-(3-methyl-but-2-enyl)-cyclohex-2-enone was prepared from the corresponding cyclohexa-2,4-dien-1-one by selective hydrogenation of the 4,5-double bond. The method was extended to 2-methyl-naphthalen-1-ol and 1-methyl-naphthalen-2-ol resulting in 2-(*R*)-methyl-2-(3-methylbut-2-enyl)-2*H*-naphthalen-1-one and 1-(*S*)-methyl-1-(3-methylbut-2-enyl)-1*H*-naphthalen-2-one, respectively.

1. Introduction

Cyclohexenones belong to the standard skeletons in organic chemistry but short syntheses of chiral *gem*-disubstituted derivatives remain scarce. Chiral 3,6,6-trialkylated and 3,4,4-trialkylated cyclohex-2-en-1-ones are accessible through intramolecular aldol condensation of α,α-disubstituted-2,6-heptane-diones.[1a] The chemoselectivity can be controlled by choosing appropriate reaction conditions.[1b] Cyclohexa-2,4-dienones, which were used in various natural product synthesis,[2] are accessible by direct alkylation of *ortho* substituted phenols.[3] Optically active cyclohexadienones can be prepared by a multistep route involving an asymmetric variation of the Birch reduction–alkylation reaction.[4] To the best of our knowledge, the specific and enantioselective alkylation of phenolates leading to optically active cyclohexadienones has not been described.

2,6-Dialkylated phenoxide ions can act as ambident cyclic ketone enolates and can be C-alkylated under aprotic conditions, leading to cyclohexa-2,4-dien-1-ones with a new quaternary stereogenic center at C(6).[3] Earlier attempts to selectively hydrogenate the 4,5-double bond generated allylphenols by Pd-catalyzed sigmatropic rearrangements.[5] During the investigation of the Lewis-acid catalyzed rearrangements of allyl cyclohexenones,[6] we developed a convenient multi-gram synthesis of olfactorily interesting tri- and tetraalkylated cyclohex-2-en-1-ones by a simple C-alkylation/hydrogenation sequence (Table 1). This straightforward route also prompted us to investigate the possibility of introducing optical activity in the intermediate cyclohexa-2,4-dien-1-ones by deprotonation of phenols with a chiral base. To access this novel strategy, chiral lithium amide bases and amine complexes were applied, which have been successfully used by other groups in a variety of enantioselective deprotonation reactions.[7,10]

We herein report the results of both the alkylation/hydrogenation protocol and the first asymmetric alkylation of phenols and naphthols resulting in optically active cyclohexa-2,4-dien-1-ones.

2. Results and discussion

Substituted phenols **1a**–**c** were deprotonated with NaH in toluene, followed by alkylation with alkyl and benzyl chlorides **2**. Care had to be taken to keep the temperature at about 15 °C during the alkylation to minimize the rearrangement of the 6-allyl cyclohexadienones into allylphenols. In order to avoid isolation of the thermally

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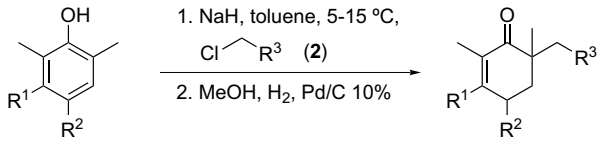
Table 1. Synthesis of substituted cyclohexenones by direct alkylation of phenols

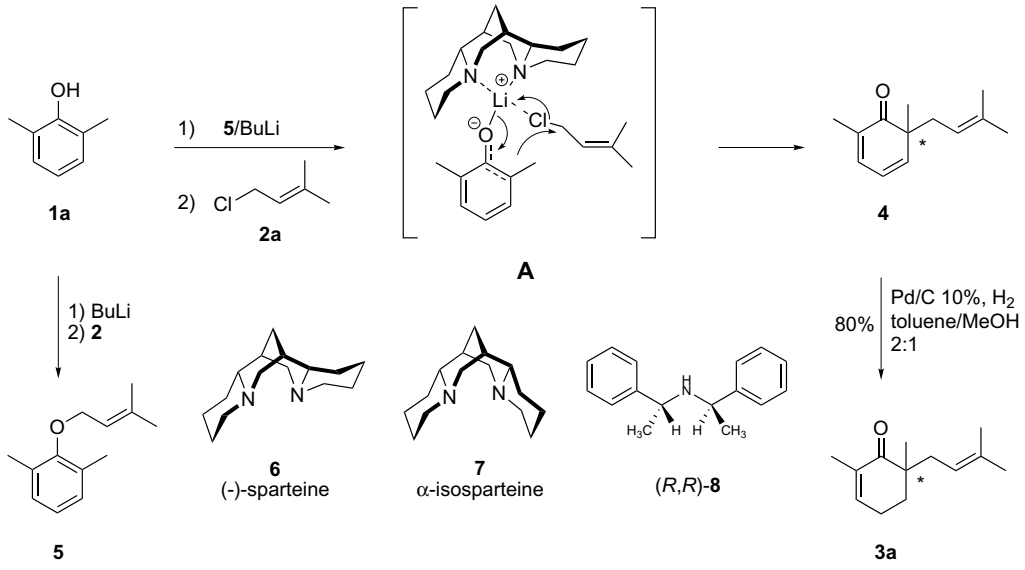


1a-g **3a-g**

	R^1	R^2	R^3	Yield (%)
a	H	H	$CH{=}C(CH_3)_2$	81
b	H	CH_3	$CH{=}C(CH_3)_2$	54
c	CH_3	H	$CH{=}C(CH_3)_2$	40
d	H	H	C_6H_5	62
e	H	H	$CH{=}CCH_3C(CH_3)_3$	58
f	H	H	$CH{=}C(CH_3)CH_2CCl_3$	71
g	H	H	$CH{=}C_6H_{10}$	50
h	H	H	$CH{=}CH_2$	Traces

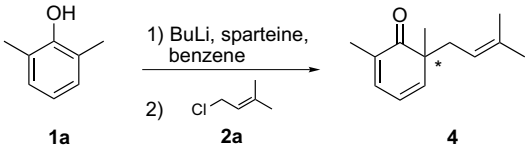
unstable and acid sensitive dienones, an in situ hydrogenation of the 4,5-double bonds seemed to be most convenient in terms of preparative ease. This was achieved by subsequently adding methanol and Pd on charcoal to the reaction mixture. The order of addition is important as the addition of methanol causes sodium chloride to precipitate, which renders the catalyst less reactive if added first. Under these conditions, the hydrogen up take was quick and exothermal, making external cooling necessary. In the absence of methanol, no hydrogenation took place and the dienones rearranged to give both allylphenols and allylphenyl ethers. To an increasing degree, this holds true for less substituted allyl substituents. For instance, compound **3h** was only identified in trace amounts. Presumably, a Pd promoted Cope rearrangement of the intermediate 6-allylcyclohexadienone competes in these cases.[5] The allyl cyclohexenones **3a–g** (Table 1) obtained in this way exhibited interesting olfactory properties as described in Experimental.

In the first attempt, a series of 11 chiral nitrogen containing ligands, commonly used in asymmetric synthesis, and readily available natural products containing secondary and tertiary nitrogen atoms were tested for their potential to enantioselectively form lithium carbanion pairs of phenols to be alkylated by allylhalides. Chiral compounds included (1*R*,2*R*)-(+)-1,2-diamino-cyclohexane-*N*,*N*′-bis(2′-diphenylphosphinobenzoyl),[8a] bis-quinine phthalazine $(Q)_2$-PHAL,[8b] (*R*,*R*)-(+)-bis-(α-methylbenzyl)-amine,[9] (+)-2,6-bis-[(4*R*)-4-phenyl-2-oxazolin-2-yl]pyridine,[8c] (−)-sparteine,[10] α-isosparteine,[11] nicotine, brucine, quinine, (*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl and (*S*)-*N*,*N*,*N*′,*N*′-tetramethyl-2,2′-diamino-1,1′-binaphthyl.[8d] The alkylation of **1a** with **2a** served as the model reaction for screening the chiral ligands. The general procedure involved the treatment of the chiral ligands with BuLi. Compound **1a** was then added to the stirred solution at 0 °C, followed by the addition of **2** (Scheme 1). The mixture was warmed to 22 °C and left stirring for 15 h. The reactivity of the phenolate complex is quite low and no conversion occurred below +20 °C. The enantiomeric enrichment of the resulting cyclohexa-2,4-dien-1-one was determined by ^{1}H NMR experiments with chiral shift reagents. Under these conditions, only (−)-sparteine and α-isosparteine afforded enantiomerically enriched **4** in moderate yields and low ee (Table 2, entries 1–3). In fact, prenyl phenylether **5** was always the major product because addition of 1 or even 2 equiv of ligand decreases the polarity of the reaction medium and therefore the amount of C-alkylation decreases accordingly. Application of other chiral bases did not lead to any enantiomeric enrichment (<5%). For example, ligand **8**, which was successfully used by Simpkins[9] and others[7] for the enantio- and diastereoselective deprotonation of ketones led to racemic **4** in comparable yield. Although sodium is the most effective counter ion for the non-enantioselective C-alkylation of phenolate ions, it is not well suited for complex formation with (−)-sparteine and consequently, no enantiotopic discrimination was observed. Based on these results, we propose that deprotonation of **1a** with sparteine/BuLi



Scheme 1. Enantioselective alkylation of phenol resulting in cyclohexa-2,4-dien-1-one.

Table 2. Alkylation of 2,6-dimethyl phenol with prenyl chloride



1a **2a** **4**

Chiral base	Yield (%)	ee (%)	$[\alpha]_D^{25}$
Li/(−)-sparteine 1 mol equiv	28	4	+16
Li/(−)-sparteine 2 mol equiv	14	8	+32
Li/α-isosparteine 1 mol equiv	17	9	+37
(*R*,*R*)-**8** 1 mol equiv	29	0	0

results in a chiral environment for the electrophilic attack of **2a**, as illustrated in the postulated enolate complex **A**.

In order to facilitate the work-up procedure of the unstable dienone, an in situ hydrogenation of the 4,5-double bond in **4** was attempted according to the conditions used in the racemic method (Scheme 1). However, no hydrogenation took place. Presumably, the palladium catalyst was poisoned by the sparteine in the reaction mixture.[12] However, it was possible to hydrogenate pure **4** over Pd/C (10%) in a mixture of toluene/MeOH 2:1 in 80% yield.

The ratio of O- versus C-alkylation of phenol strongly depends on the solvent and has been reported to work best in heterogeneous mixtures of the phenoxide in aprotic solvents. Based on this finding, we decided to perform the reaction in the solid state.[13] Solid lithium, potassium, and sodium phenoxides were mixed with (−)-sparteine resulting in dark green readily stirred mixtures. The addition of **2a** afforded **4** in irreproducible yields and enantioselectivities, which indicates a rapid interconversion between different aggregates present in the reaction mixture.[14]

(−)-Sparteine and α-isosparteine can form an intermediate quaternary ammonium salt with an alkylating agent. Allyl transfer from the chiral ammonium salt to the phenoxide would then result in the observed enantiotopic discrimination. To determine whether such a mechanism is in effect, (−)-sparteine and α-isosparteine were treated with allyl bromide in a toluene solution.

Upon standing, allyl bromide/α-isosparteine salt **9** formed fine colorless crystals. Analysis by X-ray crystallography revealed that the quaternary ammonium salt was indeed present, while the allyl moiety was attached to the convex face of α-isosparteine resulting in inversion at the participating nitrogen atom (Fig. 1).[15]

Experimental results showed that if **9** was added to a solution of lithium 2,6-dimethylphenoxide in benzene at 0 °C, no products were observed even after stirring at room temperature for 24 h. Possibly the large spartein molecule imposes too much steric constraint at the reactive center of the allylic moiety.

The low enantioselectivity of the phenol alkylation is caused by either poor facial selectivity of the symmetrically substituted phenol **1a**, by the low configurational stability

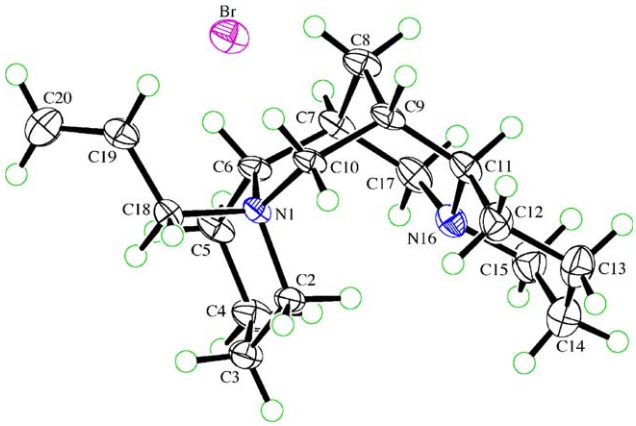
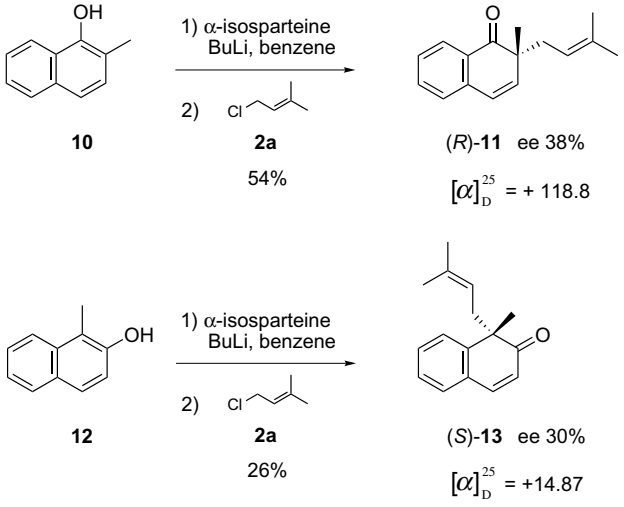


Figure 1. ORTEP-plot of the α-isosparteine/allyl bromide salt **9**. X-ray crystallographic details for compound **9**: $C_{18}H_{31}N_2^+Br^- \cdot 2C_6H_6$, $M_r = 511.59$, monoclinic, space group $P2_1$, $a = 9.6338(2)$, $b = 8.4978(2)$, $c = 16.9348(4)$ Å, $\beta = 96.8364(9)°$, $V = 1376.53(5)$ Å^3, $Z = 2$, $D_x = 1.234$ g cm^{-3}, $T = -113$ °C, crystal dimensions: $0.10 \times 0.20 \times 0.22$ mm, *Nonius KappaCCD* area-detector diffractometer, Mo Kα radiation, $\lambda = 0.71073$ Å, $\mu = 1.517$ mm^{-1}, $\theta_{max} = 27.5°$, 31067 measured reflections, 6726 symmetry-independent reflections, 5456 reflections with $I > 2\sigma(I)$, refinement on F^2 with SHELXL-97,[16] 300 parameters, 1 restraint, $R(F)$ [$I > 2\sigma(I)$ reflections] = 0.048, $wR(F^2)$ [all reflections] = 0.126, $S(F^2) = 1.065$, $\Delta\rho_{max} = 0.78$ e Å^{-3}. The asymmetric unit contains one cation, one anion, and two benzene molecules. The absolute configuration of the molecule in the crystal has been determined independently by the diffraction experiment: absolute structure parameter[17] = 0.05(1). CCDC-603895 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

of the phenolate–Li complex or its low reactivity. Due to the more extensive delocalization of charge, naphthols are more reactive than phenols and alkylation is more rapid (Scheme 2). 2-Methyl-1-naphthol **10** was deprotonated with α-isosparteine/lithium complex and alkylated with **2a**. The reaction proceeded smoothly affording (*R*)-**11** in 54% yield and 38% enantioselectivity. The alkylation of 1-methyl-2-naphthol **12** proceeded in a similar manner, leading to (*S*)-**13** in 26% yield with a slightly lower ee of 30%.



Scheme 2. Stereoselective alkylation of naphthols.

The absolute configuration of **11** and **13** was determined by vibrational circular dichroism (VCD) spectroscopy combined with Gaussian 03 quantum chemical computations.

3. Conclusion

Herein, we have shown that cyclohexenones can be prepared in a one-pot protocol through direct alkylation of phenolates followed by selective in situ hydrogenation of the 4,5-double bond. This regioselective hydrogenation can also be performed with isolated dienones using Pd/C 10% in toluene/MeOH 2:1, without any hydrogenation of the 2,3-double bond or the allylic side chain. We have also shown for the first time that it is possible to synthesize enantiomerically enriched cyclohexa-2,4-dien-1-ones by C-alkylation of phenols using a (−)-sparteine– or α-isosparteine–lithium complex as chiral base. The highest enantiomeric enrichment was observed in the products resulting from the alkylation of naphthols. Contrary to the results reported in the racemic alkylation protocols, lithium was found to be the most suitable alkali metal ion in the asymmetric variant of the phenol alkylation.

4. Experimental

4.1. General

^{1}H NMR and ^{13}C NMR spectra were measured on *Bruker AC300*, *Bruker ARX300* (both 300 MHz) or on a Bruker Avance DPX-400 spectrometer. Chemical shifts are given in parts per million relative to internal TMS, while coupling constants are reported in Hertz (Hz). Deuterated chloroform and benzene were used as solvents. Multiplicities are specified by abbreviations, s = singlet, d = doublet, t = triplet, m = multiplet, and td = triplet of doublets. In ^{13}C NMR spectra, the solvent itself served as the internal standard: $CDCl_3$ (δ(C) = 77.00 ppm, *t*, J_{CD} = 31.5 Hz). The multiplicity is designated q (quartet) for CH_3, t (triplet) for CH_2, d (doublet) for CH, and s (singlet) for fully substituted carbon atoms. GC/MS was measured routinely on a *HP MSD 5973* instrument with a 30m *HP5*/*MS* or *Varian VF5ms* column. Mass spectra were measured in electron impact (EI) mode at 70 eV, with a source temperature of 200 °C, an acceleration voltage of 5 kV, and a resolution of 10,000. High resolution mass spectra (HRMS) were recorded on a Finnigan MAT 95. IR spectra were run on *Spectrum One FT-IR*- and *Bruker Vector 22 FT-IR*-spectrometers. The relative intensities of the absorption bands are indicated as vs = very strong (>90%), s = strong (70–90%), m = medium (40–70%), w = weak (<40%). Column Chromatography was performed on Silica gel *Chemie Uetikon ZEOCHEM C-Gel C-560*, particle size 40–63 μm or aluminum oxide *Fluka type 5016 basic*, particle size 50–150 μm; pH 9.5 ± 0.5 Act. III (*Brockmann*). Standard GC analysis was performed on a *HP 5890* instrument with *HP 3396A* integrator and a DB5 30m, 0.53 mm column. The split ratio was 1:100, initial temperature 80 °C, and rate 10 °C/min. Microanalyses were obtained from Ilse Beetz, Mikroanalytisches Laboratorium, 96301 Kronach, Postf. 1164, Germany. Most products were short path distilled by the 'Kugelrohr'-method. The vacuum was provided either by a rotary slide pump (0.05 mbar) or by a water-jet vacuum pump (10 mbar).

4.2. 2,6-Dimethyl-6-(3-methyl-but-2-enyl)-cyclohex-2-enone 3a

Sodium hydride (60%, 85 g, 2.13 mol) was added in portions to a solution of 2,6-dimethylphenol (250 g, 2.05 mol) in 2 L of toluene at 10–15 °C. The resulting suspension was stirred for 45 min. The mixture was cooled to 5 °C, and 1-chloro-3-methyl-but-2-ene (prenyl chloride) (262 g, 2.13 mol, 85%) was added over 1.5 h keeping the temperature at 5 °C. The mixture was then stirred for a further 2 h at 10–15 °C. Methanol (1 L) and palladium (2.5 g, 10% on charcoal) were added and the gray suspension was hydrogenated at 0.3 bar pressure, keeping the temperature at 20–22 °C (ice bath). The suspension was then filtered through a pad of Celite. The yellow filtrate was washed with water (0.5 L), aqueous sodium hydroxide (0.5 L), and brine (0.5 L), dried ($MgSO_4$), and concentrated in vacuo. The residue was distilled over a 5 cm Vigreux column to yield 318 g (81%, bp 78–82 °C/0.05 Torr) of a colorless oil. Odor: fruity, grapefruit, minty, bergamot. IR (ATR) *v*: 2965s, 2922s, 1667vs, 1449m, 1376m, 1033m. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 3H, 6-CH_3); 1.59 (s, 3H, 3′-CH_3); 1.70 (s, 3H, 4′-H); 1.77–1.70 (m, 1H, 5_b-H); 1.76 (s, 3H, 2-CH_3); 1.91 (dt, $J_{5a,5b}$ = 13.6 Hz, $J_{5a,4}$ = 6.1 Hz, 1H, 5_a-H); 2.25–2.14 (m, 2H, 1′H); 2.34–2.28 (m, 2H, 4-H); 5.06–5.11 (m, 1H, 2′-H); 6.62 (br s, 1H, 3-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4 (q, 2-CH_3); 17.8 (q, 3′-$(CH_3)_b$); 21.8 (q, 6-CH_3); 22.9 (t, C-4); 25.9 (q, 3′-$(CH_3)_a$); 33.4 (t, C-5); 34.9 (t, C-1′); 45.0 (s, C-6); 119.7 (d, C-2′); 134.0, 133.9 (2s, C-2, C-3′); 143.4 (d, C-3); 204.0 (s, C-1). GC/MS (EI): 192 (M^+, 16), 124 (100), 109 (74), 82 (31), 69 (40), 41 (57). Anal. Calcd for $C_{13}H_{20}O$ (192.29): C, 81.20; H, 10.48. Found: C, 81.21; H, 10.47.

4.3. 2,4,6-Trimethyl-6-(3-methyl-but-2-enyl)-cyclohex-2-enone 3b

A mixture of two diastereomers in a ratio of 4/1. Odor: hesperidic, fresh, floral, grapefruit, terpenic. IR (ATR) *v*: 2962s, 2924s, 1670vs, 1453s, 1376s, 1035m, 986m. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07/1.03 (2s, 3H, $6_{a,b}$-CH_3); 1.09 (d, *J* = 6.8 Hz, 3H, 4-CH_3); 1.59–1.55 (m, 1H, 5_b-H); 1.61 (s, 3H, 3′-CH_3); 1.68 (s, 3H, 4′-CH_3); 1.71–1.67 (m, 1H, 5_a-H); 1.76 (s, 3H, 2-CH_3); 2.36–2.11 (m, 2H, 1′-H); 2.62–2.52 (m, 1H, 4-H); 5.09–5.03 (m, 1H, 2′-H); 6.43 (br s, 1H, 3-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3 (q, 2-CH_3); 17.8 (q, 3′-$(CH_3)_b$); 21.3 (q, 6-CH_3); 22.3 (q, 4-CH_3); 25.9 (q, 3′-$(CH_3)_a$); 27.9 (d, C-4); 36.4 (t, C-1′); 41.7 (t, C-5); 44.8 (s, C-6); 120.1 (d, C-2′); 133.6, 132.9 (2s, C-2, C-3′); 149.4 (d, C-3); 204.0 (s, C-1). GC/MS (EI), main isomer: 206 (M^+, 13), 164 (20), 138 (69), 123 (100), 96 (27), 69 (35), 41 (81). HRMS: 206.1679 (calcd 206.1671).

4.4. 2,3,6-Trimethyl-6-(3-methyl-but-2-enyl)-cyclohex-2-enone 3c

Odor: agrestic, minty, fruity. IR (ATR) *v*: 2915s, 1659vs, 1638s, 1376s, 1023m, 764w. ^{1}H NMR (400 MHz, $CDCl_3$)

δ 1.03 (s, 3H, 6-CH_3); 1.59 (s, 3H); 1.69–1.63 (m, 1H, 5_b-H); 1.70 (s, 3H); 1.75 (s, 3H); 1.89–1.83 (m, 1H, 5_a-H); 1.89 (s, 3H); 2.25–2.11 (m, 2H, 1′-H); 2.33–2.29 (m, 2H, 4-H); 5.09–5.05 (m, 1H, 2′-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.2 (q, 2-CH_3); 17.7 (q); 21.2 (q); 22.0 (q); 25.9 (q); 29.3 (t); 32.3 (t); 35.2 (t); 43.7 (s, C-6); 119.8 (d, C-1′); 131.8, 131.4 (2s, C-2, C-3′); 152.4 (s, C-3); 203.3 (s, C-1). GC/MS (EI): 206 (M^+, 9), 178 (15), 138 (100), 137 (98), 123 (97), 96 (50), 67 (52), 41 (62). HRMS: 206.1663 (calcd 206.1671).

4.5. 6-Benzyl-2,6-dimethylcyclohex-2-enone 3d

Odor: Fruity, minty, saffron, rosy, apple. IR (ATR) *v*: 2923s, 1666vs, 1452s, 1375m, 1027m, 702s. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 3H, 6-H); 1.91–1.60 (m, 2H, 5-H); 2.40–2.29 (m, 2H, 4-H); 2.74 (d, $J = 15$ Hz, $CH\mathit{H}_b$Ph); 2.97 (d, $J = 15$ Hz, 1H, $CH\mathit{H}_a$HPh); 6.65 (br s, 1H, 3-H); 7.28–7.09 (m, 5H, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6 (q); 22.2 (q); 22.9 (t); 33.0 (t); 42.7 (t); 45.4 (s); 126.2 (d); 127.8 (2d); 130.7 (2d); 134.8 (s); 137.8 (d); 143.6 (d); 203.7 (s). GC/MS (EI): 214 (M^+, 27), 186 (37), 123 (44), 95 (13), 91 (100), 82 (91), 77 (10), 65 (18), 54 (25), 39 (20). HRMS: 214.1343 (calcd 214.1358).

4.6. 2,6-Dimethyl-6-(3,4,4-trimethylpent-2-enyl)-cyclohex-2-enone 3e

IR (ATR) *v*: 2915s, 1659vs, 1638s, 1376s, 1023m, 764w, 1029m. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (s, 9H, 4′-$(CH_3)_3$); 1.05 (s, 3H, 6-CH_3); 1.60 (s, 3H); 1.77 (s, 3H); 1.77–1.70 (m, 1H); 1.92–183 (m, 1H); 2.22 (d, $J = 7.6$ Hz, 2H, 1′-H); 5.18–5.15 (m, 1H, 2′-H); 6.62 (br s, 1H, 3-H); 2.34–2.28 (m, 2H, 4-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8 (q); 16.4 (q); 21.8 (q); 22.8 (t); 29.0 (3q); 33.4 (t); 34.8 (t); 36.3 (s); 45.1 (s); 116.0 (d); 134.0 (s); 143.3 (d); 154.4 (s); 204.2 (s). GC/MS (EI): 234 (M^+, 8), 177 (5), 124 (100), 109 (31), 95 (20), 69 (38), 55 (35), 41 (38). HRMS: 234.1982 (calcd 234.1937).

4.7. 6-(5,5,5-Trichloro-3-methylpent-2-enyl)-2,6-dimethylcyclohex-2-enone 3f

IR (ATR) *v*: 2923m, 1667s, 1450m, 1377m, 1029m, 761s, 704vs. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (s, 3H); 1.33–1.14 (m, 2H); 1.77 (s, 3H); 1.87 (s, 3H); 2.03–1.74 (m, 2H); 2.37–2.23 (m, 4H); 3.37 (s, 2H); 5.55–5.50 (m, 1H); 6.64 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4 (q); 17.9 (q); 21.7 (q); 22.7 (t); 33.3 (t); 35.3 (t); 45.0 (s); 63.6 (t); 99.2 (s); 130.5 (s); 131.0 (d); 133.8 (s); 143.6 (d); 203.6 (s). GC/MS (EI): 309 (M^+, 3), 191 (34), 163 (11), 123 (100), 109 (32), 95 (35), 82 (60), 67 (21), 53 (26), 39 (23).

4.8. 6-(2-Cyclohexylideneethyl)-2,6-dimethylcyclohex-2-enone 3g

IR (ATR) *v*: 2924s, 2852m, 1667s, 1447m, 1373m, 1027m. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 3H); 1.56–1.45 (m, 6H); 1.76 (br s, 3H); 1.77–1.69 (m, 1H); 1.94–1.86 (m, 1H); 2.34–2.04 (m, 8H); 5.05–5.50 (m, 1H); 6.63–6.61 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4 (q); 21.7 (q); 22.9 (t); 26.7 (t); 27.6 (t); 28.6 (t); 28.7 (t); 33.3 (t); 33.7 (t); 37.4 (t); 44.8 (s); 116.1 (d); 133.9 (s); 142.1 (s); 143.3 (d); 204.2 (s). GC/MS (EI): 232 (M^+, 1), 124 (100), 109 (38), 91 (12), 79 (17), 67 (35), 55 (16), 41 (20). HRMS: 232.1848 (calcd 232.1827).

4.9. 2,6-Dimethyl-6-(3-methylbut-2-enyl)cyclohexa-2,4-dien-1-one 4

(−)-Sparteine **6** (6.00 g, 24.60 mmol) was dissolved in benzene (60.0 mL) and the solution cooled to −15 °C. Butyl lithium (15.4 mL, 24.60 mmol, 1.6 M in hexane) was added dropwise. 2,6-Dimethyl phenol **1a** (3.00 g, 24.59 mmol) was added as a solution in toluene (15.0 mL) to the bright yellow reaction mixture. The mixture was stirred at room temperature for 1 h. Prenyl chloride (3.50 g, 24.60 mmol) was added dropwise to the stirred solution. After stirring at 0 °C for 1 h, the reaction mixture was left stirring at room temperature for 15 h. The reaction was then quenched with water (100.0 mL) and extracted with ether. The organic layers were washed with a Claisen base (satd KOH/MeOH) to remove phenolic by-products, then with water and brine. The crude product was purified by chromatography over basic aluminum oxide [hexane/MtBE 95:5] and dried in vacuo. Compound **4** (0.45 g, 28% yield, 4% ee) was obtained as a colorless liquid: $[\alpha]_D^{25} = +16.6$ (*c* 1.3, EtOH). IR (ATR) *v*: 3034w, 2969m, 2923m, 1627vs, 1642s, 1582w, 1450m, 1377m, 742m. ^{1}H NMR (300 MHz, C_6D_6) δ 1.14 (s, 3H); 1.51 (s, 3H); 1.54 (d, $J = 1.1$ Hz, 3H); 1.84 (m, 3H); 2.12 (m, 1H); 2.7 (m, 1H); 5.05 (m, 1H); 5.76 (dd, $J = 5.9$, 9.5 Hz, 1H); 5.90 (m, 1H); 6.27 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.3 (q); 17.8 (q); 24.0 (q); 25.6 (q); 38.9 (t); 51.1 (q); 118.8 (d); 120.1 (d); 133.0 (s); 134.1 (s); 137.8 (d); 145.1 (d); 206 (s). EI-MS (GC/MS): 190 (M^+, 1), 175 (4), 122 (100), 107 (28), 91 (14), 69 (25), 41 (29).

4.10. α-Isosparteine 7

Neutral, dry aluminum oxide (18.00 g) was mixed with aluminum chloride (7.56 g, 56.80 mmol) under an inert atmosphere. The mixture was sealed in glass ampoules and heated at 230 °C for 6 h. The α-isosparteine was isolated by acid–base extraction and crystallized as its hydrate from wet acetone. The required amounts of α-isosparteine **7** for the experiments were dehydrated by short path distillation (120 °C, 0.05 mbar) immediately before use. α-Isosparteine hydrate can be stored in the refrigerator for extended periods of time. Mp: 108–110 °C [lit. 104–105 °C]. $[\alpha]_D^{25} = -55.0$ (*c* 1.275, MeOH) [lit. −32.6].[11]

4.11. 2,6-Dimethyl-6-(3-methylbut-2-enyl)cyclohexa-2,4-dien-1-one 4 using α-isosparteine/Li as chiral base

α-Isosparteine **7** (0.60 g, 2.46 mmol) was dissolved in toluene (6.0 mL). The solution was then cooled to −10 °C and BuLi (1.5 mL, 2.46 mmol, 1.6 M in hexane) was added dropwise. The originally colorless solution turned bright yellow. After stirring at −10 °C for 30 min, **1a** (300 mg, 2.46 mmol) was added dropwise as a solution in toluene (1.5 mL). The solution discolored immediately after the addition and then turned yellow again upon stirring for 30 min at −10 °C. Prenyl chloride (256 mg, 2.46 mmol) was added and the mixture was slowly warmed to rt and

stirred for 14 h. After chromatography over basic aluminum oxide [hexane/MtBE 95:5] and short path distillation (~50 °C, 0.05 mbar) **4**, (80 mg, 17% yield, 9% ee) was obtained as yellow oil: $[\alpha]_D^{25} = +37.0$ (*c* 0.8, EtOH).

4.12. 2-(*R*)-Methyl-2-(3-methylbut-2-enyl)-2*H*-naphthalen-1-one (*R*)-11

A solution of α-isosparteine **7** (440 mg, 1.80 mmol) in toluene (5.0 mL) was cooled to −10 °C. Butyl lithium (1.1 mL, 1.80 mmol, 1.6 M in hexane) was added dropwise. A bright yellow solution was obtained and stirred for 30 min at −10 °C. 2-Methyl-naphthalen-1-ol **10** (284 mg, 1.80 mmol) was added dropwise as a solution in toluene (2.0 mL). After stirring at −10 °C for 30 min, the solids precipitated and the mixture turned gray/green. Additional toluene (2.0 mL) was added to maintain a movable suspension. Prenyl chloride (234 mg, 1.80 mmol) was added causing the mixture to turn darker. The reaction was left stirring at rt for 15 h. More solids formed and analysis of the reaction mixture by TLC showed that all the starting materials had been consumed. Silica gel and hexane were added to the reaction mixture. The solids were removed by filtration and washed with hexane/MtBE 1:1. The filtrate was concentrated and the residue was purified by chromatography over aluminum oxide [hexane/MtBE 95:5]. Short path distillation (120 °C, 0.05 mbar) afforded **11** (220 mg, 54% yield, 38% ee) as a light-yellow oil: $[\alpha]_D^{25} = +118.8$ (*c* 1.0, EtOH). The absolute configuration was determined by VCD spectroscopy. Due to the high conformational mobility of the side chain, only VCD signals resulting from stretching vibrations of the C=O group and the C=C double bonds (the 1750–1550 cm^{-1} region) can be interpreted. The CD spectrum of **11** in acetonitrile contains only positive bands with fine structures in the 250–400 nm region. Below 250 nm, the spectrum is governed by the positive ^1L_a band at ~230 nm and a negative one below 200 nm. These bands mostly result from the phenyl chromophore. Applying the sector rule of the saturated ketones to the positive long-wavelength band at 333 nm resulted in an (*R*)-configuration of the stereogenic center assuming the axial position of the Me group. IR (ATR) *v*: 2968w, 1673s, 1644w, 1598m, 1483w, 1317w, 1268w, 981w, 790vs, 691m. ^{1}H NMR (300 MHz, C_6D_6) δ 1.20 (s, 3H); 1.43 (d, $J = 1.1$ Hz, 3H); 1.51 (s, 3H); 2.19 (m, 1H); 2.78 (dd, $J = 8.0$, 14.0 Hz, 1H); 5.09 (m, 1H); 5.84 (d, $J = 9.9$ Hz, 1H); 6.30 (d, $J = 9.7$ Hz, 1H); 6.82 (m, 1H); 6.93 (m, 1H); 7.08 (m, 1H); 8.26 (m, 1H). ^{13}C NMR (75 MHz, C_6D_6) δ 17.9 (3q); 25.6, 24.5, 39.0 (3t); 49.6 (s); 127.9, 127.2, 127.0, 214.1, 119.6 (5d); 130.0 (s); 134 (d); 134.2 (s); 138.5 (s); 140.1 (d); 202.1 (s). EI-MS (GC/MS): 226 (M^+, 1), 211 ($[M-CH_3]^+$, 1), 158 (100), 128 (24), 115 (10), 69 (19), 41 (20). Anal. Calcd for $C_{16}H_{18}O$ (226): C, 84.91; H, 8.02. Found: C, 84.96; H, 8.26.

4.13. (*S*)-1-Methyl-1-(3-methylbut-2-enyl)-1*H*-naphthalen-2-one (*S*)-13

α-Isosparteine **7** (1.00 g, 4.10 mmol) was first dissolved in benzene (10.0 mL). The solution was then cooled to 0 °C and BuLi (2.56 mL, 4.10 mmol, 1.6 M in hexane) was added dropwise. After stirring at 0 °C for 30 min, 1-methyl-naphthalen-2-ol **12** (647 mg, 4.1 mmol) was added as solution in benzene (3.0 mL). The bright yellow α-isosparteine lithium complex discolored and some solids precipitated. After 30 min at 0–5 °C prenyl chloride (533 mg, 4.10 mmol) was added in one portion. The reaction mixture was stirred for 15 h, gradually reaching room temperature. TLC analysis showed that the reaction had reached completion. Silica gel and hexane were added to the reaction mixture and the solids were removed from the suspension by filtration and washed with hexane/MtBE 1:1. The filtrate was concentrated and the residue separated by chromatography over basic aluminum oxide [hexane/MtBE 9:1]. After short path distillation (120 °C, 0.05 mbar), **13** (240 mg, 26% yield, 30% ee) was obtained as a light yellow oil: $[\alpha]_D^{25} = +14.9$ (*c* 1.0, EtOH). The CD spectrum of **13** in acetonitrile contains a broad asymmetric positive band with two maxima above 320 nm and a negative one near 300 nm. The ± sign pattern is compatible with an *M*-helicity of the enone chromophore. If assuming the axial position of the methyl group, this gives rise to an (*S*)-configuration. IR (neat) *v*: 2970w, 2913w, 1655vs, 1621w, 1597w, 1449m, 1397w, 1376w, 1299w, 1239w, 1207w, 835m, 755s. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 3H); 1.47 (s, 3H); 1.49 (m, 3H); 2.45 (m, 1H); 2.77 (m, 1H); 4.66 (m, 1H); 6.14 (d, $J = 9.9$ Hz, 1H); 7.42–7.23 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.8, 17.9 (3q); 41.8 (t); 52.03 (s); 129.9, 129.4, 126.9, 126.7, 125.4, 118.8 (6d); 130.0 (s); 134.7 (s); 145.0 (d); 146.3 (s); 204.4 (s). EI-MS (GC/MS): 226 (M^+, 1), 211 ($[M-CH_3]^+$, 1), 158 (100), 128 (22), 115 (9), 69 (20), 41 (20).

4.14. 2,6-Dimethyl-6-(3-methyl-but-2-enyl)-cyclohex-2-en-1-one 3a

2,6-Dimethyl-6-(3-methylbut-2-enyl)cyclohexa-2,4-dien-1-one **4** (2.50 g, 9.90 mmol) was mixed with toluene (10.0 mL) and methanol (5.0 mL). Palladium 10% on activated carbon (10 mg) was added and the suspension hydrogenated at atmospheric pressure for 3 h at room temperature. The catalyst was removed by filtration over Celite and the crude product was purified by chromatography over silical gel [hexane/MtBE 8:2]. 2,6-Dimethyl-6-(3-methyl-but-2-enyl)-cyclohex-2-en-1-one **3a** (1.53 g, 80% yield) was isolated as a colorless liquid. IR (CCl_4) *v*: 2966m, 2922m, 1665s, 1449m, 1375m, 1356m, 1189w, 1074w, 1032m, 979w, 942w, 876w, 840w. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 3H); 1.47 (m, 1H); 1.54 (s, 3H); 1.67 (s, 3H); 1.73 (m, 1H); 1.91–1.83 (m, 5H); 2.33 (m, 2H); 5.25 (m, 1H); 6.11 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5 (q); 17.9 (q); 21.9 (q); 23.0 (t); 26.0 (q); 33.5 (t); 35.0 (t); 45.1 (s); 119.8 (d); 134.0 (s); 134.1 (s); 143.4 (d); 204.3 (s). CI-MS (GC/MS, NH_3): 193.1 ($[M+H]^+$, 100), 194.1 (14). HRMS: (192.1514) (calcd 192.1513).

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