Asymmetric Synthesis

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# Stereoselective Synthesis of Superambrox: Stereoselective Type III Intramolecular Ene Reaction and OH-Assisted Ru-Catalyzed Isomerization**

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*Dedicated to Professor Georg Fráter on the occasion of his 65th birthday*

In the 1990s, chemists from Firmenich[1a] reported the isolation of (−)-**1** by chemical degradation of the labdane diterpene (+)-larixol.[1b] This unsaturated analogue of Ambrox[2] was named "Superambrox" as a result of its excellent odor qualities (Scheme 1).

(–)-Superambrox ((–)-**1**)
very nicely "Ambrox",
very powerful

(–)-Ambrox
amber, powerful,
very substantive

***Scheme 1.*** (−)-Superambrox and (−)-Ambrox (Laevo–Cetalox).

To our knowledge, the only synthetic approaches towards Superambrox are based on acid-mediated polyene cyclizations,[3] which afford the racemate with low stereoselectivity in only moderate yields. We now report a concise, highly selective synthesis of racemic Superambrox (±)-**1**. The creation of the C–C double bond in a highly substituted environment presents a special challenge, as this subunit is known to be prone to isomerization or skeletal rearrangement. A second difficulty lies in the stereoselective elaboration of the heterocycle.

Our synthetic plan consists of the development of a new tandem type III intramolecular ene reaction/Oppenauer oxidation of dihydro-β-C14-aldehyde (**2**), a high-tonnage raw material, thus allowing a direct approach to the decalone **3**, which has the properly positioned double bond. Acetoxylation from the less-hindered α face followed by intra-

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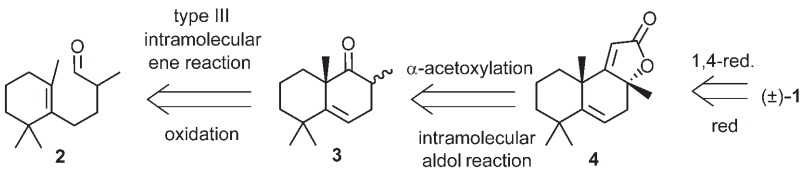
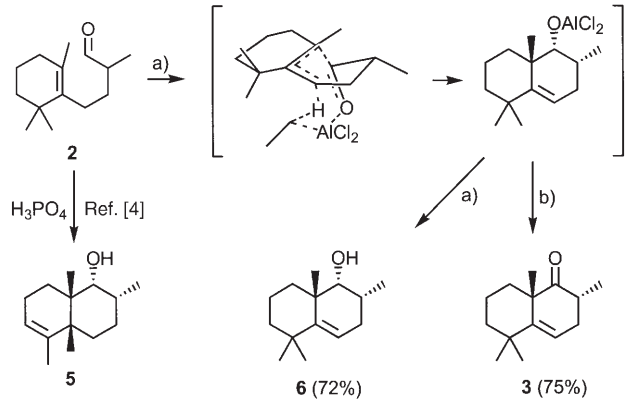
molecular aldolization of the formed acetoxy ketone should afford, after dehydration, butenolide **4**. Chemo- and diastereoselective 1,4-reduction of **4** was expected to correctly install the third stereogenic center and give access, after reduction, to Superambrox (Scheme 2).




***Scheme 2.*** Retrosynthetic analysis of (±)-Superambrox.

Earlier work[4] showed that **2** undergoes a cyclization/1,2-methyl shift under Brønsted acidic conditions to afford decalin **5** exclusively in approximately 40% yield (Scheme 3). To avoid the formation of rearrangement products, we therefore tested several Lewis acids and found that the use of $EtAlCl_2$ resulted in a clean and selective type III intramolecular ene reaction to afford the desired, nonrearranged decalin **6** in 72% yield. This unusual and probably concerted reaction[5] is thought to proceed through the participation of the ethyl group on the Al center via an eight-membered-ring transition state. When the primarily formed cyclized Al alkoxide was treated with two equivalents of chloral, an Oppenauer oxidation ensued to yield **3** in one pot and high yield (Scheme 3).[6] This hitherto unknown ketone is interesting both as a fragrance component (powdery, ionone, Myrrhone, patchouli, woody) and as a building block for higher terpenoids.[7]

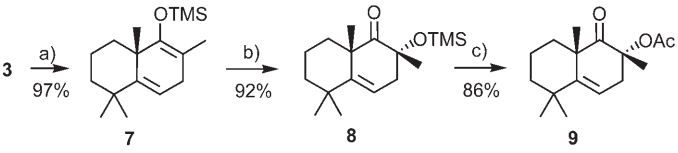



***Scheme 3.*** Preparation of decalone **3** by a type III carbonyl ene reaction/Oppenauer oxidation of **2**. a) $EtAlCl_2$ (1.0 equiv), $CH_2Cl_2$, 0°C, 30 min; b) $Cl_3CCHO$ (2.0 equiv), 0°C, 90 min.

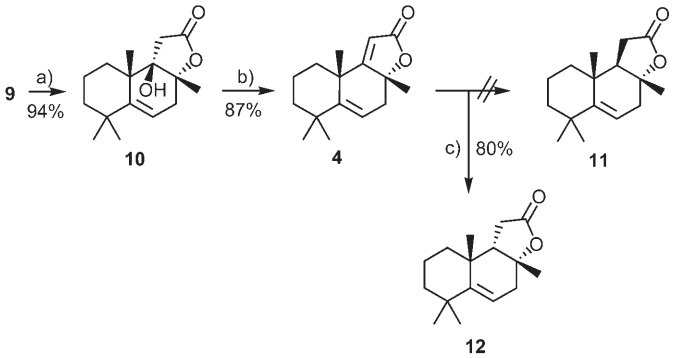
For the stereocontrolled synthesis of acetoxy ketone **9**, we surmised that site-selective epoxidation of silyl enol ether **7**, readily derived from **3**, would occur from the face opposite the neighboring axial methyl group. Indeed, application of the procedure developed by Rubottom and Juve[8] afforded the silyloxy ketone **8** in excellent yield and with perfect stereocontrol.[9] Treatment of **8** with $Ac_2O$ under acidic conditions afforded the acetoxy ketone **9** directly (Scheme 4).

Subsequent deprotonation of acetate **9** using lithium diisopropyl amide (LDA) at −70°C, resulted in a smooth intramolecular aldol reaction,[10] thus affording hydroxy lactone **10** (94% yield). The dehydration of **10** was effected with thionyl chloride in pyridine to afford **4** in 87% yield (Scheme 5).

The planned 1,4-reduction of the lactone C–C double bond in the presence of the decalin C–C double bond of **4** was expected to proceed chemo- and diastereoselectively from the face opposite the two pseudoaxial methyl groups to afford **11**. However, by using excess $NaBH_4$ and 18 mol% of $NiCl_2$ in methanol,[11] the sole product isolated was the undesired diastereomer **12**.[12] It can be seen from molecular modeling studies that the bicyclic subunit represented by the middle ring and the lactone is bent, thus allowing ready nucleophilic attack from the convex face of **4**.




***Scheme 4.*** Stereoselective introduction of the acetoxy function by epoxidation of **7**. a) LDA (1.25 equiv), THF, −5°C, 30 min; then TMSCl (2.4 equiv), −30→−10°C, 10 min; b) *m*CPBA (1.1 equiv), $CH_2Cl_2$, 0°C, 90 min; c) $Ac_2O/H_2O$ (10:1), $TsOH\cdot H_2O$ (5% by weight), 20–30°C, 1 h. *m*CPBA = *meta*-chloroperoxybenzoic acid, TMS = trimethylsilyl, Ts = *para*-toluenesulfonyl.

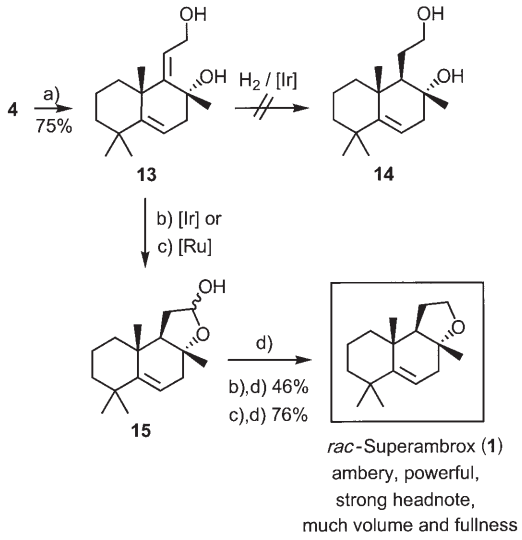



***Scheme 5.*** Synthesis and 1,4-reduction of **4**. a) LDA (1.25 equiv), THF, −70°C, 20 min; b) $SOCl_2$ (5.0 equiv), pyridine, −30°C, 15 min; c) $NaBH_4$, (3.9 equiv), $NiCl_2$ (0.18 equiv), MeOH, −10°C, 1 h.

We therefore reduced lactone **4** to diol **13** in the hope that OH-assisted hydrogenation with the Crabtree catalyst $[Ir(cod)(py)(PCy_3)][PF_6]$ (cod = 1,5-cyclooctadiene, py = pyridine, Cy = cyclohexyl) would occur exclusively at the proximal C–C double bond and from the bottom face, occupied by the tertiary alcohol, to afford **14** (Scheme 6).

To our surprise, no hydrogenation took place, but a diastereoselective, OH-directed isomerization that led to




***Scheme 6.*** OH-directed isomerization of **13**. a) $LiAlH_4$ (1.00 equiv), $Et_2O$, room temperature, 1 h; b) $[Ir(cod)(py)(PCy_3)][PF_6]$ (2 mol%; Crabtree catalyst), $H_2$, $CH_2Cl_2$, room temperature, 30 min; c) $[RuH(\eta^5\text{-}C_8H_{11})_2][BF_4]$ (0.5 mol%; Chaudret catalyst), $CH_2Cl_2$, room temperature, 90 min; d) $Et_3SiH$ (2.0 equiv), Amberlyst 15, room temperature, 1 h; e) TsCl (1.2 equiv), pyridine, 0°C→RT, 1 h.

lactol **15** occurred instead! Subsequent reduction of **15** using $Et_3SiH$ under acidic conditions[13] afforded isomerically pure Superambrox (**1**), which exhibited the expected strong, rich ambery odor, as the only volatile material in 46% yield.[14] Alternatively, the same isomerization took place readily at room temperature with only 0.5 mol% of the Chaudret Ru catalyst $[RuH(\eta^5\text{-}C_8H_{11})_2][BF_4]$.[15] After reduction of lactol **15**, **1** was isolated in 76% yield from **13**. We are currently studying the mechanism of this new OH-assisted isomerization[16] and expanding its scope to the synthesis of other *trans*-fused tetrahydrofurans.

In conclusion, we have achieved the first stereoselective synthesis of Superambrox (**1**) in 27% overall yield, based on two original highly selective reactions: the type III intramolecular ene reaction and the OH-assisted Ru- (or Ir-) catalyzed C–C double-bond isomerization. As the key precursor **3** can be prepared in enantiomerically pure form by resolution of aldehyde **2**,[7] this approach will also allow the synthesis of enantiomerically pure Superambrox.

## Experimental Section

(±)-**3**: A solution of $EtAlCl_2$ in hexane (1M, 192 mL, 192 mmol; depending on the quality of $EtAlCl_2$, it may be beneficial to use a 5–10 mol% excess of reagent) was added under $N_2$ over 12 min to a cooled ($-10 < T < -5$°C), stirred solution of (±)-**2** (40.0 g, 192 mmol) in $CH_2Cl_2$ (500 mL). The orange reaction mixture was stirred for 30 min at 0°C and treated over 7 min with chloral (37.5 mL, 56.6 g, 384 mmol). The reaction mixture was stirred for 90 min at 0°C and poured with stirring into an Erlenmeyer flask containing 5% HCl, ice, and $Et_2O$. After stirring for 5 min, the phases were separated, and the organic phase was washed successively ($H_2O$, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl), dried ($Na_2SO_4$), and concentrated (62.9 g). Bulb-to-bulb distillations in three portions (oven temp.: 125°C/0.02 mbar) afforded 42.6 g of distillate (79% yield by GC analysis) and 5.14 g of residue. Purification of the distillate (containing chloral-derived by-products) by flash chromatography on $SiO_2$ (400 g) twice with cyclohexane/EtOAc (98:2) as eluent afforded 29.6 g of **3** (75%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 5.54$ (m, 1H), 2.99 (m, 1H; NOE interactions with angular Me), 2.61 (m, 1H), 2.02 (m, 1H), 1.68–1.82 (m, 2H), 1.59 (m, 1H), 1.41–1.52 (m, 2H), 1.37 (s, 3H), 1.21 (m, 1H), 1.18 (s, 3H), 1.08 (s, 3H), 1.05 ppm (d, $J = 6$ Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 216.6$ (s), 149.1 (s), 117.7 (d), 47.8 (s), 41.0 (t), 37.2 (d), 36.5 (s), 35.8 (t), 33.4 (t), 32.3 (q), 29.6 (q), 27.6 (q), 18.0 (t), 14.4 ppm (q); MS: *m/z* (%): 206 [$M^+$] (46), 163 (18), 150 (47), 135 (100), 107 (19), 93 (16), 91 (13).

(±)-**1**: In a first flask, a solution of **13** (2.00 g, 8.00 mmol) in dry $CH_2Cl_2$ (20 mL; dried over 4-Å molecular sieves ) was degassed (freezing in liquid $N_2$, then vacuum, the purging with $N_2$—the process was repeated twice). A Schlenk tube was charged (in the glove box) with the Chaudret Ru catalyst (16.0 mg, 0.04 mmol, 0.5 mol%). The content of the first flask was added to the catalyst under $N_2$, and the reaction mixture was stirred at room temperature. A yellow precipitate formed after 5 min. As shown by TLC analysis, all the starting material **13** was consumed after 90 min. The formed lactol **15** was treated with $Et_3SiH$ (1.86 g, 2.54 mL, 16.0 mmol) and Amberlyst 15 (4.00 g). The reaction mixture was stirred open to the air[13b] for 1 h at room temperature, filtered, and concentrated to afford 2.57 g (contains $(Et_3Si)_2O$) of product.

The experiment was repeated on the same scale and afforded 2.83 g of crude product. Purification of the combined products (5.40 g) by flash chromatography on $SiO_2$ (180 g) with cyclohexane/EtOAc (96:4) as the eluent afforded 2.14 g of $(Et_3Si)_2O$ and 2.85 g of **1** (76%). The analytical data are identical with those given in references [1a] and [1b], but as both references contain minor errors in the $^1$H NMR spectra, we report here the correct spectral data: $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 5.44$ (dd, $J = 4$, 4 Hz, 1H), 3.97 (ddd, $J = 9$, 8, 3 Hz, 1H; NOE interactions with Me group on the THF ring ($\delta = 1.05$ ppm)), 3.85 (ddd, $J = 8$, 8, 8 Hz, 1H), 2.23 (m, 2H), 1.76–1.93 (m, 3H), 1.63–1.74 (m, 2H), 1.40–1.52 (m, 2H), 1.10–1.30 (m, 2H), 1.13 (s, 3H), 1.12 (s, 3H), 1.09 (s, 3H), 1.05 ppm (s, 3H; NOE interactions with one H of $CH_2O$ ($\delta = 3.97$ ppm)); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 18.3$ (t), 19.5 (q), 21.8 (q), 23.4 (t), 29.0 (q), 33.2 (q), 36.2 (s), 38.3 (s), 41.5 (t), 42.0 (t), 42.3 (t), 57.3 (d), 65.4 (t), 78.3 (s), 117.6 (d), 149.8 ppm (s); MS: *m/z* (%): 234 [$M^+$] (8), 219 (24), 175 (8), 150 (72), 135 (100), 84 (57), 43 (23).

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