Mechanistic Investigation of the Domino Oxy-Cope/Ene/Claisen Reaction and Its Application to the Synthesis of Desdimethyl Ambliol B

Louis Barriault,* Irina Denissova, Nathalie Goulet

Centre for Catalysis Research and Innovation, University of Ottawa, Department of Chemistry, 10 Marie Curie, Ottawa, Ontario, K1N 6N5, Canada
Fax +1(613)5625170; E-mail: lbarriau@uottawa.ca

Received: 20.03.2012; Accepted: 22.03.2012

Abstract: We report an efficient and highly diastereoselective oxy-Cope/ene/Claisen reaction for the synthesis of decalin frameworks possessing four contiguous stereogenic centers. A detailed mechanistic investigation and its application to a short and protecting group free synthesis of desdimethyl ambliol B are presented.

Key words: oxy-Cope/ene/Claisen, domino, sigmatropic, diastereoselectivity, macrocycle

The development of efficient synthetic methods for the rapid assembly of complex polycyclic frameworks from simple substrates constitutes an important research endeavor in organic synthesis. In addition, the ever-increasing need for efficient and waste-minimizing processes is becoming more and more important, whilst the use of domino reactions has emerged as an attractive strategy for the generation of multiple carbon–carbon bonds.[1] The stereoselective formation of quaternary carbon centers is a problem frequently encountered during the synthesis of carbocycles.[2] As examples, the bioactive molecules ambliol B (**1**),[3] dysidiolide (**2**)[4] and agelasimine A (**3**)[5] all bear a quaternary carbon at C-5 and a tertiary alcohol at C-1 (Figure 1).

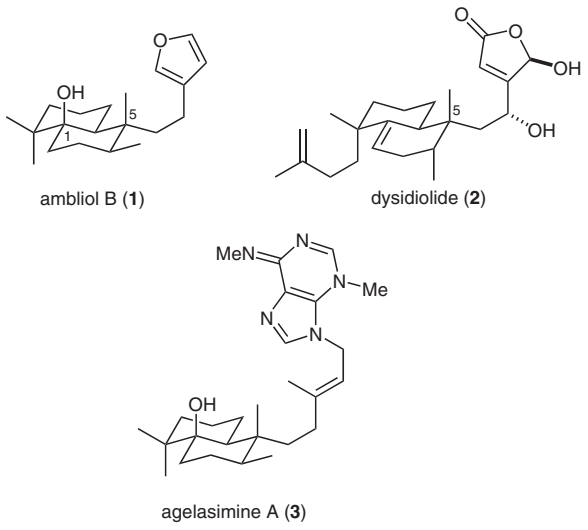
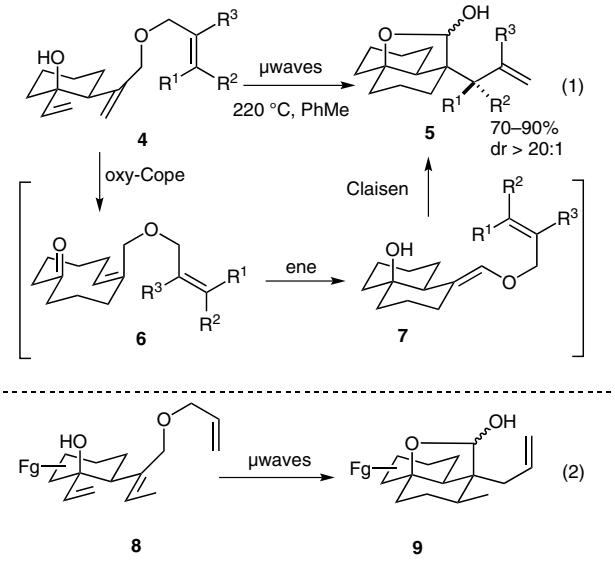


Figure 1 Structures of natural clerodane diterpenes

SYNTHESIS 2012, 44, 1833–1840
Advanced online publication: 01.06.2012
DOI: 10.1055/s-0031-1291144; Art ID: SS-2012-C0291-ST

In 2002, we reported a highly diastereoselective cascade oxy-Cope/ene/Claisen reaction of 1,2-divinylcyclohexanol **4** to generate decalin framework **5** possessing four contiguous stereogenic centers (Scheme 1, equation 1).[6] Upon heating at 220 °C, the alcohol **4** was converted into ketone **6** via an oxy-Cope–tautomerization rearrangement. Compound **6** is poised to undergo a transannular carbonyl-ene reaction to give enol ether **7**, which is set up for a Claisen rearrangement on the less hindered face to afford **5**. In the light of these results, we envisaged the syntheses of compounds **1** and **3**, via a common intermediate **9** which could be obtained through a domino oxy-Cope/ene/Claisen reaction of **8** (Scheme 1, equation 2).



Scheme 1 General mechanism for the domino oxy-Cope/ene/Claisen reaction; Fg = functional group

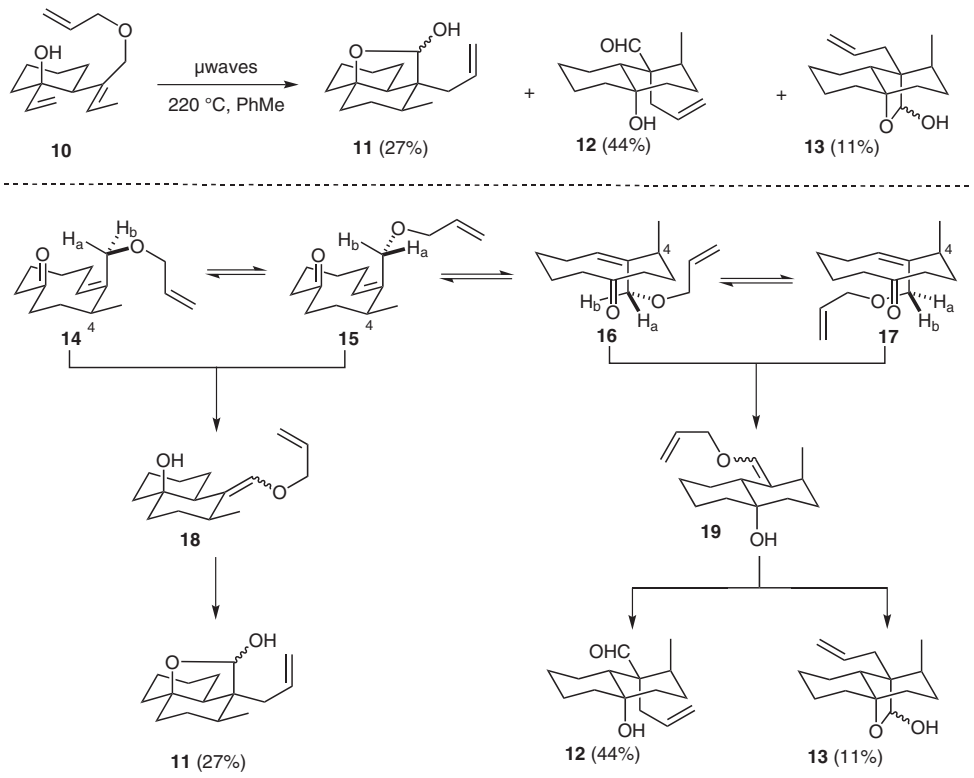
To evaluate the feasibility of this approach, allyl ether **10** was heated at 220 °C for three hours. To our dismay, the desired decalin **11** was obtained in only 27% yield along with a mixture of two other diastereomers, **12** (44%) and **13** (11%) (Scheme 2). In an effort to rationalize the product distribution, it was decided to investigate the ene reaction and Claisen rearrangement transition states. The transition states of the ene reaction leading to decalin **18** requires that the methyl at C-4 is oriented equatorially. Consequently, the corresponding transition states of macrocycles **14** and **15** exhibit *syn*-pentane and 1,3-allylic interactions, respectively. On the other hand, the formation

of decalin **19** necessitates the methyl at C-4 to be positioned axially in the transition states of macrocycles **16** and **17**. Finally, the Claisen rearrangement of **18** proceeds *anti* to the tertiary alcohol to give tricyclic **11**. Owing to the orientation of the C-4 methyl in decalin **19**, the sigmatropic shift occurs preferentially *syn* to the alcohol affording aldehyde **12** as the major product. The preferential formation of decalins **12** and **13** over **11** strongly suggests that: 1) the rotation barrier of the trisubstituted olefin is a lower energy process competing with the ene reaction, and 2) the chirality transfer efficacy in the domino process relies upon conformational preferences of the macrocyclic transition state for the ene reactions. In this article, we report a detailed mechanistic analysis of the domino oxy-Cope/ene/Claisen reaction and its application toward the stereoselective synthesis of desdimethyl ambliol B.

If it is assumed that the transannular ene reaction is governed by the Curtin–Hammett principle, the ratio of products should correspond to the relative values for the absolute energies for the two transition states.[7] It can be proposed that the diastereoselectivity of the domino reaction could be dictated using a remote chiral center located on the macrocycle.[8] To validate this approach, 1,2-divinyl-1-cyclohexanols **20a–c** and **21a–c**, readily prepared from 2-chloro-1-cyclohexanone, were subjected to microwave irradiation at 220 °C for one to three hours (Table 1).[9]

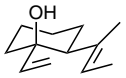
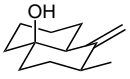
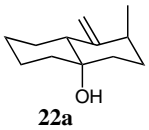
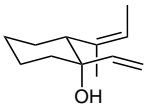
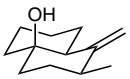
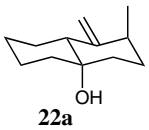
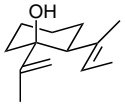
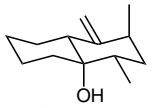
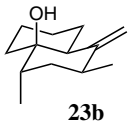
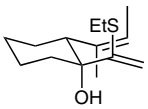
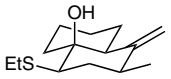
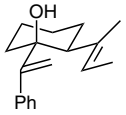
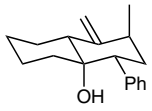
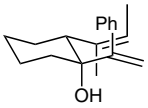
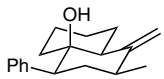
The thermal rearrangement of **20a** gave a 3.2:1 mixture of **23a** and **22a** in 70% yield (Table 1, entry 1). The major compound possessed the methyl at C-4 *syn* to the alcohol. The product distribution can be rationalized as follows. The oxy-Cope rearrangement of **20a** (R = H) gives 10-membered ring macrocycle **A**, which can undergo a ring inversion to give diastereomer **B** (Scheme 3). After tautomerization, a rapid equilibrium between ketone **C** and **D** takes place (note that when R = H, macrocycles **C** and **D** are identical to **E** and **F**). The corresponding transition state for the conversion of **D→22a** has the methyl oriented in the axial position, while the methyl is equatorial in the transition state for the ene reaction of **C→23a**. The observed ratio of 3.2:1 corresponds to a difference of 1.14 kcal/mol (calculated at 493 K, 220 °C) between transition states **C→23a** and **D→22a** leading to **23a** and **22a**, respectively. Taking into account that the A_{Me} is 1.74 kcal/mol (at 300 K), it can be proposed that the absolute value for the transition state of **D→22a** should be higher in energy than that leading to **23a**, thus explaining the observed diastereoselectivity. Assuming that the ene reaction is under Curtin–Hammett control, the thermal rearrangement of **21a** (R = H) should give the same ratio of **23a** (**25a**) and **22a** (**24a**). Alcohol **21a** was irradiated with microwaves at 220 °C to afford **23a** and **22a** in a ratio of 3.2:1 and 60% yield (Table 1, entry 2). This clearly demonstrates that the transannular ene reaction is under Curtin–Hammett control.

Table 1 (entry 3) revealed that replacement of R = H by R = Me, as in substrate **20b**, led to a mixture of **22b** and **23b** in 77% yield in a diastereomeric ratio of 3.4:1. Interestingly, the major product had the methyl at C-4 in the axial position suggesting that the stereocenter at C-2 governed the diastereoselectivity of the reaction. When R was changed from a hydrogen into an ethyl sulfide (Table 1,

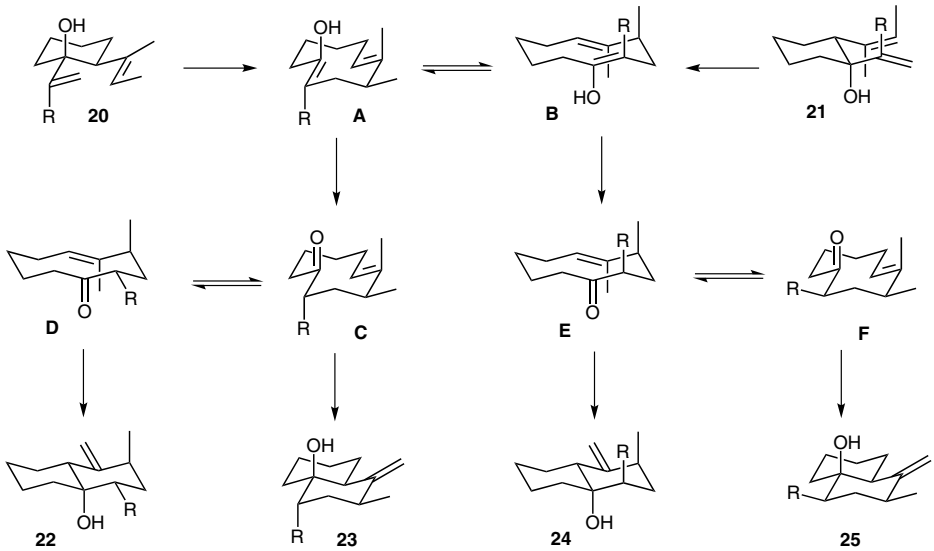


Scheme 2 Proposed mechanism for the domino oxy-Cope/ene/Claisen reaction

Table 1 Thermal Rearrangement of 1,2-Divinylcyclohexanols

Entry	Substrate	Product	Yield (dr)
1	 **20a**	 **23a** +  **22a**	70% (3.2:1)
2	 **21a**	 **23a** +  **22a**	60% (3.2:1)
3	 **20b**	 **22b** +  **23b**	77% (3.4:1)
4	 **21b**	 **25b**	81% (>20:1)
5	 **20c**	 **22c**	93% (>20:1)
6	 **21c**	 **25c**	64% (>20:1)

entry 4), the diastereoselectivity of the reaction increased from 3.2:1 (Table 1, entry 2) to 20:1 in 81% yield in favor of decalin **25b**. It is important to point out that the existence of a rapid equilibrium between **A** and **B** (R = SEt) can be excluded when R ≠ H since its existence would predict the formation of decalins **22b** and **23b**. These results are in agreement with a high energy barrier to rotation of tetrasubstituted enols in 10-membered rings.[10] Heating of

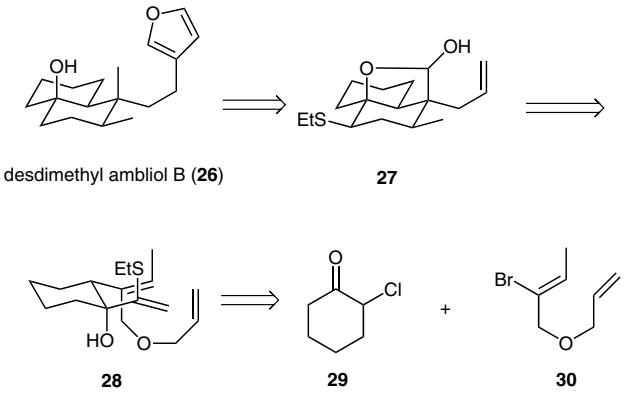


Scheme 3 Proposed mechanism of the oxy-Cope/ene/Claisen

20c (R = Ph) afforded compound **22c** in 93% yield as the sole isomer (Table 1, entry 5). Subjection of **21c** to microwave irradiation gave decalin **25c** in 64% yield as the only detectable isomer (Table 1, entry 6).

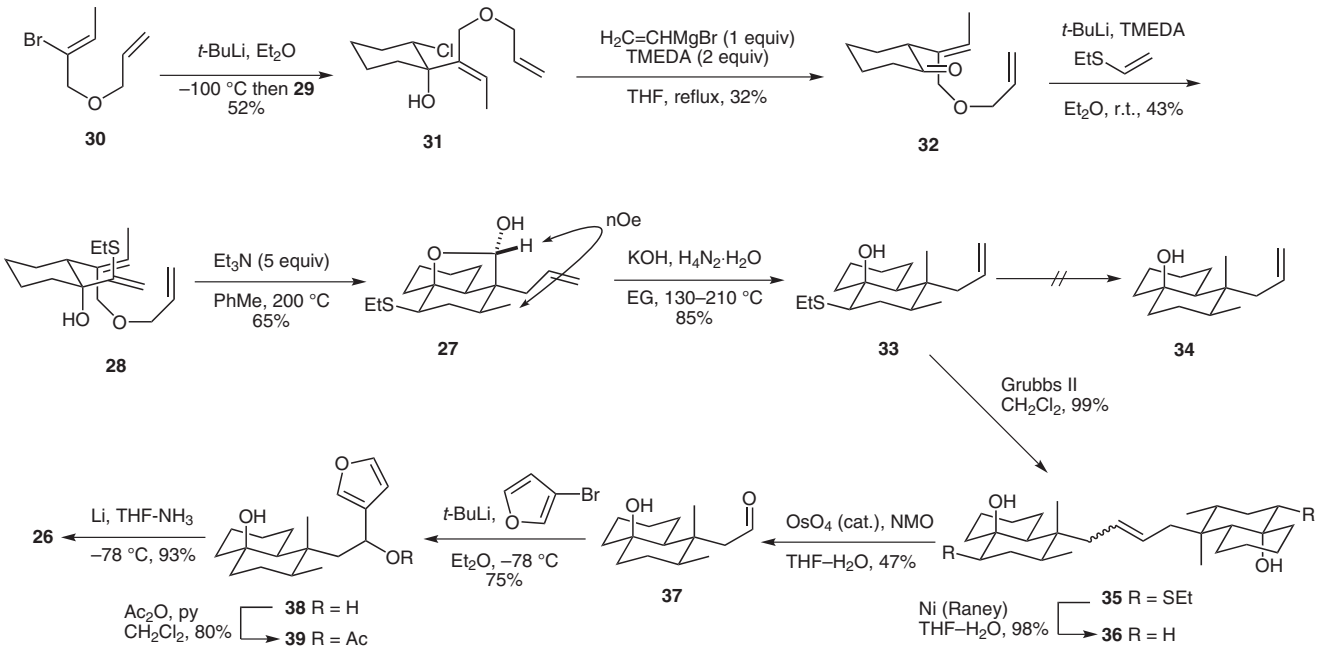
These results confirmed that: 1) the transannular ene reaction was governed by the Curtin–Hammett principle, and 2) the diastereoselectivity of the reaction could be directed by a stereogenic center at C-2. Having determined the origin of the high selectivity of the domino reaction, we next applied this cascade process to the synthesis of a clerodane diterpene analogue, desdimethyl ambliol B (**26**) (Scheme 4).

Our retrosynthetic analysis revealed immediately that **26** could be prepared from lactol **27**. The latter could be efficiently generated through a domino oxy-Cope/ene/Claisen reaction of **28** which in turn could be rapidly assembled from commercially available 2-chlorocyclohexanone (**29**) and vinyl bromide **30**[11] (Scheme 4).



Scheme 4 Retrosynthetic analysis of desdimethyl ambliol B (**26**)

The synthesis began with the treatment of vinyl bromide **30** with *tert*-butyllithium in diethyl ether at –100 °C followed by the addition of **29** to give chlorohydrine **31** in 52% yield (Scheme 5). The latter was converted into ketone **32**, in 32% yield, via a 1,2-shift using one equivalent of vinylmagnesium bromide in the presence of two equivalents of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine in tetrahydrofuran at reflux temperature.[12] A second alkylation using vinylethyl sulfide gave the desired alcohol **28** in 43% yield (dr >20:1). As expected, the thermal rearrangement of **28** at 200 °C provided lactol **27** in 65% yield as the only detectable diastereomer. The relative configuration of **27** was established without ambiguity by 2D NMR spectroscopy. Reduction of the lactol moiety into the corresponding methyl analogue was realized using potassium hydroxide and hydrazine hydrate, in ethyl glycol (EG) at reflux temperature, to give decalin **33** in 85% yield. With compound **33** in hand, the removal of the ethyl sulfinyl group was envisaged to afford alkene **34**. Frustratingly, all our attempts to obtain alkene **34** via reduction of the C–S bond, or aldehyde **37** through oxidation of **33** were unsuccessful. Thus, we envisioned that increasing the steric bulk toward the alkene would prevent any further overreduction. Decalin **33** underwent an alkene dimerization using Grubbs II catalyst to give dimer **35** in quantitative yield.[13] Cleavage of the C–S bond using Raney nickel in tetrahydrofuran–water produced compound **36** in 98% yield. This was followed by a Lemieux–Johnson oxidation to afford the desired aldehyde **37** in 47% yield. The unstable aldehyde **37** was converted into furan **38** (75% yield), which upon treatment with acetic anhydride in a solution of dichloromethane–pyridine gave acetate **39** in 80% yield. Finally, reduction of the acetate group with elemental lithium in condensed ammonia at –78 °C provided desdimethyl ambliol B (**26**) in 93% yield.



Scheme 5 Synthesis of desdimethyl ambliol B (**26**)

In conclusion, a careful examination of the reaction mechanism revealed that the diastereoselectivity of the oxy-Cope/ene/Claisen reaction was controlled by the conformational preferences of the macrocycles at the transition state for the transannular ene reaction. The effectiveness of this domino process was confirmed via a short synthesis of desdimethyl ambliol B (**26**) in 11 steps from vinyl bromide **30**. The application of the domino oxy-Cope/ene/Claisen reaction in the synthesis of other natural clerodane diterpenes is underway and will be reported in due course.

All reactions were carried out under dry N_2 or Ar atmospheres, in flame-dried glassware or sealed tubes equipped with a magnetic stir bar and a rubber septum, unless otherwise indicated. THF and Et_2O were freshly distilled from Na/benzophenone. Toluene, CH_2Cl_2 and Et_3N were freshly distilled from CaH_2. Other commercially available reagents were used without purification, unless otherwise indicated. Reactions were monitored by TLC analysis of aliquots using aluminum and glass sheets pre-coated (0.2 mm and 0.25 mm layer thickness, respectively) with silica gel 60 F_{254} (E. Merck). TLC plates were viewed under UV light and stained with *p*-anisaldehyde or phosphomolybdic acid staining solution. Flash chromatography was carried out on Silicycle silica gel (0.35–0.75 mm, 60 Å pore size).IR spectra were recorded on a Bomen Michaelson 100 FTIR spectrometer. ^{1}H NMR spectra were recorded on Bruker Avance 300 MHz, 400 MHz and 500 MHz spectrometers; ^{13}C NMR spectra were recorded at 75 MHz, 100 MHz and 125 MHz. HRMS spectra were obtained using a Kratos Analytical Concept instrument. Microwave reactions were conducted in a CEM Model ESP-1500 Plus oven equipped with a pressure monitoring device and an EST-300 Plus fibre optic temperature probe. All experiments were performed in a quartz tube previously washed with aqueous *i*-PrOH–NaOH solution.

Microwave-Assisted Domino Reaction; General Procedure

To a soln of divinyl cyclohexanol in toluene (0.1 M) in a quartz tube (previously washed with aq *i*-propanol–NaOH soln) equipped with a carboflon^{TM} insert was added freshly distilled Et_3N (10 equiv). The resulting soln was deoxygenated with Ar for 0.5 h, and the tube sealed and heated in a CEM microwave oven at 220 °C for 1 h. The mixture was then cooled to r.t. The soln was transferred to a round-bottom flask and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (EtOAc–hexanes, 20:80) afforded the corresponding decalin.

(±)-(2*S*,4a*R*,8a*S*)-2-Methyl-1-methylenedecahydronaphthalen-4a-ol (23a) and (±)-(2*S*,4a*S*,8a*R*)-2-Methyl-1-methylenedecahydronaphthalen-4a-ol (22a)

Yield: 21 mg (70%, mixture of **23a** and **22a**); colorless oil.

IR (neat): 3549, 3479, 2933, 2859 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (data for **23a**) = 4.92 (dd, *J* = 1.6 Hz, 1.6 Hz, 1 H), 4.84 (br s, 1 H), 4.70 (br s, 1 H), 4.57 (dd, *J* = 1.9 Hz, 1.9 Hz, 1 H), 2.58 (q, *J* = 6.7 Hz, 1 H), 2.22 (m, 1 H), 2.03–1.20 (m, 28 H), 1.09 (d, *J* = 7.0 Hz, 3 H), 1.05 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (mixture of **23a** and **22a**) = 154.7, 154.1, 108.7, 106.0, 72.4, 72.3, 50.4, 44.3, 40.3, 39.0, 38.9, 38.8, 35.0, 33.1, 29.2, 26.4, 26.3, 24.5, 24.2, 21.7, 21.6, 19.1, 18.7.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{12}H_{20}O$: 180.1514; found: 180.1503.

(±)-(2*S*,4*S*,4a*S*,8a*R*)-2,4-Dimethyl-1-methylenedecahydronaphthalen-4a-ol (22b)

Yield: 34 mg (60%); colorless oil.

IR (neat): 3571, 2931, 2853, 1460 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.89–4.87 (m, 1 H), 4.58 (dd, *J* = 1.8 Hz, 1.8 Hz, 1 H), 2.59–2.51 (m, 1 H), 2.20–2.14 (m, 1 H), 1.98–1.91 (m, 1 H), 1.80–1.65 (m, 2 H), 1.60–1.41 (m, 5 H), 1.35–1.06 (m, 7 H), 0.81 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.4 (C), 108.9 (CH_2), 73.8 (C), 44.6 (CH), 39.1 (CH), 38.7 (CH_2), 36.3 (CH), 35.6 (CH_2), 26.2 (CH_2), 24.5 (CH_2), 21.9 (CH_2), 19.9 (CH_3), 14.8 (CH_3).

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{13}H_{22}O$: 194.1671; found: 194.1676.

(±)-(2*S*,4*R*,4a*R*,8a*R*)-2-Methyl-1-methylene-4-phenyldecahydronaphthalen-4a-ol (22c)

Yield: 65 mg (93%); colorless oil.

IR (neat): 3555, 3083, 3060, 2931, 2894 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.15 (m, 5 H), 4.89–4.87 (m, 1 H), 4.61 (dd, *J* = 1.9 Hz, 1.9 Hz, 1 H), 2.67 (dd, *J* = 3.7 Hz, 13.6 Hz, 1 H), 2.53–2.44 (m, 1 H), 2.24–2.14 (m, 2 H), 1.67–1.36 (m, 6 H), 1.29–1.11 (m, 3 H), 1.08 (d, *J* = 7.2 Hz, 3 H), 1.03–0.92 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.9 (C), 142.6 (C), 128.3 (2 CH), 126.82 (2 CH), 126.81 (CH), 109.3 (CH_2), 73.9 (C), 49.3 (CH), 45.0 (CH), 39.1 (CH), 37.2 (CH_2), 36.9 (CH_2), 26.2 (CH_2), 24.5 (CH_2), 21.7 (CH_2), 19.8 (CH_3).

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{18}H_{24}O$: 256.1827; found: 256.1846.

(±)-(2*S*,4*R*,4a*S*,8a*S*)-4-(Ethylthio)-2-methyl-1-methylenedecahydronaphthalen-4a-ol (25b)

Yield: 11 mg (81%); colorless oil.

IR (neat): 3524, 2931, 2854, 1644, 1449 cm^{-1}.

^{1}H NMR (500 MHz, C_6D_6): δ = 4.77 (s, 1 H), 4.69 (s, 1 H), 2.54–2.50 (m, 1 H), 2.41–2.29 (m, 3 H), 1.93 (ddd, *J* = 4.0 Hz, 4.0 Hz, 13.0 Hz, 1 H), 1.84–1.79 (m, 1 H), 1.74–1.57 (m, 4 H), 1.54–1.45 (m, 3 H), 1.25 (s, 1 H), 1.13–1.08 (m, 4 H), 0.99–0.92 (m, 4 H).

^{13}C NMR (75 MHz, C_6D_6): δ = 152.6 (C), 105.8 (CH_2), 74.2 (C), 55.4 (CH), 50.4 (CH), 41.6 (CH_2), 38.7 (CH), 37.5 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 24.9 (CH_2), 21.8 (CH_2), 18.0 (CH_3), 15.5 (CH_3).

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{14}H_{24}OS$: 240.1548; found: 240.1534.

(±)-(2*S*,4*S*,4a*S*,8a*S*)-2-Methyl-1-methylene-4-phenyldecahydronaphthalen-4a-ol (25c)

Yield: 16 mg (64%); yellowish oil.

IR (neat): 3553, 3087, 3060, 2931, 2855, 1643 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25–7.11 (m, 5 H), 4.84 (d, *J* = 1.1 Hz, 1 H), 4.71 (s, 1 H), 2.37 (dd, *J* = 4.7 Hz, 12.1 Hz, 1 H), 1.96–1.86 (m, 1 H), 1.82–1.77 (m, 1 H), 1.68–1.39 (m, 7 H), 1.29–1.21 (m, 1 H), 1.15–1.05 (m, 2 H), 1.01–0.91 (m, 4 H).

^{13}C NMR (75 MHz, C_6D_6): δ = 153.9 (C), 142.8 (C), 128.2 (2 CH), 128.0 (2 CH), 126.6 (CH), 106.2 (CH_2), 73.3 (C), 55.2 (CH), 50.6 (CH), 40.7 (CH_2), 38.7 (CH), 37.1 (CH_2), 26.2 (CH_2), 24.8 (CH_2), 21.7 (CH_2), 18.3 (CH_3).

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{18}H_{24}O$: 256.1827; found: 256.1818.

(±)-(1*S*,2*S*)-1-[(*Z*)-1-(Allyloxy)but-2-en-2-yl]-2-chlorocyclohexanol (31)

To a soln of vinyl bromide **30** (2.46 g, 12.9 mmol) in Et_2O (100 mL) was added dropwise *t*-BuLi (17.8 mL, 23.2 mmol, 1.3 M in pentane) at –100 °C. After stirring for 1 h, a soln of ketone **29** (1.5 mL, 12.9 mmol) was added at –100 °C. The mixture was gradually warmed to –60 °C and then cooled to –100 °C. H_2O (100 mL) was added and the mixture allowed to warm to r.t. The mixture was extracted with Et_2O (3 × 100 mL) and the combined organic phase dried over

$MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (EtOAc–hexanes, 5:95).

Yield: 1.64 g (52%); colorless oil.

IR (neat): 3571, 3494, 2938, 1648 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.92–5.85 (m, 1 H), 5.60 (q, *J* = 7.4 Hz, 1 H), 5.25 (dddd, *J* = 17.3 Hz, 1.7 Hz, 1.7 Hz, 1.7 Hz, 1 H), 5.16 (dddd, *J* = 10.4 Hz, 1.7 Hz, 1.4 Hz, 1.4 Hz, 1 H), 4.43 (dd, *J* = 11.9 Hz, 4.6 Hz, 1 H), 4.23 (d, *J* = 11.1 Hz, 1 H), 4.02 (dddd, *J* = 12.7 Hz, 5.3 Hz, 1.4 Hz, 1.4 Hz, 1 H), 3.88 (ddd, *J* = 12.7 Hz, 5.7 Hz, 1.4 Hz, 1 H), 3.81 (d, *J* = 11.1 Hz, 1 H), 3.30 (br s, 1 H), 2.07 (ddd, *J* = 15.9 Hz, 12.7 Hz, 3.8 Hz, 1 H), 1.96–1.92 (m, 2 H), 1.86 (d, *J* = 7.4 Hz, 3 H), 1.80–1.64 (m, 3 H), 1.47–1.41 (m, 1 H), 1.36–1.25 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.2 (C), 134.2 (CH), 127.5 (CH), 116.2 (CH_2), 76.3 (C), 75.6 (CH_2), 70.2 (CH_2), 66.4 (CH), 37.1 (CH_2), 32.1 (CH_2), 26.0 (CH_2), 20.1 (CH_2), 14.8 (CH_3).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{13}H_{21}O_2Cl$: 244.1230; found: 244.1194.

(±)-(*E*)-2-[1-(Allyloxy)but-2-en-2-yl]cyclohexanone (32)
To a soln of **31** (9.96 g, 40.7 mmol) in THF (400 mL) was added TMEDA (18 mL, 122.1 mmol) followed by vinylmagnesium bromide (51 mL, 44.8 mmol, 0.9 M in THF). The resulting mixture was heated to reflux temperature and stirred for 2 h. The mixture was cooled to r.t. and sat. aq NH_4Cl soln (400 mL) was added. The mixture was extracted with EtOAc (3 × 100 mL) and the combined organic phase dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (EtOAc–hexanes, 10:90) to give ketone **32**.

Yield: 2.63 g (32%); yellowish oil.

IR (neat): 2936, 2861, 1711, 1644 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.93–5.78 (m, 1 H), 5.72 (q, *J* = 6.9 Hz, 1 H), 5.22 (dddd, *J* = 17.3 Hz, 1.7 Hz, 1.7 Hz, 1.7 Hz, 1 H), 5.12 (dddd, *J* = 10.4 Hz, 1.7 Hz, 1.4 Hz, 1.4 Hz, 1 H), 3.93–3.87 (m, 4 H), 3.29 (dd, *J* = 12.7 Hz, 5.6 Hz, 1 H), 2.37–2.23 (m, 1 H), 2.12–1.81 (m, 4 H), 1.78–1.60 (m, 2 H), 1.55 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 209.7 (C), 134.9 (CH), 134.3 (C), 126.5 (CH), 116.7 (CH_2), 73.6 (CH_2), 70.6 (CH_2), 51.2 (CH), 42.0 (CH_2), 31.6 (CH_2), 26.6 (CH_2), 25.3 (CH_2), 13.8 (CH_3).

HRMS (EI): *m*/*z* [M^+ – $CH_2CH{=}CH_2$] calcd for $C_{10}H_{15}O_2$: 167.1072; found: 167.1075.

(±)-(1*R*,2*R*)-2-[(*E*)-1-(Allyloxy)but-2-en-2-yl]-1-[1-(ethylthio)vinyl]cyclohexanol (28)
To a soln of ethyl(vinyl)sulfane (0.62 mL, 6.1 mmol) and TMEDA (0.92 mL, 6.1 mmol) in Et_2O (10 mL) was added dropwise *n*-BuLi (2.5 mL, 6.1 mmol, 2.4 M in hexanes) at 0 °C. The mixture was warmed to r.t. and stirred for 15 min. A soln of ketone **32** (212 mg, 1 mmol) in Et_2O (2 mL) was added to the reaction mixture. After stirring for 2 h, H_2O (50 mL) was added and the mixture extracted with Et_2O (3 × 100 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (EtOAc–hexanes, 20:80) to give the title product.

Yield: 126 mg (43%); yellowish oil.

IR (neat): 3383, 2937, 1646 cm^{-1}.

^1H NMR (500 MHz, C_6D_6): δ = 5.91–5.83 (m, 1 H), 5.82 (q, *J* = 6.8 Hz, 1 H), 5.40 (d, *J* = 2.0 Hz, 1 H), 5.30 (dddd, *J* = 17.3 Hz, 1.7 Hz, 1.7 Hz, 1.7 Hz, 1 H), 5.12 (dddd, *J* = 10.5 Hz, 1.5 Hz, 1.5 Hz, 1.4 Hz, 1 H), 4.82 (s, 1 H), 4.17 (d, *J* = 11.7 Hz, 1 H), 3.94–3.89 (m, 1 H), 3.93 (s, 1 H), 3.62 (dddd, *J* = 12.9 Hz, 5.7 Hz, 1.5 Hz, 1.5 Hz, 1 H), 3.31 (dd, *J* = 12.6 Hz, 3.2 Hz, 1 H), 2.57–2.45 (m, 2 H), 2.29–2.12 (m, 4 H), 1.88–1.83 (m, 1 H), 1.81 (d, *J* = 6.9 Hz, 3 H), 1.68–1.62 (m, 1 H), 1.49–1.40 (m, 2 H), 1.16 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (125 MHz, C_6D_6): δ = 154.9 (C), 137.7 (C), 134.2 (CH), 129.9 (CH), 116.6 (CH_2), 103.9 (CH_2), 76.4 (C), 74.0 (CH_2), 69.7 (CH_2), 44.8 (CH), 40.1 (CH_2), 28.3 (CH_2), 26.6 (CH_2), 26.1 (CH_2), 21.8 (CH_2), 13.6 (CH_3), 12.7 (CH_3).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{17}H_{28}O_2S$: 296.1810; found: 296.1799.

(1*S*,2*S*,4*R*,4a*S*,8a*S*)-1-Allyl-4-(ethylthio)-2-methyloctahydro-1*H*-4a,1-(epoxymethano)naphthalen-10-ol (27)
To a soln of **28** (14 mg, 0.046 mmol) in toluene (15 mL) was added Et_3N (0.02 mL, 0.19 mmol). The resulting soln was degassed using Ar (30 min) and then heated at 200 °C in a sealed tube for 48 h. The mixture was cooled to r.t. and then concentrated. The residue was purified by flash chromatography (EtOAc–hexanes, 20:80) to give the desired lactol.

Yield: 9 mg (65%); yellowish oil.

IR (neat): 3403, 2926, 2851, 1641 cm^{-1}.

^1H NMR (500 MHz, C_6D_6): δ = 5.76–5.68 (m, 1 H), 5.21–5.14 (m, 2 H), 4.88 (d, *J* = 3.6 Hz, 1 H), 2.64–2.52 (m, 2 H), 2.30 (d, *J* = 3.6 Hz, 1 H), 2.25 (dd, *J* = 11.6 Hz, 5.6 Hz, 1 H), 2.14 (dd, *J* = 15.6 Hz, 8.4 Hz, 1 H), 2.09–2.02 (m, 1 H), 1.99 (ddd, *J* = 12.8 Hz, 5.6 Hz, 5.2 Hz, 1 H), 1.76–1.30 (m, 6 H), 1.26 (t, *J* = 7.4 Hz, 3 H), 1.19 (dd, *J* = 11.9 Hz, 6.3 Hz, 1 H), 1.08–0.99 (m, 2 H), 0.80 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (125 MHz, C_6D_6): δ = 135.7 (CH), 117.0 (CH_2), 99.1 (CH), 85.4 (C), 54.6 (CH), 52.5 (C), 50.1 (CH), 38.6 (CH_2), 35.7 (CH), 33.5 (CH_2), 31.6 (CH_2), 25.3 (CH_2), 25.2 (CH_2), 24.5 (CH_2), 22.2 (CH_2), 16.3 (CH_3), 15.4 (CH_3).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{17}H_{28}O_2S$: 296.1810; found: 296.1818.

(±)-(1*R*,2*S*,4*R*,4a*S*,8a*S*)-1-Allyl-4-(ethylthio)-1,2-dimethyldecahydronaphthalen-4a-ol (33)
A soln of lactol **27** (310 mg, 1.04 mmol) in ethylene glycol (10 mL) was degassed under reduced pressure for 45 min, after which hydrated hydrazine (0.25 mL, 5.2 mmol) was added. The soln was heated at 130 °C for 1 h and then cooled to r.t. KOH (580 mg, 10.4 mmol) was added and the resulting mixture heated at 210 °C for 2 h. The mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 50 mL). The combined organic phase was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (EtOAc–hexanes, 3:97) to give alkene **33**.

Yield: 249 mg (85%); colorless oil.

IR (neat): 3528, 3074, 2930, 1643 cm^{-1}.

^1H NMR (500 MHz, C_6D_6): δ = 5.79–5.70 (m, 1 H), 5.11 (d, *J* = 10.2 Hz, 1 H), 5.04 (d, *J* = 17.0 Hz, 1 H), 2.34–2.28 (m, 3 H), 2.13–1.88 (m, 4 H), 1.79–1.65 (m, 4 H), 1.56–1.44 (m, 4 H), 1.16–1.08 (m, 5 H), 0.99 (s, 3 H), 0.91–0.86 (m, 1 H), 0.83 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (125 MHz, C_6D_6): δ = 135.2 (CH), 117.1 (CH_2), 74.1 (C), 57.0 (CH), 48.5 (CH), 41.8 (CH_2), 40.0 (CH_2), 39.6 (C), 37.8 (CH), 35.9 (CH_2), 27.6 (CH_2), 27.2 (CH_2), 22.1 (CH_2), 22.0 (CH_2), 17.0 (CH_3), 15.9 (CH_3), 15.6 (CH_3).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{17}H_{30}OS$: 282.2017; found: 282.1995.

(±)-(1*S*,2*R*,4*S*,4a*R*,8a*R*)-4-(Ethylthio)-1-{4-[(1*R*,2*S*,4*R*,4a*S*,8a*S*)-4-(ethylthio)-4a-hydroxy-1,2-dimethyldecahydronaphthalen-1-yl]but-2-enyl}-1,2-dimethyldecahydronaphthalen-4a-ol (35)
To a degassed soln of **33** (22 mg, 0.077 mol) in CH_2Cl_2 (2 mL) was added Grubbs II catalyst (7 mg, 0.0077 mol) under Ar. After heating at reflux temperature for 2 h, the soln was concentrated. The residue was purified by flash chromatography (EtOAc–hexanes, 3:97) to give dimer **35**.

Yield: 21 mg (99%); white foam.

IR (neat): 3516, 2929, 2855, 1446 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 5.45–5.43 (m, 2 H), 2.55–2.45 (m, 2 H), 2.40–2.30 (m, 4 H), 2.20–2.05 (m, 4 H), 2.00–1.85 (m, 4 H), 1.80–1.20 (m, 22 H), 1.10–1.00 (m, 6 H), 1.06 (s, 6 H), 0.93 (d, *J* = 6.7 Hz, 6 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 129.0, 74.1, 57.1, 48.7, 40.6, 40.2, 39.9, 37.9, 35.8, 27.6, 27.4, 22.1, 22.0, 16.9, 15.9, 15.4.

HRMS (EI): *m*/*z* [M^+] calcd for $C_{32}H_{56}O_2S_2$: 536.3722; found: 536.3713.

(±)-(1*S*,2*R*,4a*S*,8a*R*)-1-{4-[(1*R*,2*S*,4a*R*,8a*S*)-4a-Hydroxy-1,2-dimethyldecahydronaphthalen-1-yl]but-2-enyl}-1,2-dimethyldecahydronaphthalen-4a-ol (36)

To a soln of Raney nickel (180 mL) in H_2O (1 mL) was added a soln of dimer **35** (9 mg, 0.017 mmol) in THF (3 mL) and the mixture heated at reflux temperature for 18 h. The resulting suspension was filtered through Celite then concentrated. The residue was purified by flash chromatography (EtOAc–hexanes, 8:92) to give the title product **36**.

Yield: 7 mg (98%); white foam.

IR (neat): 3491, 2926, 2858, 1446 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 5.35–5.33 (m, 2 H), 2.25–2.15 (m, 2 H), 2.00–1.90 (m, 2 H), 1.80–1.60 (m, 4 H), 1.60–1.40 (m, 5 H), 1.40–1.20 (m, 21 H), 1.03 (s, 6 H), 0.98 (d, *J* = 6.7 Hz, 6 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 129.0, 71.1, 47.4, 42.5, 41.5, 40.4, 39.8, 37.3, 27.2, 26.8, 21.7, 21.4, 16.9, 16.0.

(±)-2-[(1*R*,2*S*,4a*R*,8a*S*)-4a-Hydroxy-1,2-dimethyldecahydronaphthalen-1-yl]acetaldehyde (37)

To a soln of dimer **36** (42 mg, 0.10 mmol) in THF (2.5 mL) and H_2O (0.5 mL) was added OsO_4 (4% in H_2O, 0.012 mmol, 0.07 mL) and sodium periodate (128 mg, 0.60 mmol). The mixture was stirred for 2 h then sat. aq Na_2SO_3 soln (5 mL) was added. After stirring for 30 min, the mixture was extracted with EtOAc (3 × 20 mL). The combined organic phase was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (EtOAc–hexanes, 10:90) to give the desired product.

Yield: 21 mg (47%); colorless oil.

IR (neat): 3481, 2925, 2862, 1712 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 9.62 (dd, *J* = 3.4 Hz, 3.1 Hz, 1 H), 2.15 (dd, *J* = 14.8 Hz, 3.4 Hz, 1 H), 2.07 (dd, *J* = 14.8 Hz, 3.1 Hz, 1 H), 1.74–1.62 (m, 2 H), 1.55–1.01 (m, 12 H), 0.89 (s, 3 H), 0.87 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 201.7 (CH), 70.8 (C), 50.6 (CH_2), 49.1 (CH), 42.0 (CH_2), 40.91 (CH_2), 40.89 (C), 39.1 (CH), 26.8 (CH_2), 26.5 (CH_2), 21.7 (CH_2), 21.4 (CH_2), 16.3 (CH_3), 16.2 (CH_3).

HRMS (EI): *m*/*z* [$M^+ - C_2H_3O$] calcd for $C_{12}H_{21}O$: 181.1592; found: 181.1600.

(±)-(1*R*,2*S*,4a*R*,8a*S*)-1-[2-(Furan-3-yl)-2-hydroxyethyl]-1,2-dimethyldecahydronaphthalen-4a-ol (38)

To a soln of 3-bromofuran (0.02 mL, 0.126 mmol) in Et_2O (4 mL) was added *t*-BuLi (0.17 mL, 0.238 mmol, 1.4 M in pentane) at –78 °C. After stirring for 2 h, sat. aq NH_4Cl soln (6 mL) was added. The mixture was extracted with EtOAc (3 × 15 mL). The combined organic phase was washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (EtOAc–hexanes, 10:90) to give furan **38** as a mixture of diastereomers (1:1).

Yield: 11 mg (75%); yellowish oil.

IR (neat): 3434, 2925, 2858, 1442 cm^{-1}.

^1H NMR (500 MHz, C_6D_6): δ = 7.16–7.12 (m, 2 H), 6.26–6.24 (m, 1 H), 4.59–4.57 (m, 1 H), 2.01–1.13 (m, 16 H), 1.09 and 0.82 (d, *J* = 6.7 Hz, 3 H), 1.00 (s, 3 H).

^{13}C NMR (125 MHz, C_6D_6): δ (diastereomer A) = 143.2 (CH), 138.1 (CH), 132.0 (C), 108.6 (CH), 71.3 (C), 63.2 (CH), 47.8 (CH), 45.1 (CH_2), 42.6 (CH_2), 41.4 (CH_2), 39.2 (C), 37.4 (CH), 27.0 (CH_2), 26.9 (CH_2), 22.0 (CH_2), 21.7 (CH_2), 17.2 (CH_3), 16.2 (CH_3).

^{13}C NMR (125 MHz, C_6D_6): δ (diastereomer B) = 143.2 (CH), 138.3 (CH), 131.6 (C), 108.7 (CH), 71.1 (C), 63.4 (CH), 47.3 (CH), 44.9 (CH_2), 42.5 (CH_2), 41.4 (CH_2), 39.1 (C), 37.9 (CH), 27.0 (CH_2), 26.8 (CH_2), 21.9 (CH_2), 21.6 (CH_2), 17.4 (CH_3), 16.7 (CH_3).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{18}H_{28}O_3$: 292.2038; found: 292.2064.

(±)-1-(Furan-3-yl)-2-[(1*R*,2*S*,4a*R*,8a*S*)-4a-hydroxy-1,2-dimethyldecahydronaphthalen-1-yl]ethyl Acetate (39)

Ac_2O (0.06 mL, 0.633 mmol) was added to a soln of **38** (11 mg, 0.038 mmol) in pyridine (0.8 mL) and CH_2Cl_2 (3 mL). After stirring overnight, DMAP (10 mg, 0.082 mmol) was added and the mixture stirred for a further 6 h. Sat. aq NH_4Cl soln (6 mL) was added and the mixture extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (EtOAc–hexanes, 10:90) to give acetate **39** as a mixture of diastereomers (1:1).

Yield: 10 mg (80%); yellowish oil.

IR (neat): 3535, 3148, 2937, 1735 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 7.28 and 7.25 (m, 1 H), 7.01–6.99 (m, 1 H), 6.28–6.26 (m, 1 H), 6.10–6.05 (m, 1 H), 2.14 and 2.01 (dd, *J* = 15.9 Hz, 8.6 Hz, 1 H), 1.82–1.69 (m, 4 H), 1.67 and 1.63 (s, 3 H), 1.60–1.12 (m, 13 H), 1.02 and 0.68 (d, *J* = 6.7 Hz, 3 H), 0.93 (s, 3 H).

^{13}C NMR (100 MHz, C_6D_6): δ (diastereomer A) = 169.3 (C), 143.3 (CH), 140.0 (CH), 128.1 (C), 109.0 (CH), 71.1 (C), 64.8 (CH), 47.4 (CH), 42.6 (CH_2), 41.9 (CH_2), 41.3 (CH_2), 39.3 (C), 38.0 (CH), 26.9 (CH_2), 26.6 (CH_2), 21.6 (CH_2), 21.5 (CH_2), 20.6 (CH_3), 17.2 (CH_3), 16.4 (CH_3).

^{13}C NMR (125 MHz, C_6D_6): δ (diastereomer B) = 169.3 (C), 143.3 (CH), 140.0 (CH), 128.3 (C), 109.0 (CH), 71.1 (C), 64.6 (CH), 47.8 (CH), 42.6 (CH_2), 41.9 (CH_2), 41.2 (CH_2), 39.3 (C), 37.4 (CH), 27.3 (CH_2), 26.7 (CH_2), 21.8 (CH_2), 21.7 (CH_2), 20.9 (CH_3), 17.1 (CH_3), 16.0 (CH_3).

HRMS (EI): *m*/*z* [$M^+ - C_2H_4O_2$] calcd for $C_{18}H_{26}O_2$: 274.1933; found: 274.1890.

Desdimethyl ambliol B (26)

A soln of **39** (20 mg, 0.060 mmol) in THF (3 mL) was added to a soln of Li (10 mg) in NH_3 (15 mL) at –78 °C. After stirring for 15 min, the excess Li was quenched by the addition of MeOH (5 mL) and the mixture was warmed to r.t. After complete evaporation of NH_3, H_2O (20 mL) was added and the mixture extracted with Et_2O (3 × 20 mL). The combined organic phase was washed with 10% NaOH (20 mL) and H_2O (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (EtOAc–hexanes, 7:93) to give the title product as a mixture of diastereomers (1:1).

Yield: 15.4 mg (93%); yellowish oil.

IR (neat): 3493, 2929, 2871 cm^{-1}.

^1H NMR (500 MHz, C_6D_6): δ = 7.34 (s, 1 H), 7.20 (s, 1 H), 6.25 (s, 1 H), 2.31 (td, *J* = 13.7 Hz, 4.3 Hz, 1 H), 2.18 (td, *J* = 13.7 Hz, 4.3 Hz, 1 H), 1.81–1.18 (m, 16 H), 0.84 (d, *J* = 6.7 Hz, 3 H), 0.83 (s, 3 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 142.8 (CH), 138.6 (CH), 125.8 (C), 111.1 (CH), 71.0 (C), 47.1 (CH), 42.4 (CH_2), 41.4 (CH_2), 38.6 (C),

37.7 (CH_2), 36.9 (CH), 27.1 (CH_2), 26.8 (CH_2), 21.6 (CH_2), 21.3 (CH_2), 18.2 (CH_2), 17.4 (CH_3), 15.9 (CH_3).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{18}H_{28}O_2$: 276.2089; found: 276.2062.

Acknowledgment

We thank NSERC, Merck Frosst Canada, Boehringer Ingelheim, the Government of Ontario (PREA) and the University of Ottawa for generous funding. N.G. thanks NSERC (PGS-M).

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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