

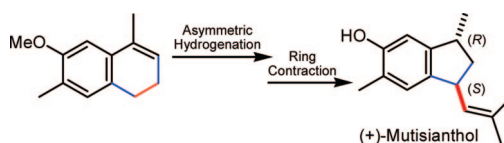
(+)- and (-)-Mutisianthol: First Total Synthesis, Absolute Configuration, and Antitumor Activity[†]

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The first synthesis of the natural product (+)-mutisianthol was accomplished in 11 steps and in 21% overall yield from 2-methylanisole. The synthesis of its enantiomer was also performed in a similar overall yield. The absolute configuration of the sesquiterpene (+)-mutisianthol was assigned as (1*S*,3*R*). Key steps in the route are the asymmetric hydrogenation of a nonfunctionalized olefin using chiral iridium catalysts and the ring contraction of 1,2-dihydronaphthalenes using thallium(III) or iodine(III). The target molecules show moderate activity against the human tumor cell lines SF-295, HCT-8, and MDA-MB-435.

Introduction

The phenolic sesquiterpene mutisianthol was isolated by Bohlmann and co-workers in 1979, from the roots of *Mutisia homoeantha*.¹ On the basis of spectroscopic data, the relative configuration of this natural indane was assigned as **1**, which embodies a *cis*-1,3-disubstituted cyclopentyl unit. Mutisianthol has been isolated as the dextrorotatory enantiomer, but its absolute configuration has not yet been assigned. Nearly two decades after Bohlmann's work, Ho and co-workers² reported the first total synthesis of (±)-mutisianthol. In the first route, the authors obtained the acetylated *cis*-indane **2**, exhibiting a structure very similar to that of **1**. However, comparing the NMR spectra of this intermediate with those of the natural compound, the authors considered that the relative configuration of mutisianthol should be *trans*. Eventually, a new route was elaborated to give **3**, which showed spectroscopic data identical to that of the natural compound (Figure 1). This synthesis was achieved in 15 steps and in 3% yield from *p*-methylacetophenone. Thus,

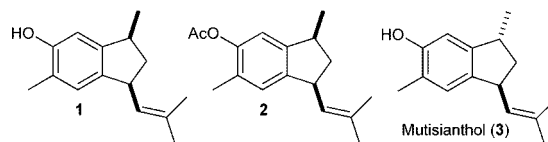


FIGURE 1. Structure of mutisianthol and related indanes.

mutisianthol is one of several examples of a natural product whose structure was misassigned and later on corrected by chemical synthesis.³ In the past decade, several approaches were investigated for the synthesis of indanes through the ring contraction⁴ of readily available 1,2-dihydronaphthalenes mediated by thallium(III)⁵ or by iodine(III),⁶ including applications in total synthesis.^{5d,g,6} One of the targets was (±)-mutisianthol, which was synthesized in 12 steps and in 8% yield from 2-methylanisole.^{5d}

[†] Dedicated with deep respect to Prof. Nicola Petragnani on the occasion of his 80th birthday.

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[¶] Deceased.

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The chemical synthesis of small-molecule natural products has an important role in the development of chemistry⁷ and in the discovery of new compounds with biological activity.⁸ This is particularly evident in the search for new anticancer candidates.⁹ In this context, we herein describe the first asymmetric synthesis of (+)-mutisianthol and its enantiomer, unraveling the previously unknown absolute configuration of the two stereogenic centers of this natural sesquiterpene. In addition, results regarding the antitumor activity of the target molecules and related indanes are reported.

Results and Discussion

The strategy for the asymmetric synthesis of mutisianthol was based mainly on our previous synthesis of the racemate^{5d} and on the asymmetric hydrogenation of olefins using iridium catalysts.¹⁰ Thus, it was planned to obtain target molecule **3** from aldehyde **4** through Wittig reaction and deprotection. The ring contraction of the optically active olefin **5** using either Ti(III) or I(III) would give the aldehyde **4**, which bears the 1,3-*trans*-disubstituted indane unit. Olefin **5** would be prepared from tetralone **6** by reduction and dehydration. We envisioned that the 4-methyl-1-tetralone **6** could be obtained in high enantiomeric excess through the asymmetric hydrogenation of the 4-methyl-1,2-dihydronaphthalene **7**, followed by benzylic oxidation. Alkene **7** would be obtained from 2-methylanisole (**8**) (Scheme 1). The retrosynthesis shown is for (1*S*,3*R*)-mutisianthol, which was eventually identified as the natural product. However, as the absolute configuration was unknown at the beginning of this work, a flexible synthetic plan was chosen to allow the stereoselective synthesis of both enantiomers. We therefore decided to use asymmetric hydrogenation of olefin **7** as a key step, which should deliver either the (+)- or the (–)-enantiomer by proper choice of the catalyst.¹¹

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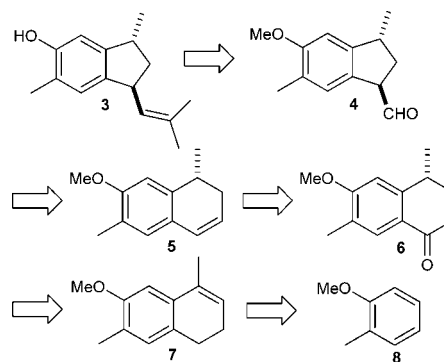
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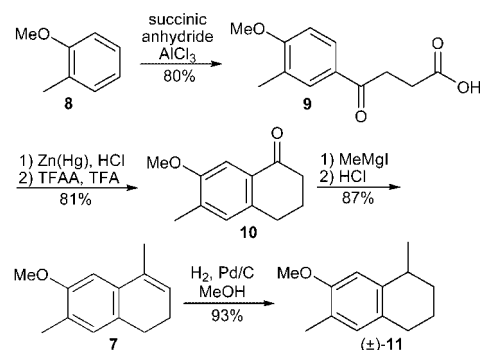
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SCHEME 1. Retrosynthetic Analysis for the Asymmetric Synthesis of Mutisianthol



SCHEME 2. Preparation of Olefin 7 and of Racemic (±)-11



With the above plan in mind, the total synthesis of mutisianthol was initiated. Olefin **7** was obtained in four steps from commercially available 2-methylanisole (**8**) in 56% yield.^{5d,12} Tetrahydronaphthalene (±)-**11** was obtained by hydrogenation of the 1,2-dihydronaphthalene **7** over Pd/C, in 93% yield. Racemic (±)-**11** was used as reference for establishing separation conditions for its two enantiomeric forms (Scheme 2).

Because 1,2-dihydronaphthalene **12**, which is similar to **7**, had been hydrogenated with high enantiomeric excess using chiral iridium catalysts (Scheme 3 and Figure 2),^{13,14} we envisaged that tetrahydronaphthalene **11** could be also obtained in high enantiomeric purity.

Initially, we expected that olefins **7** and **12** would give comparable results in the iridium-catalyzed enantioselective hydrogenation. However, after an initial screening of catalysts A–C, we were surprised to see that this was not the case (Table 1). Although dihydronaphthalene **12** was converted to **13** in 95% ee using complex A without any byproducts,¹⁴ **11** was obtained in only 68% ee under the same conditions. Even more surprising was the formation of 23% of naphthalene **14** (entry 1). We had observed this side reaction only with some tetrasubstituted dihydronaphthalenes,¹⁵ but never in the enantioselective hydrogenation of **12**. Other catalysts such as B and C gave significantly less aromatic side product (entries 2 and 3);

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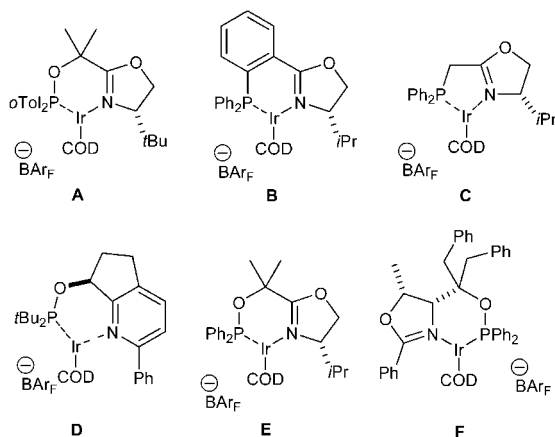


FIGURE 2. Structure of iridium catalysts A–F.

SCHEME 3. Asymmetric Hydrogenation of Olefin 12

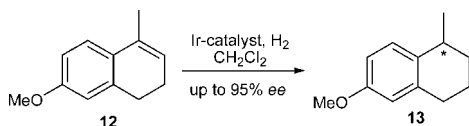
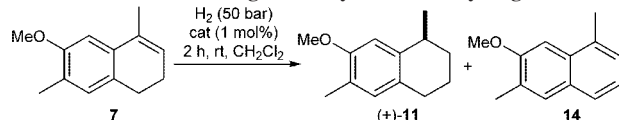


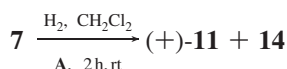
TABLE 1. First Screening of Catalysts for the Hydrogenation of 7



entry	catalyst	conversion (%)	products ^a 11:14	ee of 11 (%)
1	A	<99	77:23	68 (+)
2	B	<99	97:3	34 (+)
3	C	<99	99:1	5 (+)

^a Ratio determined by GC analysis.

TABLE 2. Hydrogenation of Olefin 7 with Catalyst A

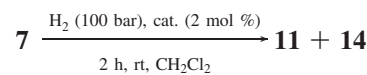


entry	conditions	conversion (%)	products ^a 11:14	ee (%)
1	2.0 mol %, 50 bar	<99	82:18	74 (+)
2	1.0 mol %, 50 bar	<99	77:23	68 (+)
3	0.5 mol %, 50 bar	<99	68:32	50 (+)
4 ^b	2.0 mol %, 50 bar	<99	87:13	80 (+)
5 ^b	1.5 mol %, 50 bar	<99	83:17	77 (+)
6 ^b	1.0 mol %, 50 bar	<99	82:18	74 (+)
7 ^b	0.5 mol %, 50 bar	<99	73:27	58 (+)
8 ^b	2.0 mol %, 100 bar	<99	91:9	87 (+)

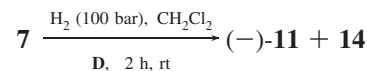
^a Ratio determined by GC analysis. ^b CH₂Cl₂ was stirred over activated aluminum oxide and filtered prior to use.

however, the enantiomeric excesses were very low (34% and 5%, respectively).

With these initial results, we decided to optimize the reaction conditions using complex A (Table 2). Lowering the catalyst loading to less than 1 mol % gave lower enantiomeric excess and significantly higher amounts of aromatic side product. For example, with a catalyst loading of 0.5 mol % of complex A, (+)-11 was obtained in only 50% ee, whereas 32% of 14 was formed (entry 3). Using 2 mol % of A, an enantiomeric excess of 74% was obtained, along with 18% of 14 (entry 1). When the solvent CH₂Cl₂ was stirred over activated aluminum oxide

TABLE 3. Second Screening of Catalysts for the Hydrogenation of 7^a

entry	catalyst	conversion (%)	products ^b 11:14	ee (%) of 11
1	D	<99	98:2	92 (-)
2	E	<99	94:6	82 (+)
3	F	<99	99:1	69 (-)

^a CH₂Cl₂ was stirred over activated aluminum oxide and filtered prior to use. ^b Ratio determined by GC analysis.TABLE 4. Hydrogenation of Olefin 7 with catalyst D^a

entry	catalyst load (mol %)	conversion (%)	products ^b 11:14	ee (%)
1	2.0	<99	98:2	92 (-)
2	1.5	<99	98:2	92 (-)
3	1.0	<99	97:3	91 (-)
4	0.5	<99	96:4	89 (-)
5	0.1	16	8:8	4 (-)

^a CH₂Cl₂ was stirred over activated aluminum oxide and filtered prior to use. ^b Ratio determined by GC analysis.

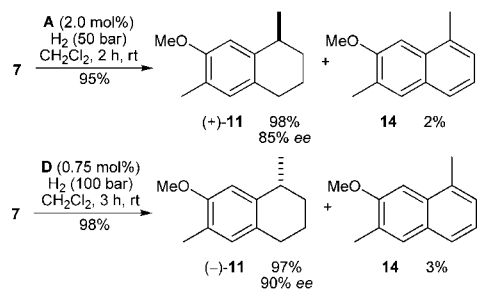
and then filtered prior to use, higher enantiomeric excesses could be obtained and the formation of aromatic side product was reduced. With 2 mol % of A, tetrahydronaphthalene (+)-11 was obtained in 80% ee and 13% of naphthalene 14 was formed (entry 4). To suppress the undesired aromatization, we assumed that higher pressure would be beneficial. Indeed, we obtained significantly better results using 100 bar of hydrogen instead of 50 bar. Using 1 mmol of 7, 2 mol % of complex A, and 100 bar of hydrogen, we obtained tetrahydronaphthalene (+)-5 in 87% ee and the aromatic side product 14 in only 9% (entry 8). At 50 bar, product (+)-11 was obtained in 80% ee together with 15% of 14 (entry 4).

With these optimized conditions (high pressure, high catalyst loading, and freshly dried solvent), we screened other iridium catalysts (Table 3) and obtained superior results using complex D, which gave (-)-11, i.e., the opposite enantiomer previously obtained with catalyst A. The hydrogenation proceeded with only 2% of side product formation and gave tetrahydronaphthalene (-)-11 with an enantiomeric excess of 92% (entry 1). Using complex E, 82% ee and 6% of 14 was obtained (entry 2), while complex F gave 69% ee and only 1% of 14 (entry 3).

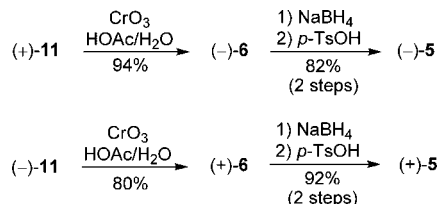
As observed for complex A, lowering the catalyst loading of D resulted in a lower enantiomeric excess for (-)-11 and an increase of 14 (Table 4). Using 1 mol % of D, tetrahydronaphthalene (-)-11 was obtained in 91% ee together with 3% of aromatic side product (entry 3). With 0.5 mol % of catalyst loading, (-)-11 was obtained with 89% ee and 4% of 14 (entry 4). At even lower catalyst loading (0.1 mol %), only 8% of (-)-11 was obtained with an ee of 4%. Naphthalene 14 was obtained in 8% and the remaining was unreacted starting material.

To obtain the required amount of (+)-11 for the synthesis, 7 was hydrogenated in the presence of A under a pressure of 100 bar. Under these conditions, 9% of naphthalene 14 was formed. For the preparation of (-)-11, we decided to use a catalyst loading of 0.75 mol % and a pressure of 100 bar, which gave the desired product in 98% yield, including 3% of naphthalene

SCHEME 4. Asymmetric Hydrogenations of Olefin 7



SCHEME 5. Preparation of 1,2-Dihydronaphthalenes (+)- and (-)-5



14. Under these conditions, (-)-11 was obtained in 90% ee. Thus, we had both (+)- and (-)-11 in hand for further transformations (Scheme 4).

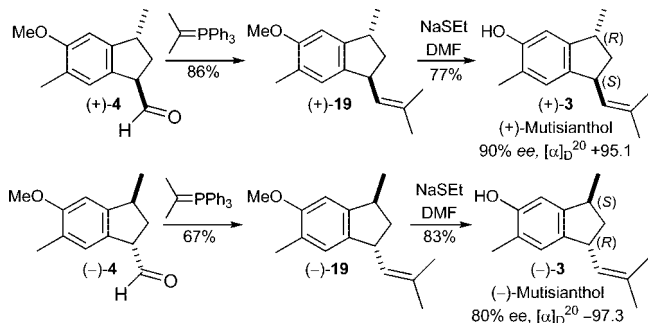
After having developed an efficient method to perform the asymmetric hydrogenation of olefin 7, the benzylic oxidation of the tetralins (+)- and (-)-11 was required. This transformation was best performed (see Supporting Information for other conditions) in AcOH/H₂O with careful addition of a slight excess of chromium oxide, which gave the desired tetralones (-)- and (+)-6 in 94% and 80% yield, respectively. In these oxidations, the secondary benzylic position of tetralin 11 was oxidized selectively without any racemization while the tertiary benzylic position remained untouched. During the development of this synthesis, Chavan and co-workers¹⁶ reported the asymmetric synthesis of (-)-heritol from tetralone (+)-(*R*)-6, which was prepared from (+)-(*R*)-citronellal. On the basis of their synthesis, we assigned the absolute configuration of (+)-(*R*) and (-)-(*S*)-6 and, consequently, of all optically active compounds described in this article. Tetralones (+)- and (-)-6 were then transformed into the corresponding 1,2-dihydronaphthalenes (+)- and (-)-5, respectively, through reduction with NaBH₄ followed by dehydration with *p*-toluene sulfonic acid in toluene (Scheme 5).^{5d,e} A slightly lower yield (72%) was obtained for the dehydration of (-)-6 in benzene.

Treating (-)-5 with thallium(III) trinitrate (TTN) in trimethylorthoformate (TMOF)^{5a,c,d} led to the ketal (-)-15, in 94% yield (Table 5, entry 1). To introduce the propenyl moiety of mutisianthol, the aldehyde moiety of (-)-15 was unmasked by heating in AcOH,^{5d} which gave (-)-4 in 72% yield. Acetonitrile is also a suitable solvent for the rearrangement of olefins mediated by TTN.^{5h} Additionally, under this condition aldehyde (-)-4 would be isolated directly, avoiding the deprotection. First, we treated the olefin (±)-16 using TTN in CH₃CN in the presence of molecular sieves and under inert atmosphere, which led to (±)-17 (entry 2). Under similar conditions, (-)-5 gave (-)-4 in 74% yield (entry 3). The inert atmosphere and the molecular sieves are not crucial for the ring contraction, as shown in the reactions of (±)- and (+)-5 (entries 4 and 5,

TABLE 5. Ring Contraction Reactions with 1.1 equiv of TTN or HTIB

entry	substrate	conditions	product (yield)
1		TTN, TMOF, 0 °C, 1 min	
2		TTN, MeCN, MS 3 Å, 0 °C, 5 min	
3	(-)-5	TTN, MeCN, 0 °C, MS 3 Å, 5 min	
4	(±)-5	TTN, MeCN, 0 °C, 5 min	(±)-4 (89%)
5	(+)-5	TTN, MeCN, 0 °C, 15 min	(+)-4 (80%)
6	(-)-5	HTIB, MeOH, 0 °C-rt, 15 min	

SCHEME 6. Completion of the Syntheses of Mutisianthol

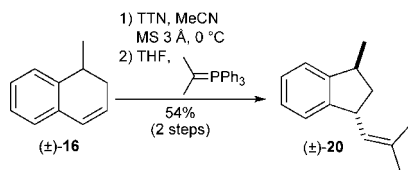


respectively). The substitution of the toxic thallium(III) salt by the iodine(III) reagent [hydroxy(tosyloxy)iodo]benzene (HTIB) was also evaluated. Oxidation of (-)-5 with HTIB⁶ gave the desired ketal (-)-15, in 66% yield, together with 18, which was isolated in 10% yield, as a mixture of diastereomers (entry 6). The mechanism for the thallium(III)- or iodine(III)-mediated ring contraction of 1,2-dihydronaphthalenes has been previously discussed.^{5,6}

Wittig reaction of aldehydes (+)- and (-)-4 with (CH₃)₂C=PPh₃^{5d,17,18} gave (+)- and (-)-19 in 86% and 67% yield, respectively. Finally, (+)- and (-)-mutisianthol (3) were obtained as white solids in good yield by reaction of (+)- and (-)-19 with Na/EtSH in DMF.^{5d,19} The spectroscopic data of the target molecules were in agreement with those described in the literature.^{1,2,5d} Moreover, based on the value of [α]²⁴_D reported (+94, *c* 0.11, CHCl₃),¹ the absolute configuration of natural (+)-mutisianthol was assigned as (1*S*,3*R*), whereas (-)-mutisianthol is (1*R*,3*S*) (Scheme 6).

For studies regarding biological activity, we also prepared the olefin (±)-20, which bears the main structural features of mutisianthol except for the substituents on the aromatic ring.

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SCHEME 7. Synthesis of the Olefin (\pm)-25TABLE 6. Cytotoxic Activity of Mutisianthol and Derivatives on Tumor Cell Lines^a

entry	compound	IC ₅₀ (CI 95%) μ g/mL		
		SF295	HCT-8	MDA-MB-435
1	doxorubicin	0.48	0.01	0.24
2	(+)-mutisianthol (+)-3	4.39	3.84	6.73
3	(-)-mutisianthol (-)-3	5.27	7.83	2.69
4	(\pm)-20	<25	<25	<25
5	(+)-19	<25	19.08	<25
6	(-)-19	19.42	<25	<25
7	(\pm)-19	25.08	<25	<25
8	(-)-4	<25	<25	20.19

^aData are presented as IC₅₀ values and 95% confidence interval obtained by nonlinear regression from three independent experiments.

Ring contraction of the 1,2-dihydronaphthalene (\pm)-16 mediated by TTN gave aldehyde (\pm)-17. Wittig reaction on this aldehyde led to (\pm)-20 in 54% yield for the two steps (Scheme 7).

Once the total synthesis was successfully concluded, we decided to investigate the antitumor activity of mutisianthol and analogous compounds, whose biological properties have not yet been investigated. We tested the cytotoxicity of these compounds using three tumor cell lines: MDA-MB-435 (human melanoma), HCT-8 (human colon), and SF-295 (human brain), using doxorubicin as positive control. Natural (+)-mutisianthol displays moderate cytotoxicity against the three cell lines when compared with doxorubicin (Table 6, entry 1), showing IC₅₀ values of 4.39 μ g/mL in SF295, 3.84 μ g/mL in HCT-8, and 6.73 μ g/mL in MDA-MB-435 cells (entry 2). Similarly, non-natural mutisianthol (-)-3 also shows moderate activity (5.27 μ g/mL in SF295, 7.83 μ g/mL in HCT-8, and 2.69 μ g/mL in MDA-MB-435 cells, entry 3). The natural enantiomer is slightly more active in SF295 and twice as active in HCT-8 but less active in MDA-MB-435 than the (-)-enantiomer. On the other hand, the structural analog (\pm)-20 displays low activity in all tumor cell lines (entry 4), showing that the substituents on the aromatic ring are important for biological activity. The phenol group and isopropenyl moiety are also essential for activity, considering the results with protected mutisianthol 19 (entries 5–7) and with the aldehyde (-)-4 (entry 8).

Conclusion

The first asymmetric synthesis of the natural product (+)-mutisianthol was accomplished in 11 steps and in 21% overall yield from 2-methylanisole. The synthesis of its enantiomer was also performed in the same number of steps in 17% overall yield (see Supporting Information for a summary of the syntheses). Compared with our previous synthesis,^{5d} the route described herein is not only asymmetric but also one step shorter. Moreover, the reactions were further optimized, and consequently, the overall yield increased from 8% to 17–21%. The key steps are (i) the asymmetric hydrogenation of the nonfunctionalized olefin 7 using chiral iridium catalysts and (ii) the ring contraction of the 1,2-dihydronaphthalenes (+)- and (-)-5 using thallium(III) or iodine(III), which allowed the construction of

the *trans*-1,3-disubstituted-indane. The absolute configuration of the natural sesquiterpene (+)-mutisianthol was established as (1*S*,3*R*). Finally, we found that that mutisianthol has a moderate activity against the tumor cells SF-295, HCT-8, and MDA-MB-435.

Experimental Section

(-)-(*R*)-1,2,3,4-Tetrahydro-7-methoxy-1,6-dimethylnaphthalene (-)-11. In a glovebox a glass inlay was charged with olefin 7 (0.38 g, 2.0 mmol), Ir-catalyst **D** (23 mg, 0.015 mmol) and CH₂Cl₂ (10 mL). The inlay and a magnetic stirring bar were put into an autoclave. The autoclave was sealed and then purged with H₂. A pressure of 100 bar of H₂ was applied, and the mixture was stirred for 3 h. The pressure was released, and the solvent was removed under reduced pressure. The crude mixture was taken up in 2 mL of hexanes, passed through a plug of silica (1 cm \times 0.5 cm), and rinsed with hexanes until no UV-active compound was further eluted (spotted on TLC). The solvent was evaporated to leave (-)-11 (0.38 g, 2.0 mmol, 98%) as colorless oil. GC analysis showed a mixture of **14**²⁰ (3%) and (-)-11 (97%); *R*_f 0.58 (5% EtOAc/hexanes); IR (film) 2928, 2854, 1617, 1508, 1250 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.28 (3H, d, *J* = 6.9 Hz), 1.4–1.8 (2H, m), 1.8–2.0 (2H, m), 2.16 (3H, s), 2.6–2.7 (2H, m), 2.8–2.9 (1H, m), 3.80 (3H, s), 6.65 (1H, s), 6.82 (1H, s); ¹³C NMR (75 MHz, CDCl₃) δ 15.7 (CH₃), 20.6 (CH₂), 23.0 (CH₃), 29.0 (CH₂), 31.6 (CH₂), 32.6 (CH), 55.4 (CH₃), 109.6 (CH), 124.0 (C), 128.3 (C), 131.1 (CH), 140.3 (C), 155.8 (C); LRMS *m/z* (%) 190 (M⁺, 57), 175 (100); HRMS *m/z* C₁₃H₁₈O (M + H)⁺ calcd 191.1430, found 191.1430; [α]_D²⁰ -15.5 (*c* 1.04, CHCl₃), 90% ee.

(+)-(*R*)-3,4-Dihydro-6-methoxy-4,7-dimethylnaphthalen-1(2*H*)-one (+)-6. A magnetically stirred solution of (-)-11 (0.34 g, 1.8 mmol) in glacial HOAc (11 mL) was cooled to 0 °C. The ice-bath was removed, and a solution of CrO₃ (0.25 g, 2.5 mmol, 1.3 equiv) in HOAc/H₂O (8:2, 3.6 mL) was slowly dropwise. The temperature of the reaction mixture was allowed to reach rt. After completion of reaction (ca. 10 min after addition of oxidant), the reaction mixture was diluted with water. The solution was transferred to a separatory funnel and was carefully neutralized by addition of a saturated solution of NaHCO₃. The crude product, a yellow solid insoluble in water, was extracted with Et₂O. The organic phase was washed with brine and dried over anhydrous MgSO₄. The solvent was removed under reduced pressure. The crude yellow solid was purified by flash chromatography (gradient elution, hexanes/EtOAc, 9:1–6:4), to give (+)-6 (80%, 0.31 g, 1.5 mmol). Alternatively, the crude product can be purified by recrystallization with hexanes (about 2 mL for 0.1 g of (+)-6): mp 115.0–116.0 °C (lit.¹⁶ 110 °C); *R*_f 0.37 (20% EtOAc/hexanes); [α]_D²¹ +19.7 (*c* 1.08, CHCl₃); [lit.¹⁶ [α]_D²⁵ +26.87 (*c* 0.9, CHCl₃)].

(+)-(*R*)-1,2-Dihydro-7-methoxy-1,6-dimethylnaphthalene (+)-5. To a stirred solution of the tetralone (+)-6 (0.24 g, 1.2 mmol) in THF (4.4 mL) and in anhydrous MeOH (11 mL) was added dropwise NaBH₄ (0.22 g, 5.9 mmol, 5 equiv) at 0 °C. The mixture was stirred for 105 min at rt. The reaction was quenched with brine and extracted with EtOAc. The organic phase was dried over anhydrous MgSO₄, and the solvent was removed under reduced pressure. The resulting yellow oil was immediately diluted in anhydrous toluene (10 mL), and a few crystals of *p*-TsOH were added. The mixture was stirred for 1.5 h at rt. The reaction was quenched with 5% aqueous solution of NaHCO₃ and extracted with EtOAc. The organic phase was washed with brine and dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure giving yellow oil. The product was purified by flash chromatography (hexanes/EtOAc, 9:1, as eluent) to give (+)-5 (92%, 0.21 g, 1.1 mmol) as a colorless oil: *R*_f 0.56 (10% EtOAc/

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hexanes); IR (film) 2957, 2834, 1611, 1500, 1256 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.22 (3H, d, $J = 7.0$ Hz), 2.07 (1H, dddd, $J = 16.9, 6.9, 5.0,$ and 1.7 Hz), 2.16 (3H, s), 2.43 (1H, dddd, $J = 16.9, 6.8, 4.2$ and 2.4 Hz), 2.88 (1H, sextet, $J = 7.0$ Hz), 3.83 (3H, s), 5.79 (1H, dt, $J = 9.5$ and 4.6 Hz), 6.34 (1H, dt, $J = 9.5$ and 1.6 Hz), 6.66 (1H, s), 6.82 (1H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 15.7 (CH_3), 20.3 (CH_3), 31.1 (CH_2), 32.0 (CH), 55.4 (CH_3), 108.5 (CH), 123.9 (C), 124.2 (CH), 125.9 (C), 126.8 (CH), 128.8 (CH), 139.4 (C), 156.8 (C); LRMS m/z (%) 188 (M^+ , 68), 173 (100), 158 (80). HRMS m/z $\text{C}_{13}\text{H}_{16}\text{O}$ ($\text{M} + \text{H}$) $^+$ calcd 189.1274, found 189.1271; $[\alpha]^{21}_{\text{D}} +35.1$ (c 1.07, CHCl_3), 90% ee.

(+)-(1R,3R)-5-Methoxy-3,6-dimethyl-indan-1-carbaldehyde (+)-4. To a stirred solution of (+)-5 (0.28 g, 1.5 mmol) in anhydrous CH_3CN (12 mL) was added TTN (0.73 g, 1.6 mmol, 1.1 equiv), which promptly dissolved. The mixture was stirred for 1 min at 0 °C when an abundant precipitation was observed. The ice bath was removed, and the solution was stirred for 15 min. The resulting suspension was filtered through a silica gel pad (ca. 10 cm), using CH_2Cl_2 as eluent. The filtrate was washed with H_2O (twice) and brine and dried over anhydrous MgSO_4 . The solvent was removed under reduced pressure giving an orange oil, which was immediately purified by flash chromatography (hexanes/ $\text{EtOAc}/\text{CH}_2\text{Cl}_2$, 8:1:1, as eluent), to give (+)-4 (80%, 0.25 g, 1.2 mmol) as a colorless oil: R_f 0.37 (10% $\text{EtOAc}/\text{hexanes}$); IR (film) 2956, 2926, 2833, 2712, 1721, 1613, 1493 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.29 (3H, d, $J = 6.9$ Hz), 1.87 (1H, ddd, $J = 13.2, 8.5$ and 7.3 Hz), 2.20 (3H, s), 2.66 (1H, ddd, $J = 13.2, 7.9$ and 3.8 Hz), 3.30 (1H, sextet, $J = 7.1$ Hz), 3.81–3.86 (1H, m), 3.83 (3H, s), 6.71 (1H, s), 7.04 (1H, s), 9.58 (1H, d, $J = 2.9$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ 16.3 (CH_3), 20.8 (CH_3), 35.1 (CH_2), 38.8 (CH), 55.4 (CH_3), 56.2 (CH), 105.8 (CH), 125.6 (C), 126.8 (CH), 128.9 (C), 148.3 (C), 158.3 (C), 200.7 (CH); LRMS m/z (%) 204 (M^+ , 10), 175 (100), 160 (18). HRMS m/z $\text{C}_{13}\text{H}_{16}\text{O}_2$ ($\text{M} + \text{H}$) $^+$ calcd 205.1223, found 205.1221; $[\alpha]^{21}_{\text{D}} +57.3$ (c 1.12, CHCl_3), 90% ee.

(+)-(1S,3R)-5-Methoxy-3,6-dimethyl-1-(2-methylprop-1-enyl)-1H-indane (+)-19. To a stirred solution of $\text{Ph}_3\text{PCH}(\text{CH}_3)_2\text{Br}^{17}$ (0.17 g, 0.44 mmol, 2.1 equiv) in anhydrous THF (3 mL) and under inert atmosphere was added dropwise $n\text{-BuLi}$ (1.56 M in hexanes, 0.28 mL, 0.44 mmol) at 10 °C. The mixture was stirred for 20 min at 10 °C, resulting in a red solution. A solution of the aldehyde (+)-4 (43 mg, 0.21 mmol) in anhydrous THF (3 mL) was added dropwise. The resulting yellow solution was stirred for 40 min at 0 °C. The reaction was quenched with H_2O and extracted with Et_2O . The organic phase was washed with brine and dried over anhydrous MgSO_4 . The solvent was removed under reduced pressure giving a yellow solid, which was purified by flash chromatography (hexanes/ $\text{CH}_2\text{Cl}_2/\text{EtOAc}$, 8:1:1, as eluent) to give (+)-19 (86%, 41 mg, 0.18 mmol) as a colorless oil: R_f 0.64 (10% $\text{EtOAc}/\text{hexanes}$); IR (film) 2954, 2924, 1613, 1491, 1299 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.23 (3H, d, $J = 7.0$ Hz), 1.74 (3H, d, $J = 1.5$ Hz), 1.78

(3H, d, $J = 1.5$ Hz), 1.90–2.00 (2H, m), 2.18 (3H, s), 3.2–3.3 (1H, m), 3.82 (3H, s), 3.96–4.01 (1H, m), 5.11–5.14 (1H, m), 6.67 (1H, s), 6.83 (1H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 16.3 (CH_3), 18.1 (CH_3), 21.0 (CH_3), 25.8 (CH_3), 38.5 (CH), 41.6 (CH), 42.5 (CH_2), 55.5 (CH_3), 105.6 (CH), 124.9 (C), 126.2 (CH), 128.7 (CH), 131.1 (C), 137.9 (C), 147.2 (C), 157.0 (C); LRMS m/z (%) 230 (M^+ , 66), 215 (100), 201 (96), 186 (26), 128 (43), 115 (46); HRMS m/z $\text{C}_{16}\text{H}_{22}\text{O}$ ($\text{M} + \text{Na}$) $^+$ calcd 253.1563, found 253.1566; $[\alpha]^{20}_{\text{D}} +117.5$ (c 1.01, CHCl_3), 90% ee.

(+)-(1S,3R)-Mutisianthol (+)-3. Under N_2 , 0.48 g of NaH (0.29 g, 12 mmol, 60% in mineral oil) was washed with anhydrous hexanes (3 times). After a few minutes, anhydrous DMF (6.7 mL) was added. To this mixture was slowly added a solution of EtSH (0.58 mL, 7.8 mmol, 30 equiv) in anhydrous DMF (0.5 mL) at 0 °C, and the resulting yellow solution was stirred for 20 min at rt. A solution of (+)-19 (58 mg, 0.25 mmol) in anhydrous DMF (1.5 mL) was then added dropwise, and the resulting mixture was stirred for 5 h at 130 °C, becoming slightly brown. The mixture was cooled to rt, and a saturated solution of NH_4Cl was added. The mixture was extracted with Et_2O , and the organic phase was washed with H_2O and brine and dried over anhydrous MgSO_4 . The solvent was removed under reduced pressure. The resulting brown oil was purified by flash chromatography (hexanes/ EtOAc , 7:3, as eluent) to give a yellow oil, which was purified by flash chromatography (hexanes/ EtOAc , 9:1, as eluent), affording the (+)-3 (77%, 43 mg, 0.20 mmol) as a white solid: mp 97.0–98.0 °C; R_f 0.38 (30% $\text{EtOAc}/\text{hexanes}$); IR (KBr) 3368, 2951, 2931, 2897, 2861, 1619, 1447, 1295 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.20 (3H, d, $J = 7.0$ Hz), 1.74 (3H, d, $J = 1.0$ Hz), 1.78 (3H, d, $J = 1.5$ Hz), 1.88–1.98 (2H, m), 2.20 (3H, s), 3.16–3.23 (1H, m), 3.95–3.99 (1H, m), 4.58 (1H, br s), 5.10–5.12 (1H, m), 6.61 (1H, s), 6.81 (1H, s); ^{13}C NMR (125 MHz, CDCl_3) δ 15.8 (CH_3), 18.1 (CH_3), 20.9 (CH_3), 25.8 (CH_3), 38.1 (CH), 41.5 (CH), 42.4 (CH_2), 110.1 (CH), 121.7 (C), 126.3 (CH), 128.6 (CH), 131.2 (C), 138.7 (C), 147.9 (C), 152.7 (C); LRMS m/z (%) 216 (M^+ , 40), 201 (100), 115 (23); HRMS m/z $\text{C}_{15}\text{H}_{20}\text{O}$ ($\text{M} + \text{H}$) $^+$ calcd 217.1587, found 217.1584; $[\alpha]^{20}_{\text{D}} +95.1$ (c 1.05, CHCl_3), 90% ee; [lit.¹ (+)-3 $[\alpha]^{24}_{\text{D}} +94.0$ (c 0.11, CHCl_3)].

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Supporting Information Available: Spectroscopic data and experimental procedures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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