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Resolution of sclareolide as a key intermediate for the synthesis of Ambrox®

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Abstract

Sclareolide was efficiently resolved by a diastereomeric salt formation method using homochiral *erythro*-2-amino-1,2-diphenylethanol (ADPE) as a resolving agent. © 1998 Elsevier Science Ltd. All rights reserved.

1. Introduction

In recent years, it has become more and more difficult to obtain many kinds of animal perfumes because of the reduction in the world's resources and the conservation movement with regard to wild animals.[1] Ambergris, a metabolite of the sperm whale, is one of the most valuable animal perfumes, taking rank with civet and musk.[1,2] The major constituent of ambergris is a triterpene alcohol ambrein **1** with an amber-like odor. During drifting in the sea for many years, **1** is oxidatively decomposed by the action of seawater, air, and sunlight to give some odorous compounds (Scheme 1).[2,3] In these compounds, Ambrox® **2** in particular has a very strong amber-like odor and it is reported that the odor of (−)-**2** is much stronger than that of (+)-**2**.[1,3] Although considerable effort has been paid to the total asymmetric syntheses of **2** for a long time, some reports have been known to prepare enantiomerically pure **2**.[3–7] In two of them,[5,6] resolution was applied in key steps to obtain enantiomerically pure intermediates.

Based on our previous work,[8] a diastereomeric salt formation method seems effective for the resolution of sclareolide **3**, one of the key intermediates of Ambrox®, and is economical when the resolving agents are recovered. In this paper, we report the resolution of **3** using various homochiral amines as resolving agents. Synthesis of enantiomerically pure **2** is demonstrated by the use of resolved **3** (Scheme 2).

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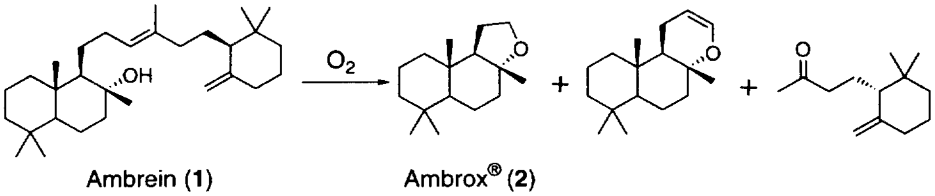
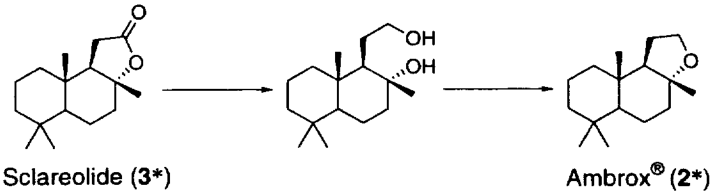


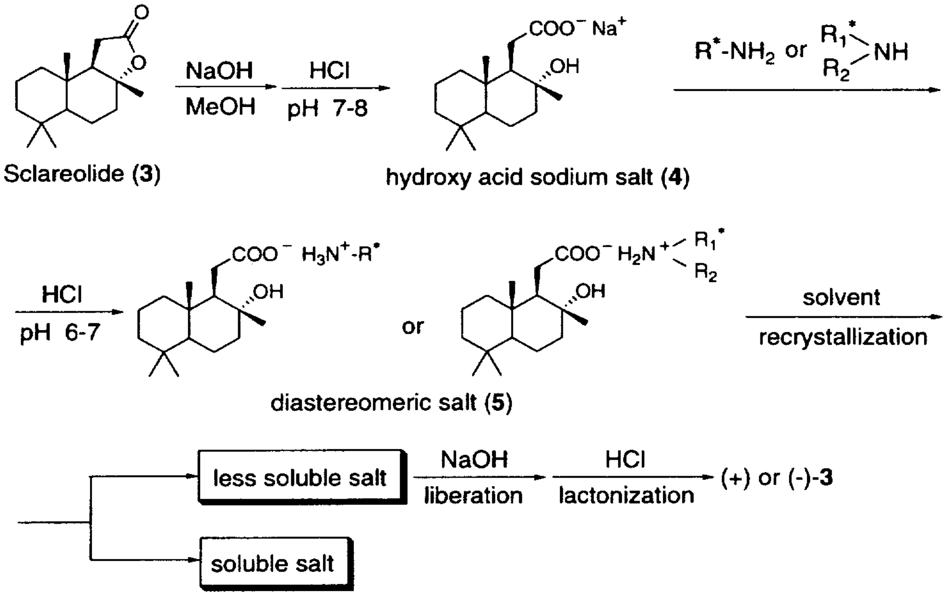
Scheme 1. Decomposition of ambrein (1)



Scheme 2. Leading to Ambrox® (2*) from sclareolide (3*)

2. Results and discussion

The racemic sclareolide **3** was prepared from β-ionone in 3 steps (17% overall yield) with a slight modification of the method reported by Oritani et al.[2,4,6] The racemate, (±)-**3**, was hydrolyzed with sodium hydroxide in methanol to give a hydroxy acid sodium salt **4**. Treatment of **4** with various homochiral amines as resolving agents gave diastereomeric salts **5**. A diastereomerically pure salt was afforded by recrystallization of **5** from various solvents. Enantiomerically pure **3** was obtained by liberation of recrystallized **5*** with sodium hydroxide, and by following lactonization with hydrochloric acid (Scheme 3). The enantiomeric purity of resolved **3*** was determined using HPLC equipped with a chiral column (Daicel Chiralpak AD).



Scheme 3. Preparation of enantiomerically pure sclareolide (3*)

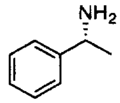
Seven homochiral amines, α-methylbenzylamine (MBA) **6**, *cis*-2-(benzylamino)-cyclohexanemethanol (*cis*-amine) **7**, 1-(1-naphthyl)ethylamine (NEA) **8**, 1-phenyl-2-(*p*-tolyl)ethylamine (PTE) **9**,

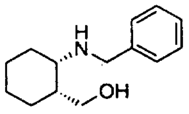
Table 1
Resolution of (±)-**3** by a diastereomeric salt formation method

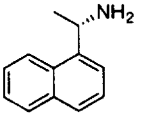
Resolving Agent	Solvent	Yield / % [a]	m.p. / °C [b]	$[\alpha]_D$ [c]	o.p. / %e.e. [h]	Resolving Efficiency [i]
(*R*)-(+)-**6**	EtOH	34	119.0-120.0	+0.1 [d]	2.7	0.9
(1*R*,2*S*)-(+)-**7**	EtOH	31	120.0-121.5	+0.5 [f]	3.4	1.1
(*S*)-(-)-**8**	AcOEt : 2-PrOH = 3 : 2	84	114.5-117.0	+22.6 [d]	52	44
(*S*)-(+)-**9**	2-PrOH : EtOH = 2 : 3	76	116.0-120.0	-29.4 [g]	63	48
(*S*)-(-)-**10**	2-PrOH : EtOH = 1 : 2	48	107.0-116.0	+27.9 [g]	69	33
(*S*)-(+)-**11**	2-PrOH	89	111.5-118.0	+14.0 [f]	47	42
(1*S*,2*R*)-(+)-**12**	EtOH : MeOH = 3 : 2	43	121.0-124.0	+43.7 [d]	>99	43
(1*R*,2*S*)-(-)-**12**	EtOH : MeOH = 3 : 2	43	123.5-125.0	-43.8 [e]	>99	43
			124.0-126.0 [j]	+45.3 [d,j]		

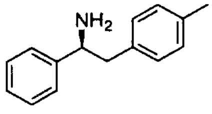
a: Based on half the amount of racemate of **3**. b: m.p. of resolved **3**. c: Specific rotation of **3**. d: *c* 1.0 MeOH e: *c* 0.6 MeOH f: *c* 0.4 MeOH g: *c* 0.3 MeOH h: Enantiomeric purity of **3** determined by HPLC equipped with a chiral column (DAICEL CHIRALPAK AD). i: Yield (%) × o.p (%e.e.) ÷ 100 j: The data of the authentic sample obtained from Aldrich Chemicals Co.

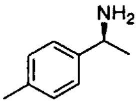
1-(*p*-tolyl)ethylamine (TEA) **10**, 2-amino-1-butanol (2AB) **11**, and *erythro*-2-amino-1,2-diphenylethanol (ADPE) **12**, were examined as resolving agents. The results of resolution of (±)-**3** are summarized in Table 1. Among those various amines, ADPE was found to be the most efficient resolving agent to give the enantiomerically pure **3** (>99% ee) after a single recrystallization of the less soluble diastereomeric salt **5**, while MBA and *cis*-amine were ineffective in this case. (−)-Ambrox®; m.p. 75.0–76.5°C (lit.[9] m.p. 77.0–77.5°C), $[\alpha]_D$ −25.0 (*c* 1.0 $CHCl_3$) {lit.[9] $[\alpha]_D$ −24.7 (in $CHCl_3$)} was prepared from enatiomerically pure (+)-**3** without racemization. Thus, a practical synthetic route of enatiomerically pure (−)-**2** was established.

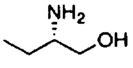

MBA (**6**)

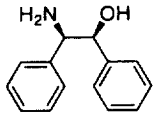

cis-Amine (**7**)


NEA (**8**)


PTE (**9**)


TEA (**10**)


2AB (**11**)


ADPE (**12**)

In summary, the resolution of sclareolide **3** was efficiently achieved by the diastereomeric salt formation method using homochiral ADPE as the resolving agent, and highly pure (+)- and (−)-**3** were obtained as the key intermediates of both enantiomers of Ambrox®.

3. Experimental

3.1. General

All melting point (m.p.) values were uncorrected. Specific rotations were measured with a JASCO DIP-370 polarimeter.

3.2. (±)-Sclareolide [(3aR*,5aS*,9aS*,9bR*)-1,2,3a,4,5,5a,6,7,8,9,9a,9b-dodecahydro-3a,6,6,9a-tetramethylnaphtho[2,1-b]furan-2-one] (±)-3

The preparation of (±)-**3** was based on the method reported by Oritani et al.[6]

Dihydro-β-ionone: to β-ionone (203 mg, 1.06 mmol) was added a solution of Raney nickel (W-2 type) (780 mg) in EtOH (5 ml). After stirring for 2 days at 75°C, the mixture was filtered with Celite and the filtrate was concentrated to give the product (195 mg, 0.95 mmol, 90% yield).

β-Monocyclofarnesyl acid: to a suspension of carboxyethyl triphenyl phosphonium chloride (22.7 g, 61.1 mmol) in THF (200 ml) was added *n*-BuLi (74 ml of 1.66 M hexane soln, 122.8 mmol) at −78°C. The mixture was stirred for 1.5 h, warmed to room temperature for a few minutes, and again cooled to −78°C. To the solution was added, dropwise, a solution of dihydro-β-ionone (6.0 g, 30.7 mmol) in THF (5 ml). The mixture was then stirred for 6.5 h at this temperature, then for a further 3 h at −45°C, before being allowed to warm to room temperature gradually. The next day, after adding 1 N HCl aq. (90 ml), the mixture was extracted with AcOEt (100 ml×3). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane:AcOEt=12:1–2:3) to give β-monocyclofarnesyl acid, 4-methyl-6-(2′,6′,6′-trimethylcyclohex-1′-enyl)-3-hexanoic acid (4.0 g, 15.4 mmol, 50% yield).

(±)-Sclareolide (±)-3: to a solution of chlorosulfuric acid (0.53 ml, 8.0 mmol) in 2-nitropropane (8 ml) was added a solution of the β-monocyclofarnesyl acid (501 mg, 2.0 mmol) in 2-nitropropane (8 ml) at −78°C. After stirring for 45 min, sat. aq. $NaHCO_3$ (10 ml) was added and the mixture was extracted with Et_2O (10 ml×3). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. After purification by column chromatography (silica gel, hexane:AcOEt=5:1), recrystallization from hexane gave (±)-**3** (198 mg, 0.79 mmol, 40% yield) in 17% overall yield.

3.3. (+)-Sclareolide [(3aR,5aS,9aS,9bR)-(+)-1,2,3a,4,5,5a,6,7,8,9,9a,9b-dodecahydro-3a,6,6,9a-tetramethylnaphtho[2,1-b]furan-2-one] (+)-3

The optimum procedure using (+)-ADPE is described as follows. To a solution of (±)-**3** (470 mg, 1.88 mmol) in methanol (3 ml) at 60°C, was added a solution of NaOH (306 mg, 7.65 mmol) in methanol (10 ml). The mixture was stirred for 2 h at the same temperature, and then 2 N HCl aq. was added until pH 7–8 at room temperature was reached. A solution of (+)-ADPE (403 mg, 1.89 mmol) in methanol (6 ml) was added to the mixture, then 2 N HCl aq. was added until pH 6–7 was reached. After stirring for 40 min, the mixture became muddy, while the mixtures with other amines remained clear. Following the replacement of solvent from the mixture of water and methanol to ethanol, most of the precipitated sodium chloride was filtered off, and then the diastereomeric salt **5** was obtained as a white powder. The diastereomeric salt **5** (897 mg; containing a small quantity of sodium chloride) was recrystallized from the mixture of ethanol (6 ml) and methanol (4 ml) to give the less soluble salt (175 mg, 0.36 mmol) as colorless prisms; m.p. 176.0–177.0°C, $[\alpha]_D$ +66.7 (*c* 1.0 MeOH). The less soluble salt was then decomposed by 1 M aq. sodium hydroxide solution (2 ml) and the resolving agent (+)-ADPE was extracted with diethyl ether.

The remaining hydroxy acid sodium salt **5** was transformed to the lactone by addition of 2 N HCl aq. (2 ml), and following stirring for 4 h at 60°C. After sodium chloride was separated in the same manner as described earlier, the residual solid was purified by preparative TLC (hexane:AcOEt=4:1) to give (+)-**3** (45 mg, 0.18 mmol), which was recrystallized from hexane to yield colorless plates; m.p. 121.0–124.0°C, $[\alpha]_D$ +47.3 (*c* 1.0 MeOH). By HPLC analysis {column, Daicel Chiralpak AD (250×4.6 mm ID); eluent, 3% 2-propanol in hexane; flow rate, 0.4 ml/min; detection, 220 nm UV; retention time, (+)-**3**, 31 min, (−)-**3**, 37 min}, the enantiomeric purity of (+)-**3** was over 99% ee.

3.4. (−)-Ambrox® [(3aR,5aS,9aS,9bR)-(−)-1,2,3a,4,5,5a,6,7,8,9,9a,9b-dodecahydro-3a,6,6,9a-tetramethylnaphtho[2,1-b]furan] (−)-2

(−)-**2** was prepared according to the literature[2,4,6] as follows. To a suspension of $LiAlH_4$ (78 mg, 2.06 mmol) in THF (4 ml) was added a solution of enantiomerically pure (+)-**3** (500 mg, 2.00 mmol) in THF (2 ml) at 0°C. After stirring for 4 h at room temperature, the reaction was quenched by adding satd aq. Na_2SO_4 and the organic layer was concentrated. The residue was recrystallized from AcOEt to give the corresponding (−)-diol (see Scheme 2) as colorless needles (379 mg, 1.50 mmol, 75% yield); m.p. 132.0–133.5°C, $[\alpha]_D$ −16.8 (*c* 1.0 $CHCl_3$).[3] Its enatiomeric purity of more than 99% ee was determined by HPLC analysis using its mono-(R)-MTPA (α-methoxy-α-(trifluoromethyl)phenylacetic acid) ester of the primary hydroxyl group {column, Daicel Chiralcel OD-H (250×4.6 mm ID); eluent, 5% 2-propanol in hexane; flow rate, 0.5 ml/min; detection, 254 nm UV; retention time, (−)-isomer, 18 min, (+)-isomer, 20 min}. The (−)-diol (255 mg, 1.00 mmol) was cyclized by *p*-toluenesulfonyl chloride (384 mg, 2.01 mmol) in pyridine (15 ml) at 0°C. After stirring for 14 h at room temperature, water (30 ml) was added and the mixture was extracted with Et_2O (30 ml×3). The combined organic layer was washed with satd aq. $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane:AcOEt=20:1) and recrystallized from $EtOH \cdot H_2O$ to yield colorless plates (174 mg, 0.75 mmol, 75% yield); m.p. 75.0–76.5°C, $[\alpha]_D$ −25.0 (*c* 1.0 $CHCl_3$) (56% overall yield).

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