Synthesis of (±)-Ambrox from (*E*)-Nerolidol and *β*-Ionone *via* Allylic Alcohol [2,3] Sigmatropic Rearrangement

Alejandro F. Barrero,*,† Joaquín Altarejos,‡ Enrique J. Alvarez-Manzaneda,† José M. Ramos,† and Sofía Salido†

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Granada, 18071 Granada, Spain, and Departamento de Química Inorgánica y Orgánica, Facultad de Ciencias Experimentales, Universidad de Jaén, 23071 Jaén, Spain

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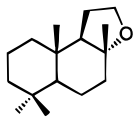
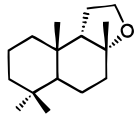
Ambergris is a metabolite of sperm whales (*Physeter macrocephalus* L.) which accumulates as concretions in the gut of the animal.[1] After several years of aging, as a result of the action of sunlight, air, and water, the final ambergris combines a unique odor with fixative properties particularly prized by perfumers. Release of the ambergris fragrance is related principally to the presence of the (−)-norlabdane oxide **1**, registered by Firmenich S. A. under the trademark Ambrox, which has inherited the best attributes of the increasingly more scarce natural material, and today constitutes its most important commercial substitute. This fact has prompted chemists to develop synthetic routes for the production of (−)-ambrox as well as for the racemic compound (±)-ambrox whose odor is somewhat different[2] from that of the natural product. Since its initial preparation in 1950,[3] several syntheses of (−)-ambrox have been developed from naturally-occurring sesquiterpenes or diterpenes such as (−)-drimenol,[4] (−)-sclareol,[3,5] (−)-manoyl oxide,[6] (−)-abietic acid,[7] (−)-levopimaric acid[8] and (−)-labdanolic acid,[9] and recently, from the monoterpenes (+)-carvone[10] and thujone.[11] With respect to the racemate (±)-ambrox, diverse total syntheses have been performed based on biogenetic-type cyclizations from farnesic acid, monocyclofarnesic acid, or derivatives of these.[12] Among the cyclization agents employed in these processes are $SnCl_4$,[13] $Sn(OTf)_2$,[14] $BF_3{\cdot}Et_2O$,[15] CF_3-$COOH$,[16] $HCOOH-H_2SO_4$,[17] and more recently the "superacids" FSO_3H[12c,18] and $ClSO_3H$.[19]

The present authors have recently described the synthesis of *levo* (−)-ambrox from the labdane-type diterpenes (−)-sclareol,[20] (+)-*cis*-abienol,[20,21] and (+)-communic acids.[22] In this context, the authors are now pleased to report new syntheses of racemic (±)-ambrox from (+)-(*E*)-nerolidol (**3**) and *β*-ionone (**11**), in which the stereospecific formation of the diastereomer (±)-9-*epi*-ambrox (**2**) was also carried out. Compound (−)-**2**[2,23] was prepared from (+)-sclareolide[2] and also through a stereocontrolled enantioselective process based on the anionic oxy-Cope rearrangement.[24] The racemate (±)-**2** was obtained in superacid cyclizations of hydroxypolyenes.[12c]



1

(±)-ambrox



2

(±)-9-*epi*-ambrox

In our approach to (±)-ambrox (**1**) from (+)-(*E*)-nerolidol (**3**) and *β*-ionone (**11**) the key step is the [2,3] sigmatropic rearrangement of an allylic alcohol to the homologous amide[25] promoted by heating the corresponding alcohol with *N*,*N*-dimethylformamide dimethyl acetal

† Universidad de Granada.

‡ Universidad de Jaén.

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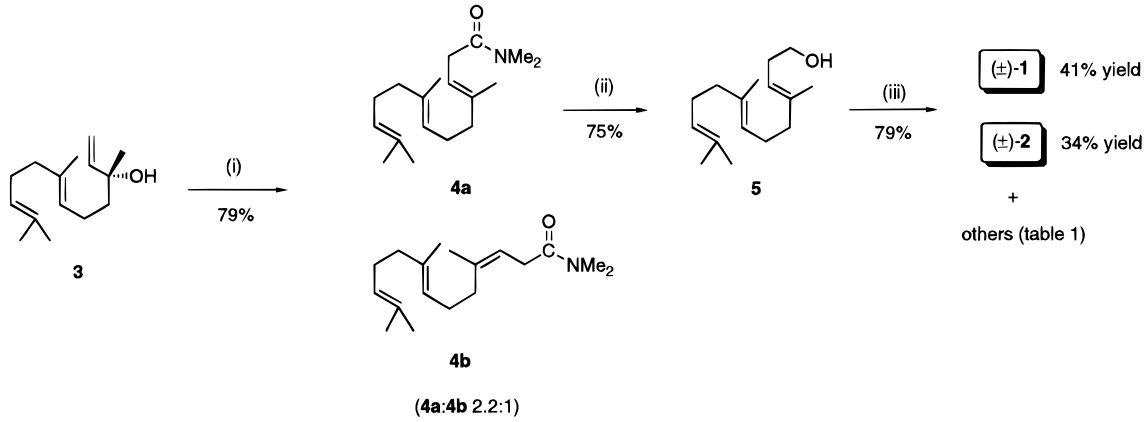
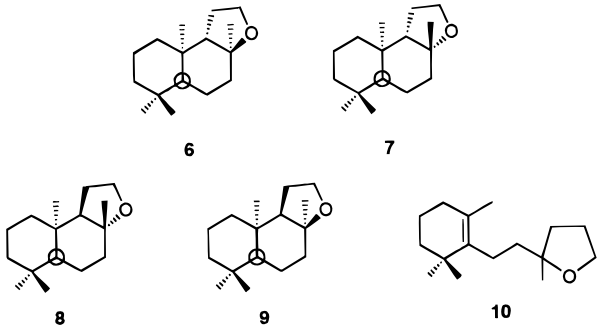
Scheme 1 [2,3] Sigmatropic Rearrangement of (*E*)-Nerolidol (3). Superacid-Mediated Cyclization of 5 into (±)-Ambrox (1) and (±)-9-*epi*-Ambrox (2)



Reaction conditions:
(i) DMFDMA, xylene, reflux, 13h. (ii) $LiBEt_3H$, THF, -78°C, 7h. (iii) $ClSO_3H$, $PrNO_2$, -78°C, 6 min.

Table 1. Acid-Catalyzed Reactions of Alcohols 5 and 15



			product distribution (%)[a]						
entry	starting material	cyclization agent	**1**	**2**	**6**	**7**	**8**	**9**	**10**
1	**5**	$ClSO_3H$	45.1	36.5	1.0	0.6	2.9	–	–
2	**15a**	$ClSO_3H$	47.8	37.7	2.6	0.8	7.0	–	–
3	**15b**	$ClSO_3H$	0.8	82.9	–	13.2	1.7	2.2	–
4	**15a**	*p*-TsOH	0.9	<0.2	–	–	–	–	81.2
5	**15a**	$SnCl_4$	12.3	11.6	–	4.7	4.5	1.7	17.3
6	**15a**	H_2SO_4	42.3	26.5	–	2.7	5.0	2.4	13.0

[a] GC analysis of crude reaction.

(DMFDMA). With this reaction the carbon required to complete the C_{16}-skeleton of ambrox is directly incorporated into either the nerolidol molecule (**3**) or into the monocyclic alcohol analog **15a**, the latter having been prepared from β-ionone in adequate yield. Thus, the refluxing of a mixture of (+)-(*E*)-nerolidol (**3**) and DMFDMA in xylene for 13 h yielded an *E*/*Z* mixture of the β,γ-unsaturated amides **4a** and **4b** (2.2:1) in 79% yield (Scheme 1). The easy separation of both amides by column chromatography allowed us to record their spectroscopic data separately and to perform the reduction of **4a** with $LiBEt_3H$ in THF at −78 °C to give the alcohol **5** (75% yield). The cyclization of **5** was carried out with the superacid $ClSO_3H$ in 1-nitropropane at −78 °C, giving a diastereomeric mixture formed mainly of (±)-**1** (41% yield) and (±)-9-*epi*-ambrox (**2**) (34% yield).[26] Besides these, other minor compounds with a *cis* A/B ring junction (**6**−**10**) were also analyzed by GC-MS and identified by comparison with authentic samples (Table 1; entry 1).[27]

In the synthesis from β-ionone (**11**) the precursor of (±)-**1** is (*E*)-monocyclohomofarnesol (**15a**), prepared by reducing the (*E*)-amide **14a**, which is obtained through the same [2,3] sigmatropic rearrangement developed in the nerolidol approach, now produced from monocyclonerolidol (**13**) (Scheme 2). The preliminary preparation of allylic alcohol **13** was accomplished in two steps: (a) the selective Δ^3 hydrogenation of β-ionone (**11**) using tri-*n*-butyltin hydride together with azoisobutyronitrile as a source of free radicals[28] to give **12** in 91% yield, and (b) the reaction of **12** with vinylmagnesium bromide in THF at 10 °C to give **13** in 96% yield. The treatment of **15a** with $ClSO_3H$ under the same conditions as before led to a mixture of (±)-**1** (43%) and (±)-**2** (34%), similar in composition to that obtained from the acyclic analog **5**

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(26) These yields were calculated taking into account the percentages recorded by the GC analysis of the crude reaction (Table 1; entry 1) and the loss of weight of cyclized crude material with respect to the starting material **5**.

(27) A copy of the original mass spectral charts of compounds **2**, **6**-**10** were kindly provided by Roger L. Snowden (Firmenich SA, Geneva, Switzerland). For spectral characterization see refs 2 and 23.

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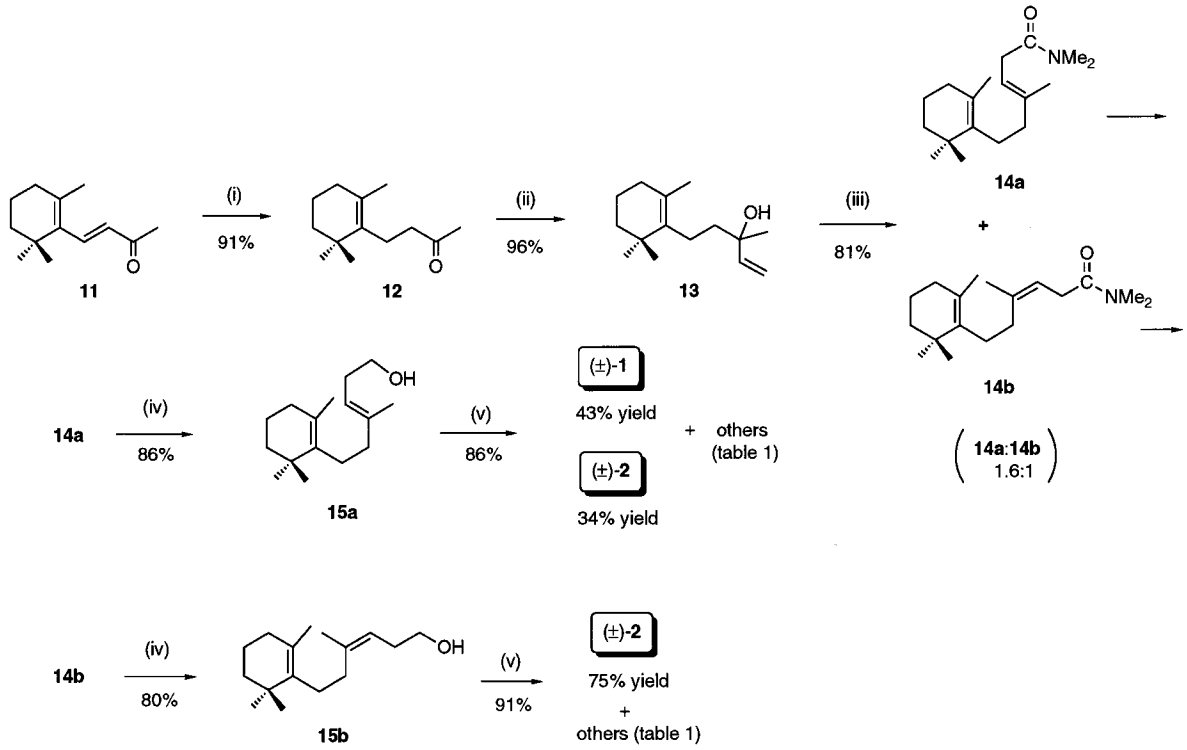
Scheme 2 [2,3] Sigmatropic Rearrangement of Allylic Alcohol 13 Prepared from β-Ionone (11). Stereospecific Superacid-Mediated Cyclizations of 15a and 15b into (±)-Ambrox (1) and (±)-9-*epi*-Ambrox (2)



Reaction conditions:

(i) Bu_3SnH, cat. AIBN, 80°C, 12h. (ii) 1M $(CH_2{=}CH)MgBr$, THF, 10°C, 20 min. (iii) DMFDMA, xylene, reflux, 13h. (iv) $LiBEt_3H$, THF, -78°C, 5h. (v) $ClSO_3H$, $PrNO_2$, -78°C, 9 min.

(Table 1). The action of $ClSO_3H$ on **5** and **15a** is parallel to that observed with the other superacid FSO_3H on the same alcohols,[12c] which means that both reagents induce biomimetic acid-mediated cyclizations with an internal nucleophilic termination by a hydroxyl group through the same reaction mechanism.[12c] In contrast to the behavior of alcohol **15a**, the reaction of (*Z*)-monocyclohomofarnesol (**15b**) with $ClSO_3H$ (Table 1; entry 3) yielded a crude product basically composed of (±)-**2** (only traces of **1** were detected) which means that cyclization of **15a** to **1** competes with its isomerization to **15b**, whose cyclization to **2** is more rapid in the superacid medium. In order to compare results, different cyclization agents, such as *p*-TsOH, $SnCl_4$ or H_2SO_4, were also tested with **15a**. Whereas the use of *p*-TsOH (entry 4) yields principally the monocyclized compound **10**, and $SnCl_4$ (entry 5) does not yield a synthetically useful result, it is worth noting that the use of simple commercial sulfuric acid (entry 6) yielded a crude product with a very similar composition to that obtained with the superacid (entry 2).

In conclusion, a new straightforward approach to the preparation of racemic ambrox starting from β-ionone and (*E*)-nerolidol has been developed. This is based on the utilization of the rarely employed [2,3] sigmatropic rearrangement for creating β,γ-unsaturated dimethylamides and hence the alcohols to be cyclized.

Experimental Section

Gas chromatography (GC) was performed on a fused-silica capillary column (25 m × 0.2 mm) coated with methylsilicone using nitrogen as carrier (25 mL min^{-1}) where the temperature program was from 50 °C to 220 °C (rate 5 °C min^{-1}) and from 220 °C to 280 °C (rate 3 °C min^{-1}). The retention times (t_R) are expressed in minutes. Thin-layer chromatography (TLC) was performed on precoated 0.25 mm-thick Merck plates of silica gel 60 F_{254}. Gravity column chromatography was carried out on Merck silica gel 60 (70−230 mesh) and low-pressure column chromatography on Merck silica gel 60 (230−400 mesh). All chromatographic separations were performed using hexane/Et_2O or hexane/*t*-BuOMe mixtures of increasing polarity and monitored by TLC and/or GC. IR spectra were obtained in liquid film between NaCl plates. ^1H NMR spectra were recorded from $CDCl_3$ solutions at 300 or 400 MHz and ^{13}C NMR spectra at 75 or 100 MHz. Chemical shifts are reported in parts per million (δ) relative to TMS (δ 0.00) and coupling constants (*J*) are in hertz. Carbon substitution degrees were established by DEPT multipulse sequence. Mass spectra (MS) were recorded using an ionizing voltage of 70 eV.

Materials. β-Ionone (99% purity) was provided by Destilaciones García de la Fuente (Granada), and (+)-(*E*)-nerolidol (65% purity) was isolated from the essential oil of *Inula viscosa* L. THF was freshly distilled from Na (benzophenone) under argon. Other reagents and solvents were purchased from Aldrich Chemical Co. or Merck and were used as received.

Reaction of 3 with *N,N*-Dimethylformamide Dimethyl Acetal. A mixture of (+)-(*E*)-nerolidol (**3**) (1.30 g, 65% purity, 3.80 mmol), DMFDMA (3.80 g, 31.93 mmol), and xylene (10 mL) was refluxed for 13 h under continuous removal of methanol (Dean−Stark device). The mixture was directly concentrated *in vacuo* yielding a residue (1.47 g) which, after silica gel column chromatography, yielded Δ^{3E}-amide **4a** (575 mg, 54.6%, hexane:Et_2O 1:1, 4:6) and Δ^{3Z}-amide **4b** (258 mg, 24.4%, hexane:Et_2O 1:1).

(*E,E*)-4,8,12-Trimethyl-3,7,11-tridecatrienoic acid *N,N*-dimethylamide (4a): t_R 39.75; IR 1648 ($CONMe_2$) cm^{-1}; ^1H NMR (400 MHz) δ 1.57 (br s, 6H), 1.63 (s, 3H), 1.65 (s, 3H), 2.91, 2.97 (2 s, 6H), 3.05 (d, 6.7, 2H), 5.04−5.10 (m, 2H), 5.30 (td, 6.7, 1.1, 1H); ^{13}C NMR (100 MHz) δ 15.95, 16.41, 17.63, 25.64, 35.46, 37.31 (CH_3), 26.41, 26.67, 33.73, 39.55, 39.65 (CH_2), 116.82,

123.87, 124.27 (CH), 131.20, 135.11, 138.07, 172.05 (C); MS *m/z* (rel int) 277 (M^+, 1), 208 ($M^+ - C_5H_9$, 8), 194 ($M^+ - C_6H_{11}$, 1), 154 ($M^+ - C_9H_{15}$, 2), 141 (5), 140 ($C_8H_{14}NO^+$, 7), 121 (12), 87 (21), 72 ($CONMe_2^+$, 100), 69 (26), 41 (36).

(*E,Z*)-4,8,12-Trimethyl-3,7,11-tridecatrienoic acid *N,N*-dimethylamide (4b): t_R 38.95; IR 1648 ($CONMe_2$) cm^{-1}; ^1H NMR (400 MHz) δ 1.55 (br s, 6H), 1.63 (s, 3H), 1.70 (s, 3H), 2.88, 2.95 (2 s, 6H), 3.03 (d, 6.7, 2H), 5.01−5.10 (m, 2H), 5.29 (td, 6.7, 1.3, 1H); ^{13}C NMR (100 MHz) δ 15.85, 17.56, 23.30, 25.56, 35.36, 37.23 (CH_3), 26.06, 26.56, 32.13, 33.14, 39.60 (CH_2), 117.51, 123.68, 124.16 (CH), 131.20, 135.34, 138.03, 171.87 (C); MS *m/z* (rel int) 277 (M^+, 1), 208 (12), 195 (1), 154 (2), 141 (5), 140 (35), 121 (15), 87 (19), 72 ($CONMe_2^+$, 100), 69 (29), 41 (47).

(*E,E*)-4,8,12-Trimethyl-3,7,11-tridecatrien-1-ol (5). To a solution of amide **4a** (280 mg, 1.01 mmol) in anhyd THF (2 mL) was added dropwise (15 min) a 1 M solution of $LiBEt_3H$ (superhydride) in THF (3.6 mL) at −78 °C under argon. After stirring for 7 h at −78 °C the reaction was allowed to warm, water (5 mL) was added, and the mixture was extracted with *t*-BuOMe (3 × 20 mL). The combined organic layers were dried over anhyd Na_2SO_4 and concentrated to dryness, yielding a residue which, after silica gel purification, afforded **5** (178 mg, 74.7%, hexane:*t*-BuOMe 85:15) (lit.[12c]): t_R 30.98; IR 3343, 1047 (OH), 3050, 1670 (CH=C) cm^{-1}; ^1H NMR (300 MHz) δ 1.60 (s, 6H), 1.65 (s, 3H), 1.68 (s, 3H), 2.29 (br q, 7.3, 2H), 3.61 (*t*, 7.3, 2H), 5.06−5.17 (m, 3H); ^{13}C NMR (75 MHz) δ 15.99, 16.18, 17.64, 25.65 (CH_3), 26.47, 26.72, 31.49, 39.68, 39.77, 62.41 (CH_2), 119.86, 123.97, 124.33 (CH), 131.27, 135.25, 138.84 (C); MS *m/z* (rel int) 236 (M^+, 0.4), 167 ($M^+ - C_5H_9$, 1), 136 (6), 123 ($C_9H_{15}^+$, 9), 95 ($C_7H_{11}^+$, 9), 93 (9), 81 ($C_6H_9^+$, 33), 69 ($C_5H_9^+$, 100), 67 ($C_5H_7^+$, 15), 41 (60).

4-(2′,6′,6′-Trimethylcyclohex-1′-enyl)butan-2-one (12). Ketone **12** was prepared from *β*-ionone (**11**) by either catalytic hydrogenation (Raney-Ni/MeOH)[29] or reduction under phase transfer catalysis ($Na_2S_2O_4$, Adogen 464)[30] or free-radical reduction (Bu_3SnH, cat. AIBN),[28,31] the last method being the most effective (91% yield; purity of **12**: 98%). Spectral data of **12** (IR, ^1H NMR, ^{13}C NMR, MS) are according to that reported in the literature.[12c,28,32]

3-Methyl-5-(2′,6′,6′-trimethylcyclohex-1′-enyl)-1-penten-3-ol (13). To a 1 M solution of vinylmagnesium bromide in THF (6.3 mL) was added dropwise (20 min) a solution of **12** (925 mg, 98% purity, 4.61 mmol) in anhyd THF (2 mL) at 10 °C under argon. After stirring for 20 min at 10 °C and a further 30 min at rt, a saturated NH_4Cl solution (30 mL) was added at 0 °C and the resulting mixture extracted with *t*-BuOMe (3 × 20 mL). The extract was washed with 10% $NaHCO_3$ solution and brine, dried over anhyd Na_2SO_4, and concentrated to yield **13** (985 mg, 96.3%) (lit.[16]): t_R 25.02; IR 3416, 1109 (*tert* OH), 3085, 1640, 997, 920 ($CH=CH_2$) cm^{-1}; ^1H NMR (300 MHz) δ 0.96 (s, 6H), 1.28 (s, 3H), 1.56 (s, 3H), 1.87 (br t, 6.2, 2H), 5.06 (dd, 10.7, 1.3, 1H), 5.21 (dd, 17.4, 1.3, 1H), 5.93 (dd, 17.4, 10.7, 1H); ^{13}C NMR (75 MHz) δ 19.74, 27.49, 28.61 (CH_3), 19.48, 22.69, 32.73, 39.83, 42.30, 111.72 (CH_2), 144.91 (CH), 35.06, 73.53, 127.01, 136.59 (C); MS *m/z* (rel int) 222 (M^+, 2), 204 ($M^+ - H_2O$, 8), 189 ($M^+ - CH_3 - H_2O$, 18), 147 (10), 137 ($M^+ - C_5H_9O$, 8), 133 (25), 123 ($C_9H_{15}^+$, 40), 121 (41), 107 (31), 95 ($C_7H_{11}^+$, 100), 93 (53), 81 (61), 79 (46), 71 (44), 55 (60), 43 (92), 41 (94).

Reaction of 13 with *N,N*-Dimethylformamide Dimethyl Acetal. Alcohol **13** (950 mg, 4.28 mmol) was treated with DMFDMA (3.06 g, 25.71 mmol) in xylene (10 mL) under the same conditions described for **3** to yield a residue (1.13 g) which, after silica gel column chromatography, afforded (*E*)-amide **14a** (594 mg, 50.1%, hexane:Et_2O 1:1, 4:6) and (*Z*)-amide **14b** (365 mg, 30.9%, hexane:Et_2O 1:1).

(*E*)-4-Methyl-6-(2′,6′,6′-trimethylcyclohex-1′-enyl)-3-hexenoic acid *N,N*-dimethylamide (14a): t_R 40.95; IR 1649 ($CONMe_2$) cm^{-1}; ^1H NMR (400 MHz) δ 0.95 (s, 6H), 1.56 (s, 3H), 1.67 (s, 3H), 1.87 (*t*, 6.3, 2H), 2.04 (s, 4H), 2.92, 2.99 (2 s, 6H), 3.06 (d, 6.7, 2H), 5.33 (*t*, 6.7, 1H); ^{13}C NMR (100 MHz) δ 16.47, 19.76, 28.54, 35.46, 37.33 (CH_3), 19.46, 27.63, 32.68, 33.60, 39.75, 40.07 (CH_2), 116.26 (CH), 34.90, 127.04, 136.83, 138.91, 172.06 (C); MS *m/z* (rel int) 277 (M^+, 2), 142 (26), 141 (19), 140 ($C_8H_{14}NO^+$, 7), 126 ($C_7H_{12}NO^+$, 5), 95 (17), 87 (7), 72 ($CONMe_2^+$, 100), 41 (20).

(*Z*)-4-Methyl-6-(2′,6′,6′-trimethylcyclohex-1′-enyl)-3-hexenoic acid *N,N*-dimethylamide (14b): t_R 39.86; IR 1649 ($CONMe_2$) cm^{-1}; ^1H NMR (400 MHz) δ 0.98 (s, 6H), 1.61 (s, 3H), 1.76 (d, 1.2, 3H), 1.88 (*t*, 6.3, 2H), 1.97−2.07 (m, 4H), 2.91, 2.97 (2 s, 6H), 3.07 (d, 6.8, 2H), 5.28 (td, 6.8, 1.2, 1H); ^{13}C NMR (100 MHz) δ 19.77, 23.28, 28.54, 35.46, 37.26 (CH_3), 19.43, 26.85, 32.69, 32.87, 33.22, 39.71 (CH_2), 116.96 (CH), 34.90, 127.20, 136.80, 138.87, 171.93 (C); MS *m/z* (rel int) 277 (M^+, 2), 142 (16), 141 (18), 140 (29), 126 (5), 95 (16), 87 (16), 72 (100), 41 (22).

(*E*)-4-Methyl-6-(2′,6′,6′-trimethylcyclohex-1′-enyl)-3-hexen-1-ol (15a). (*E*)-Amide **14a** (476 mg, 1.72 mmol) was treated with superhydride (3.5 mL) for 4.5 h under the same conditions described for **4a**, to yield a residue (398 mg) which, after silica gel purification, afforded **15a** (348 mg, 85.7%, hexane:*t*-BuOMe 75:25) (lit.[12c]): t_R 31.21; IR 3337, 1047 (OH) cm^{-1}; ^1H NMR (400 MHz) δ 0.98 (s, 6H), 1.59 (s, 3H), 1.68 (s, 3H), 1.89 (*t*, 6.3, 2H), 2.05 (s, 4H), 2.29 (br q, 7.3, 6.6, 2H), 3.63 (*q*, 6.2, 2H), 5.15 (br t, 7.3, 1H); ^{13}C NMR (100 MHz) δ 16.29, 19.82, 28.60 (CH_3), 19.52, 27.87, 31.48, 32.74, 39.81, 40.34, 62.51 (CH_2), 119.07 (CH), 34.97, 127.07, 136.94, 139.90 (C); MS *m/z* (rel int) 236 (M^+, 2), 191 ($M^+ - C_2H_5O$, 2), 137 ($M^+ - C_6H_{11}O$, 65), 95 ($C_7H_{11}^+$, 100), 81 ($C_6H_9^+$, 72), 67 ($C_5H_7^+$, 28), 55 (27), 41 (64).

(*Z*)-4-Methyl-6-(2′,6′,6′-trimethylcyclohex-1′-enyl)-3-hexen-1-ol (15b). (*Z*)-amide **14b** (200 mg, 0.72 mmol) was treated with superhydride (1.5 mL) for 5 h, under the same conditions described for preparing alcohol **15a**, to yield **15b** (135 mg, 80%, hexane:*t*-BuOMe 8:2) (lit.[12c]): t_R 30.80; IR 3325, 1048 (OH) cm^{-1}; ^1H NMR (400 MHz) δ 1.00 (s, 6H), 1.63 (s, 3H), 1.77 (s, 3H), 1.90 (*t*, 6.3, 2H), 1.98−2.12 (m, 4H), 2.29 (br q, 7.3, 6.5, 2H), 3.61 (*t*, 6.5, 2H), 5.09 (br t, 7.3, 1H); ^{13}C NMR (100 MHz) δ 19.86, 23.44, 28.61 (CH_3), 19.49, 27.23, 31.46, 32.67, 32.74, 39.77, 62.62 (CH_2), 120.10 (CH), 34.92, 127.23, 136.91, 139.67 (C); MS *m/z* (rel int) 236 (M^+, 2), 221 ($M^+ - CH_3$, 1), 203 ($M^+ - CH_3 - H_2O$, 1), 191 (2), 137 (75), 95 (100), 81 (76), 67 (29), 55 (33), 41 (69).

Cyclization of 5, 15a, 15b with $ClSO_3H$ or H_2SO_4. General Procedure. To a solution of 99% $ClSO_3H$ (0.2 mL, 1.99 mmol) or 98% H_2SO_4 (0.3 mL, 5.49 mmol) in 1-nitropropane (1−2 mL) was added dropwise (1−7 min) a solution of the alcohol (80 mg, 0.34 mmol) in 1-nitropropane (2 mL) at −78 °C under argon. After stirring for 6−25 min a saturated $NaHCO_3$ solution (1−2 mL) was injected, and then further portions of solid $NaHCO_3$ were added. The mixture was extracted with *t*-BuOMe (3 × 5 mL), and the combined organic layers were dried over anhyd Na_2SO_4 and concentrated to dryness to yield a crude product which was studied directly by GC-MS and ^1H NMR. Identification of compounds **1**, **2**, and **6**−**10** was effected by comparison of their MS data with those of authentic samples.[27] The product mixture distribution is presented in Table 1. Retention times (min) are: **1** (30.93), **2** (29.79), **6** (29.89), **7** (30.02), **8** (30.78), **9** (29.54), **10** (27.80).

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Supporting Information Available: Spectral assignments and copies of ^1H NMR and ^{13}C NMR spectra of compounds **4a**, **4b**, **5**, **12**−**15** (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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