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Titanium-Catalyzed Enantioselective Synthesis of α-Ambrinol

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Abstract: We describe the first enantioselective synthesis of the odorant compound (−)-α-ambrinol (96% *ee*) from commercial geranylacetone. The key steps are a Jacobsen's asymmetric epoxidation and a titanium-catalyzed stereoselective cyclization initiated by radical epoxide opening. The oxirane ring opening proceeds with retention of configuration at the epoxide chiral center, giving a secondary alcohol which can be advantageously exploited to raise the *ee* provided by the synthetic sequence. We also synthesized (+)-α-ambrinol by a closely related procedure, showing the synthetic versatility of combining titanium-catalyzed cyclization with Jacobsen's epoxidation reactions.

Keywords: α-ambrinol; asymmetric epoxidation; catalysis; titanium; total synthesis

Introduction

Between 1988 and 1994 RajanBabu and Nugent introduced the use of bis(cyclopentadienyl)titanium chloride (Cp_2TiCl)[1] for the homolytic opening of epoxides.[2] This reagent has since become a powerful tool in organic synthesis,[3] especially after the catalytic version developed by Gansäuer et al., which uses 2,4,6-collidine hydrochloride as titanocene-regenerating agent.[4] Subsequently we developed an alternative titanocene-regenerating agent, a mixture of Me_3SiCl and 2,4,6-collidine,[5] which has been used both by us and other authors for the total synthesis of several C-3 hydroxylated terpenoids in racemic form, including monoterpenoids such as karahanaenone,[6] sesquiterpenoids such as *trans*-4(11),8-daucadiene,[6] isodri- > menediol,[7] and 3β-hydroxydihydroconfertifolin,[7] diterpenoids such as 3β-hydroxymanool,[8] rostratone,[9] barekoxide,[6] laukarlaool,[6] and sclareol oxide,[10] meroterpenoids such as zonarone and zonarol,[11] and triterpenoids such as 3β-hydroxymalabarica-14(26),17*E*,21-triene[8] and achilleol A.[12] In contrast, Cp_2TiCl has scarcely been used for the enantioselective synthesis of natural products.[13]

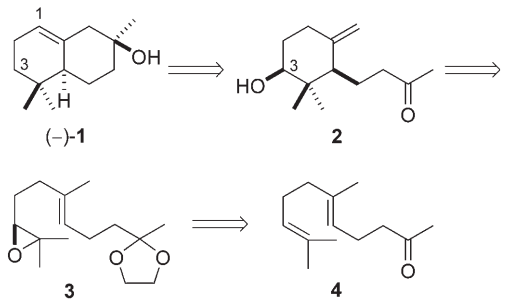
In mammals the enzyme-catalyzed enantioselective epoxidation of squalene followed by cascade-cyclization of (*S*)-2,3-oxidosqualene leads to enantiomerically pure triterpenoids and steroids.[14] Thus, the enzyme squalene epoxidase may be regarded not only as being responsible for the hydroxy group located at C-3 in sterols but also for the absolute configuration of all mammalian steroids and triterpenoids. The carbocationic character of the enzyme-catalyzed cyclization of oxidosqualene is well established.[14] Nevertheless, Breslow, Pattenden and other authors have shown that radical cascade cyclizations, initiated by different means, can advantageously compete with carbocationic cyclizations in organic synthesis.[15] Inspired by these observations, we deemed that a combined strategy of enantioselective epoxidation of commercial polyprenes, followed by Ti-catalyzed radical cyclization of the epoxy derivative obtained, might facilitate the enantioselective synthesis of cyclic terpenoids, including those lacking any OH group at C-3. To check our hypothesis we chose α-ambrinol (**1**) as synthetic target.

Results and Discussion

The levorotatory enantiomer of α-ambrinol (−)-**1** is one of the most characteristic components of ambergris, a concretion formed in the intestinal tract of some whales, and is very sought after in perfumery.[16] The dextrorotatory enantiomer (+)-**1** is also an appreciated odorant because of its strong dry, earthy, musty smell, quite different from that of the natural enantiomer.[16c] There are some procedures described for the synthesis of α-ambrinol (**1**) in racemic form.[16a,17] To the best of our knowledge, however, an enantioselective total synthesis for either (−)-**1** or (+)-**1** has not

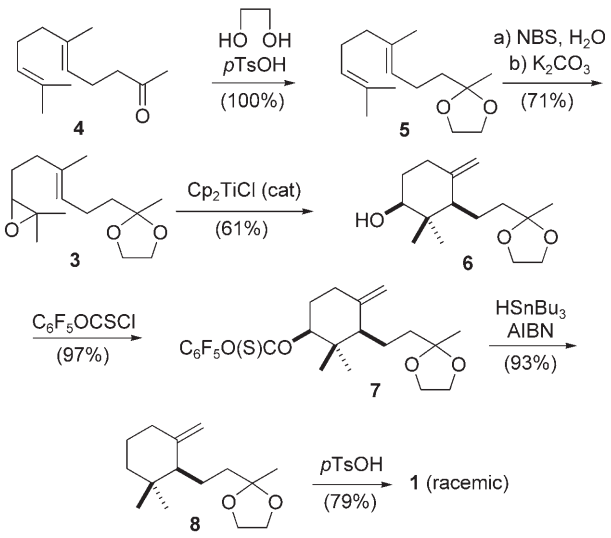
been described,[18] in spite of the known influence of chirality on odorant properties.[16c,18,19]

The retrosynthetic analysis depicted in Scheme 1 suggested to us that (−)-α-ambrinol might be obtained in relatively few steps from commercial geranylacetone (**4**). The key steps of the synthesis would be the enantioselective epoxidation of protected geranylacetone followed by the diastereoselective Ti-catalyzed cyclization of epoxide **3**.



Scheme 1. Retrosynthetic analysis for (−)-**1**.

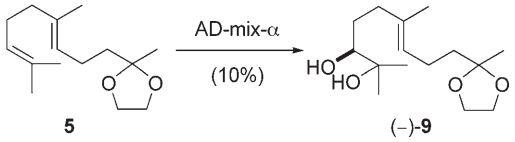
To check our retrosynthetic analysis we first prepared racemic α-ambrinol (**1**) starting from commercially available geranylacetone (**4**) (Scheme 2), which was transformed into epoxide **3** in three steps using a well-established procedure.[8] Stereoselective Ti-catalyzed cyclization of **3** afforded a 61% yield of alcohol **6**.[8] It should be noted that neither regioisomers with an endocyclic double bond nor stereoisomers of **6** were detected. Theoretical and experimental evidence reported by our group suggest that this reaction proceeds *via* stereoselective 6-*endo* cyclization of the tertiary radical generated by the Ti-catalyzed epoxide opening and, under anhydrous conditions, ends with



Scheme 2. Synthesis of racemic α-ambrinol (**1**).

the regioselective formation of the exocyclic double bond.[8] Deoxygenation of **6** according to the Barton–McCombie procedure[20] gave a 90% yield of protected ketone **8**. Finally, deprotection of the masked ketone **8** followed by Prins-type[21] stereoselective cyclization of **2** was accomplished in only one step and a 79% yield of **1** was obtained by simple acid catalysis. In this way we obtained racemic **1** in seven steps, in 31% overall yield.

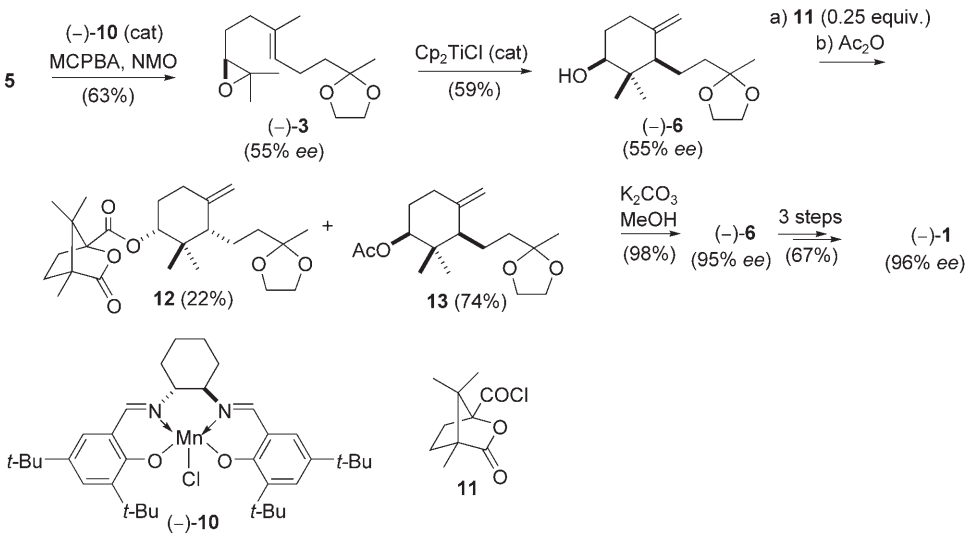
Once we were confident about the viability of the synthesis described in Scheme 2, we decided to attempt the enantioselective version of the process. Vidari et al.[22] have described an efficient, highly enantioselective dihydroxylation of geranyl acetate (92% yield, 98% *ee*) employing the AD-mix system developed by Sharpless and co-workers.[23] In our case, however, treatment of **5** with AD-mix-α gave only a 10% yield of diol (−)-**9** (Scheme 3), which still had to be transformed into epoxide **3**. This low yield prompted us to discard this procedure and assay other methods for the single-step synthesis of optically active **3**.



Scheme 3. Asymmetric dihydroxylation of **5** employing AD-mix-α.

The asymmetric epoxidation of **5** by Shi's procedure[24] gave (+)-**3** in 33% yield and a moderate enantiomeric excess (32% *ee*). Finally, the enantioselective epoxidation of **5** with the aid of the Mn-based Jacobsen's catalyst (−)-(**10**)[25] provided (−)-**3** ($[\alpha]_D^{20}$: −5.2) in a moderate 39% yield, a medium 55% *ee*,[26] and an excellent regioselectivity. What is more, 50% of the starting diene **5** was recovered unchanged. Its treatment under Jacobsen epoxidation conditions again raised the overall yield of epoxide (−)-**3** to 63% (Scheme 4). Ti-catalyzed cyclization of (−)-**3** gave alcohol (−)-**6** ($[\alpha]_D^{20}$: −4.4) with a 55% *ee*[26] identical to that of the starting epoxide. This observation confirms that the Ti-catalyzed cyclization of **3** to **6** occurs with retention of configuration at the epoxide chiral center. This supports our hypothesis that a judicious combination of asymmetric epoxidation and Ti-catalyzed radical cyclization reactions might be advantageously exploited for the enantioselective synthesis of cyclic terpenoids.

At this point we realized that (1*S*)-(−)-camphanic chloride (**11**) reacted much faster with (+)-**6** than with (−)-**6**, providing an effective tool to raise the *ee* of the levorotatory alcohol. Thus, treatment of the enantioenriched mixture of (−)-**6** and (+)-**6** (77.5/22.5

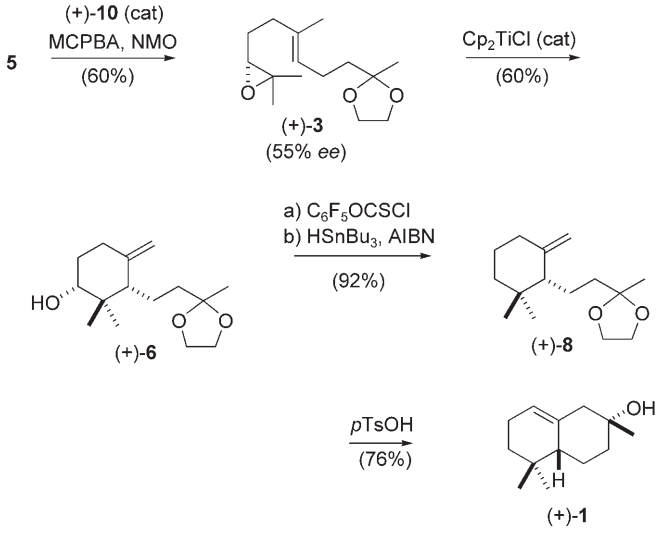


Scheme 4. Enantioselective synthesis of (−)-**1**.

ratio) with a substoichiometric proportion of **11** (0.25 equiv.), followed by addition of acetic anhydride gave (in a one-pot reaction) a mixture of camphanate **12** and acetate **13** (Scheme 4), which are easily separable by flash chromatography.[27] Simple saponification of **13** regenerated alcohol (−)-**6** ($[\alpha]_D^{20}$: −7.8) with a 95% *ee*.[26] Finally, following the same procedure depicted in Scheme 2, (−)-**6** was converted into (−)-α-ambrinol ($[\alpha]_D^{20}$: −122.2) (96% *ee*).[26] Thus, the total synthesis of (−)-**1** from commercial geranylacetone (**4**) was completed in eight steps and afforded an overall yield of 18%.

Mimicking what occurs in nature, in the synthetic sequence depicted in Scheme 4 enantioselection was introduced at the epoxidation step catalyzed by Jacobsen's complex (−)-**10**. As the antipode (+)-**10** is also commercially available, we could furthermore prepare unnatural (+)-α-ambrinol, taking advantage of this catalyst as depicted in Scheme 5. Thus, as we expected, the enantioselective epoxidation of **5** with the aid of catalyst (+)-**10** gave a 60% yield (two turnovers) of (+)-**3** with a 55% *ee*.[26]

In this way we were able to accomplish the total synthesis of enantioenriched[28] (+)-**1** ($[\alpha]_D^{20}$: +81.8) from commercial **4** in only six steps, with an overall yield of 25%. More importantly, we thus showed that the combination of Jacobsen's asymmetric epoxidation and Ti-catalyzed cyclization reactions constitutes a versatile procedure which might be used for the enantioselective synthesis of both optical antipodes of cyclic terpenoids with or without an OH group at C-3.



Scheme 5. Enantioselective synthesis of (+)-**1**.

Conclusions

We describe here the first enantioselective synthesis of the odorant (−)-α-ambrinol (96% *ee*), by combining Jacobsen's asymmetric epoxidation and Ti-catalyzed stereoselective cyclization reactions. The cyclization reaction was initiated by radical epoxide opening and proceeded with retention of configuration at the epoxide chiral center to give a secondary alcohol that can be advantageously exploited to raise the *ee* provided by the synthetic sequence. We also describe the synthesis of the unnatural enantiomer (+)-α-ambrinol by a closely related procedure, thus showing the synthetic versatility of this method. At the moment we are trying to extend this strategy to the enantioselective synthesis of other marine terpenoids with biological activity.

Experimental Section

General Details

Deoxygenated solvents and reagents were used for all reactions involving Cp_2TiCl. THF was freshly distilled from Na, while CH_2Cl_2 and benzene were freshly distilled from CaH_2. Products were purified by flash chromatography on Merck silica gel 50 (eluents are given in parenthesis). Yields refer to analytically pure samples. IR spectra were recorded using a Satellite FTIR spectrometer. Optical rotations were measured in a Perkin–Elmer 341 digital polarimeter and are reported as follows: $[\alpha]_D^{r.t.}$ (*c* in cg per 1 mL solvent). NMR spectra were recorded in a Variant 400 L900 NMR spectrometer. ^{1}H NMR: $CDCl_3$ ($\delta = 7.26$ ppm) in the indicated solvent as internal standard in the same solvent. ^{13}C NMR: $CDCl_3$ ($\delta = 77.16$ ppm) as internal standard in the same solvent; coupling constants measured in Hz and always given as $J_{H,H}$ coupling constants. Enantiomeric excesses were measured employing an HPLC Waters 2690 apparatus using a Waters PAD 996 detector and a Daicel Chiral Pak AD 0.46 cm × 25 cm column. Compound **5** has been previously described.[29] Racemic **3** was obtained as described in a previous paper.[8]

Synthesis of Epoxide (−)-3

m-Chloroperbenzoic acid (MCPBA, 70% purity) (380 mg, 1.7 mmol) was added to a mixture of compound **5** (200 mg, 0.84 mmol), 4-methylmorpholine *N*-oxide (NMO) (564 mg, 4.2 mmol), and catalyst (−)-**10** (34 mg) in CH_2Cl_2 (10 mL) at −40 °C. The mixture was stirred for 8 h at −40 °C. CH_2Cl_2 (20 mL) was then added and the solution was washed with aqueous NaOH (2 N), dried over anhydrous Na_2SO_4 and the solvent removed. The residue was submitted to flash chromatography (hexane: EtOAc, 8:2) to yield epoxide (−)-**3** as a colorless oil; yield: 134 mg (63% after 2 turnovers); $[\alpha]_D^{20}$: −5.2 (*c* 1.33, $CHCl_3$); 55% *ee*;[26] ^{1}H and ^{13}C NMR spectra matched those described in a previous paper.[8]

Synthesis of Epoxide (+)-3

Following the procedure described above but using (+)-**10** instead of (−)-**10** as catalyst, epoxide (+)-**3** was obtained as a colorless oil; yield: 60%; $[\alpha]_D^{20}$: +5.2 (*c* 1.54, $CHCl_3$); 55% *ee*.[26]

Ti-Catalyzed Cyclization of 3

Deoxygenated THF (20 mL) was added to a mixture of Cp_2TiCl_2 (98 mg, 0.39 mmol) and Mn dust (860 mg, 15.7 mmol) under an argon atmosphere and the suspension was stirred at room temperature until it turned green (about 15 min). A solution of epoxy alkene **3** (500 mg, 1.96 mmol) and 2,4,6-collidine (1.8 mL) in THF (5 mL) and Me_3SiCl (1.0 mL) were then added simultaneously and the mixture was stirred at room temperature for 1.5 h. Brine was added and the mixture was extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and the solvent removed. The residue was submitted to flash chromatography (hexane: EtOAc, 85:15) giving alcohol **6** as a colorless oil; yield: 305 mg (61%); ^{1}H and ^{13}C NMR spectra matched those previously described.[8]

Synthesis of Alcohol (−)-6

Following the procedure described above but using epoxide (−)-**3** as starting material, alcohol (−)-**6** was obtained as a colorless oil; yield: 59%; $[\alpha]_D^{20}$: −4.4 (*c* 1.2, $CHCl_3$); 55% *ee*.[26]

Synthesis of Alcohol (+)-6

Following the procedure described above but using epoxide (+)-**3** as starting material, alcohol (+)-**6** was obtained as a colorless oil; yield: 60%; $[\alpha]_D^{20}$: +4.4 (*c* 1.6, $CHCl_3$).

Enantioselective Discrimination between Alcohols (+)-6 and (−)-6 by (1*S*)-(−)-Camphanic Chloride

DMAP (47 mg, 0.39 mmol), pyridine (31 μL), and (1*S*)-(−)-camphanic chloride (21.6 mg, 0.1 mmol) were added to a solution of enantioenriched alcohol (−)-**6** (55% *ee*) (100 mg, 0.39 mmol) in CH_2Cl_2 (6 mL). The solution was stirred for 24 h at room temperature. Subsequently, Ac_2O (37 μL, 0.39 mmol) was added and the mixture was stirred for 2 h at room temperature. The solvent was then removed and the residue was submitted to flash chromatography (hexane: EtOAc, 8:2) to yield camphanate **12** (yield: 37 mg, 22%) and acetate **13** (yield: 85 mg, 74%).

Compound **12**: Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.85$ (br s, 1 H), 4.80 (dd, $J = 11.6$, 4.3 Hz, 1 H), 4.64 (br s, 1 H), 3.95 (m, 4 H), 1.33 (s, 3 H), 1.15 (s, 3 H), 1.10 (s, 3 H), 1.01 (s, 3 H), 0.97 (s, 3 H), 0.82 (s, 3 H).

Compound **13**: Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.87$ (br s, 1 H), 4.62 (br s, 1 H), 4.28 (dd, $J = 11.5$, 4.3 Hz, 1 H), 3.93 (m, 4 H), 2.43 (dt, $J = 13.0$, 4.6 Hz, 1 H), 2.05 (s, 3 H), 1.33 (s, 3 H), 0.99 (s, 3 H), 0.79 (s, 3 H).

Saponification of Acetate 13

K_2CO_3 (200 mg, 1.45 mmol) was added to a solution of acetate **13** (85 mg, 0.29 mmol) in MeOH (5 mL) and the mixture was stirred for 7 h at room temperature. The solvent was then removed, water was added and the mixture was extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, and the solvent removed. The residue was submitted to flash chromatography (hexane: EtOAc, 7:3) to afford alcohol (−)-**6** as a colorless oil; yield: 72 mg (98%); $[\alpha]_D^{20}$: −7.8 (*c* 0.8, $CHCl_3$); 95% *ee*.[26]

Preparation of Thionocarbonate 7

Pentafluorophenyl chlorothionoformate (150 mg, 0.57 mmol) was added to a solution of **6** (70 mg, 0.28 mmol) and DMAP (102 mg, 0.84 mmol) in CH_2Cl_2 (8 mL) at 0 °C and the solution was stirred at room temperature for 5 h. Fresh CH_2Cl_2 (40 mL) was then added and the mixture was washed with brine. The organic layer was dried over anhydrous Na_2SO_4, and the solvent removed. The residue was submitted to flash chromatography (hexane: EtOAc, 95:5) to afford thionocarbonate **7** as a colorless oil; yield: 130 mg (97%); IR (film): $\upsilon_{max} = 2954$, 2877, 1523, 1378, 1306, 1144, 1059, 998, 954 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.12$ (dd, $J = 11.7$, 4.2 Hz, 1 H), 4.95 (bs, 1 H), 4.71 (bs, 1 H), 3.94 (m, 4 H), 2.42–2.34 (m, 1 H), 2.12–2.02 (m, 2 H), 1.86–1.38 (m, 6 H), 1.31 (s, 3 H), 1.08 (s, 3 H), 0.91 (s, 3 H); ^{13}C NMR

(100 MHz, $CDCl_3$): $\delta = 191.7$ (C), 145.9 (C), 110.6 (CH_2), 110.4 (C), 93.0 (CH), 64.9 (CH_2), 64.8 (CH_2), 52.2 (CH), 40.3 (C), 38.2 (CH_2), 31.3 (CH_2), 27.5 (CH_2), 26.2 (CH_3), 24.1 (CH_3), 20.1 (CH_2), 18.1 (CH_3) (some signals were not observed); HR-FAB-MS: $m/z = 503.1288$, calcd. for $C_{22}H_{25}F_5O_4SNa$: 503.1291.

Thionocarbonate (−)-7

Following the procedure described above but starting from (−)-**6** (95% *ee*), thionocarbonate (−)-**7** was obtained as a colorless oil; yield: 90%; $[\alpha]_D^{20}$: −12.9 (*c* 5.5, $CHCl_3$).

Thionocarbonate (+)-7

Following the procedure described above but starting from (+)-**6** ($[\alpha]_D^{20}$: +4.4), thionocarbonate (+)-**7** was obtained as a colorless oil; yield: 97%; $[\alpha]_D^{20}$: +7.3 (*c* 1.17, $CHCl_3$).

Synthesis of Ketal 8

AIBN (8 mg, 0.05 mmol) and $HSn(n\text{-}Bu)_3$ (218 mg, 0.75 mmol) were added to a solution of thionocarbonate **7** (123 mg, 0.25 mmol) in benzene (20 mL) and the mixture was stirred at reflux for 4 h. The solvent was then removed and the residue was submitted to flash chromatography (hexane: EtOAc, 95:5) to afford **8** as a colorless oil; yield: 55 mg (93%); ^1H and ^{13}C NMR spectra matched those described elsewhere.[30]

Ketal (−)-8

Following the procedure described above but starting from thionocarbonate (−)-**7**, ketal (−)-**8** was obtained as a colorless oil; yield: 100%; $[\alpha]_D^{20}$: −14.6 (*c* 1.33, $CHCl_3$).

Ketal (+)-8

Following the procedure described above but starting from thionocarbonate (+)-**7**, ketal (+)-**8** was obtained as a colorless oil; yield: 95%; $[\alpha]_D^{20}$: +8.3 (*c* 0.67, $CHCl_3$).

Synthesis of α-Ambrinol (1)

A sample of *p*TsOH (12 mg, 0.06 mmol) was added to a solution of compound **8** (42 mg, 0.17 mmol) in 7 mL of wet CH_2Cl_2, and the mixture was stirred for 24 h at room temperature. Water was then added and the mixture was extracted with CH_2Cl_2. The organic layer was dried over anhyd Na_2SO_4 and the solvent removed. The residue was submitted to flash chromatography (hexane: EtOAc, 92:8), affording α-ambrinol (**1**) as a colorless oil; yield: 27 mg (79%); ^1H and ^{13}C NMR spectra matched those described elsewhere.[17d]

Synthesis of (−)-α-Ambrinol

Following the procedure described above but starting from ketal (−)-**8**, (−)-α-ambrinol was obtained as a colorless oil; yield: 75%; $[\alpha]_D^{20}$: −122.2 (*c* 0.83, $CHCl_3$); 96% *ee*.[26]

Synthesis of (+)-α-Ambrinol

Following the procedure described above but starting from ketal (+)-**8**, (+)-α-ambrinol was obtained as a colorless oil; yield: 76%; $[\alpha]_D^{20}$: +81.8 (*c* 0.9, $CHCl_3$).

Acknowledgements

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[27] Unfortunately, camphanate **12** and alcohol (−)-**6** showed similar R_f values. Therefore, we resorted to *in situ* acetylation of (−)-**6** to facilitate separation by flash chromatography.
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