Lithium Aldol Reactions of α-Chloroaldehydes Provide Versatile Building Blocks for Natural Product Synthesis

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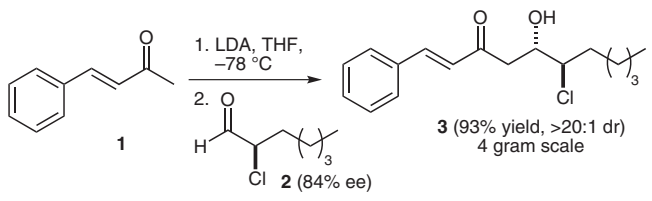
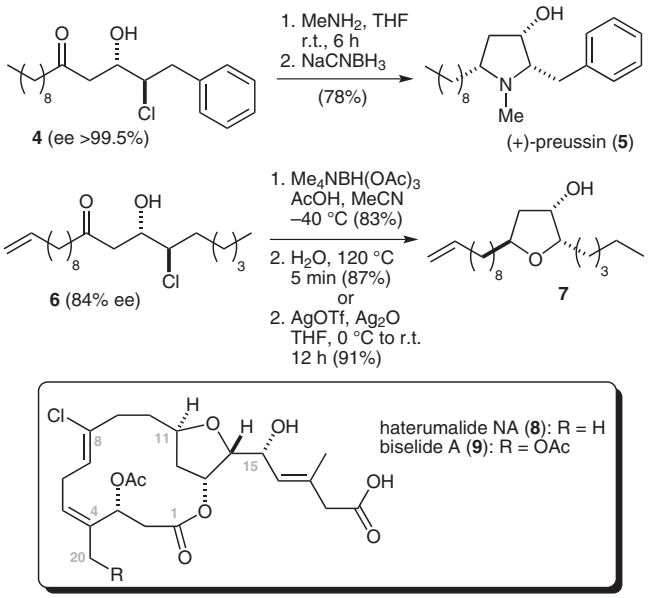
Abstract: The lithium aldol reaction of α-chloroaldehydes provides 1,2-*anti*-configured β-ketochlorohydrins. The scope of this reaction is demonstrated as well as its application to the synthesis of the C4–C15 segment of haterumalide NA.

Key words: α-chloroaldehydes, aldol reaction, stereoselective synthesis, heterocycles, natural products

The rapidly evolving field of organocatalysis continues to provide new building blocks for the asymmetric synthesis of natural products.[1] In particular, the construction of heterocyclic ring systems has been enabled through various strategies, including Michael addition/cyclization[2,3] or hetero-Diels–Alder reactions.[4] As part of our continuing studies on the stereoselective synthesis of biologically active natural products,[5] we have demonstrated that lithium aldol reactions of α-chloroaldehydes (e.g., **2**, Scheme 1) provide β-ketochlorohydrins (e.g., **3**), and that these aldol adducts are readily transformed into various heterocycles (Scheme 2). For example, treatment of β-ketochlorohydrins with a primary amine followed by a reducing agent leads to 3-hydroxypyrrolidines [e.g., (+)-preussin (**5**)].[5c] Alternatively, stereoselective reduction of the carbonyl function followed by treatment with AgOTf/Ag_2O[5a] or simply heating in water[5b] leads to 3-hydroxytetrahydrofurans (e.g., **7**). Importantly, employing the organocatalytic methods developed by MacMillan[6] and Jørgensen,[7] a range of optically enriched α-chloroaldehydes[8] are now readily available and their use renders enantioselectivity to these processes. Based on the demonstrated utility of β-ketochlorohydrins as building blocks for natural product and heterocycle synthesis,[5] and paucity of examples describing their preparation,[9,10] we sought to further explore and summarize the scope of lithium aldol reactions of α-chloroaldehydes. The results of this study along with the application of these methods to a concise synthesis of the C4 to C15 portion of the cytotoxic marine macrolides haterumalide NA (**8**)[11] and biselide A (**9**),[12] are described herein.



Scheme 1 Preparation of β-ketochlorohydrins from α-chloroaldehydes



Scheme 2 Previously demonstrated methods for heterocycle synthesis via β-ketochlorohydrins, and the cytotoxic marine macrolides haterumalide NA and biselide A

While several isolated examples of reactions involving α-chloroaldehydes and enolates have been reported,[9] the intermediate metal aldolates are often directly reduced to alkenes[9c] or converted into epoxides.[9a] As a notable exception, Stille reported the isolation of a β-ketochlorohydrin from the palladium-catalyzed coupling of tributylacetonyltin with α-chlorobutyraldehyde,[9b] and Barluenga demonstrated that the lithium enolate of ethyl acetate coupled smoothly with α-chloroisovaleraldehyde.[9d] Although in both cases the sense and degree of diastereoselectivity was not discussed, theoretical studies[13] predict the preferential formation of the 1,2-*anti* chlorohydrin in such reactions. Interestingly, Somfai has recently reported that the stereochemical outcome of Mukaiyama aldol reactions involving α-choroaldehydes is largely dependent on the size of the silyl enol ether, and that sterically hindered enol silanes afford 1,2-*syn* chlorohydrins preferentially.[10] Our interest in the reactions of α-chloroaldehydes[14] originally led us to explore the lithium aldol reaction of 4-phenyl-3-

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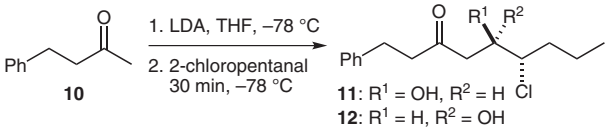
buten-2-one (**1**) with α-chloroheptanal (**2**)[5a] (Scheme 1), and we were delighted to find that this reaction affords the expected β-ketochlorohydrin **3** in excellent isolated yield on multi-gram scale. During the optimization of this process, however, we observed that the diastereochemical outcome was influenced by the rate of addition of chloroaldehyde to the lithium enolate. To gain further insight, a series of reactions were carried out at different temperatures and in different solvent mixtures. As summarized in Table 1, reaction of the lithium enolate derived from 4-phenyl-2-butanone (**10**) with 2-chloropentanal[5a] in hexane afforded a 3:1 mixture of the β-ketochlorohydrins **11** and **12**.[15] This ratio was improved to 7:1 when the reaction was carried out in THF (entry 5). It is important to note that these reactions are exothermic[16] and, as highlighted in entries 3–5, the diastereoselectivity is sensitive to reaction temperature. Consequently, α-chloroaldehydes are necessarily added slowly to the THF solution of lithium enolate in order to maintain the desired reaction temperature, and thus ensure optimal results (e.g., entry 5).

Table 1 Temperature and Solvent Effects on the Lithium Aldol Reaction

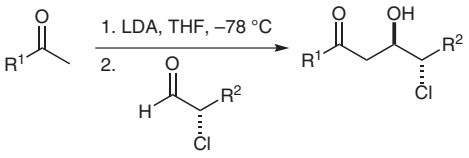


Entry	Solvent	Temp (°C)	Ratio **11**/**12**[a]
1	hexane	–78	3:1
2	hexane–Et_2O	–78	3.5:1
3	THF	–40	3:1
4	THF	–50	3.5:1
5	THF	–78	7:1

[a] Ratio determined by ^{1}H NMR spectral analysis of crude reaction mixtures.

As shown in Table 2, a wide variety of methyl ketone-derived lithium enolates engage in aldol reactions with linear or branched α-chloroaldehydes, providing 1,2-*anti* β-ketochlorohydrins in good to excellent yield and diastereoselectivity.[15] The relatively low level of stereocontrol in the aldol reactions involving α-chlorohydrocinnamaldehyde (e.g., entries 3, 8, and 10) was attributed to the β-phenyl substituent, as similarly poor diastereocontrol has been reported for the reaction of methyl ketone derived lithium enolates with α-benzyloxyhydrocinnamaldehyde.[17] In all cases, the minor 1,2-*syn* β-ketochlorohydrin (not shown) was readily separable by flash chromatography[18] and distinguishable by the downfield (typically >0.1 ppm in $CDCl_3$) chemical shift of the carbinol proton in the crude ^{1}H NMR spectra, relative to that of the 1,2-*anti* diastereomer. Finally, it was also found that lithium enolates derived from cyclohexanone also coupled smoothly with α-chloroaldehydes, affording the *anti*,*anti*-configured aldol adducts **21** and **22** in good yield (entries 11 and 12). As exemplified in Scheme 3 for **22**, the stereochemical assignment of these compounds was accomplished following reduction to the corresponding *syn*- and *anti*-diols, and subsequent conversion into the diastereomeric perhydrooxaindanes (e.g., **26** and **27**) in refluxing water.[5b] Notably, these tetrasubstituted tetrahydrofurans are available in only three steps from α-chlorohydrocinnamaldehyde and consequently, this methodology should find use in the synthesis of a variety of natural products that incorporate such heterocyclic frameworks [e.g., cheimonophyllon E[19] (**28**)].

Table 2 Lithium Aldol Reactions of α-Chloroaldehydes



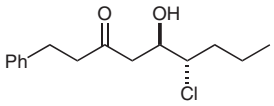
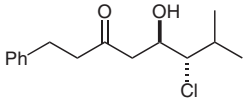
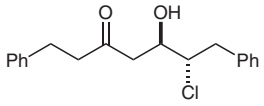
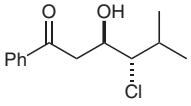
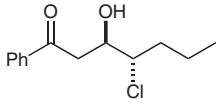
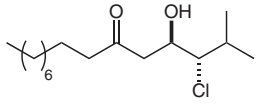
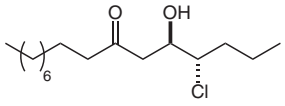
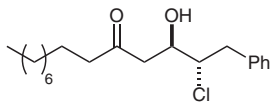
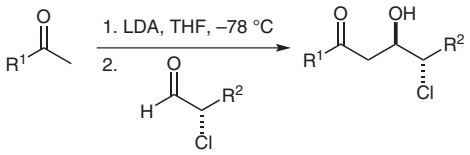
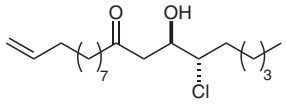
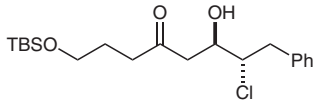
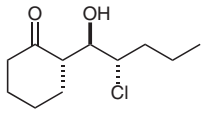
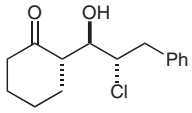
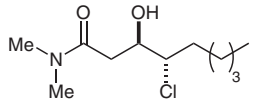
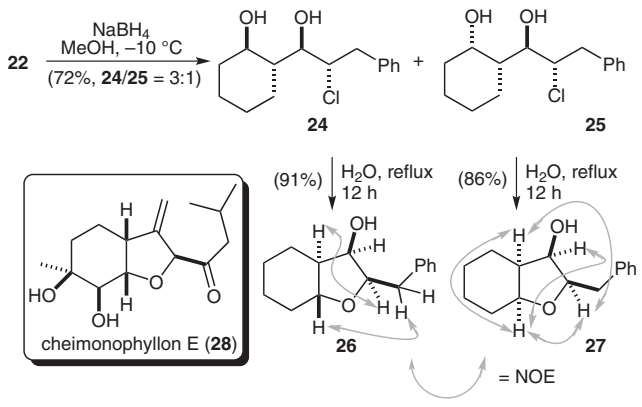
Entry	Product[a]	Yield (%)[b]	dr[c]
1	 **11**	80	7:1
2	 **12**	90	19:1
3	 **13**	75	6:1
4	 **14**	77	>20:1
5	 **15**	96	>20:1
6	 **16**	76	12:1
7	 **17**	74	ND
8	 **18**	63	4:1

Table 2 Lithium Aldol Reactions of α-Chloroaldehydes (continued)



Entry	Product[a]	Yield (%)[b]	dr[c]
9	 **19**	88	>20:1
10	 **20**	57	4:1
11	 **21**	76	9:1
12	 **22**	61	ND
13	 **23**	80	>20:1

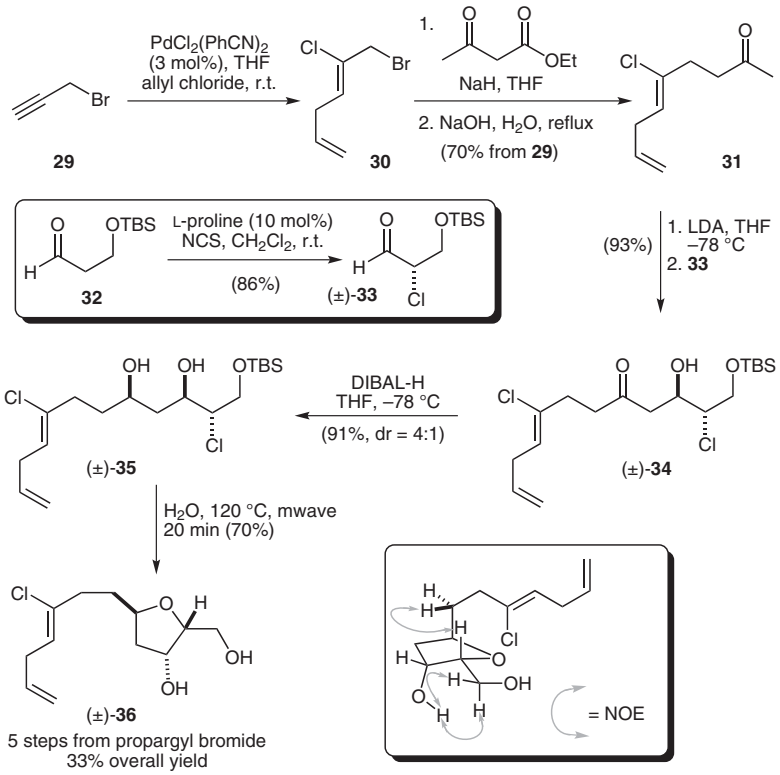
[a] Reaction conditions: To a cold (–78 °C) solution of lithium enolate was slowly added (over 15 min) the appropriate α-chloroaldehyde. The reaction was quenched with sat. aq NH_4Cl after 30 min.
[b] Isolated yield of single diastereomer.
[c] Diastereomeric ratio determined by analysis of ^1H NMR spectra recorded on crude reaction products in $CDCl_3$. ND = not determined.



Scheme 3 Synthesis of 9-oxabicyclo[4.3.0]nonanols and a structurally related natural product

Finally, the utility of β-ketochlorohydrins as building blocks for the preparation of both structurally and stereochemically complex natural products was demonstrated in a short synthesis of the C4–C15 portion of both haterumalide NA (**8**)[11] and biselide A (**9**)[12] (Scheme 2). Both of these macrolides have demonstrated potent anticancer activity[20] and, as a result, attracted considerable attention as targets for total synthesis.[21] As detailed in Scheme 4, our unique approach to the tetrahydrofuran core of these natural products initiated with the chloroallylation[22] of propargyl bromide (**29**), which afforded the vinyl chloride **30** in good yield. Alkylation of ethyl acetoacetate with this material, followed by decarboxylation[23] provided the desired methyl ketone **31** in excellent overall yield. The required α-chloroaldehyde **33** was accessed from the known aldehyde **32**[24] following treatment of the latter material with catalytic (10 mol%) L-proline and NCS in CH_2Cl_2.[7] Unfortunately, use of L-prolinamide as an organocatalyst, which should impart enantioselectivity to this chlorination reaction,[5,7,14] led to the production of significant amounts of acrolein via elimination of the β-silyloxy group. As such, the high yielding, albeit racemic process, described in Scheme 4 was adopted for these proof of concept studies. With the desired coupling partners in hand, treatment of the lithium enolate derived from **31** with the α-chloroaldehyde **33**, afforded the β-ketochlorohydrin **34** in excellent yield and diastereoselectivity. A *syn*-selective reduction of the ketone function in **34**,[5a] followed by heating the resulting chlorodiol **35** in water[5b] provided the tetrahydrofuranol **36** [the C4–C15 portion of haterumalide NA (**8**) and biselide A (**9**)] in excellent overall yield. The relative stereochemistry of the tetrahydrofuran core in **36** was confirmed by NOE analysis (see inset) and comparison of both ^1H and ^{13}C NMR spectroscopic data to that reported for a closely related tetrahydrofuran prepared by Snider en route to haterumalide NA.[21b] Remarkably, this advanced synthetic precursor to both macrolides is available in five steps from propargyl bromide and consequently, this process should prove useful in defining a concise synthesis of these potentially important natural products, work that is currently underway in our laboratory.

In summary, we have demonstrated that a wide variety of α-chloroaldehydes and ketones engage in lithium aldol reactions, providing 1,2-*anti* configured β-ketochlorohydrins in good to excellent yield and stereoselectivity. Based on the demonstrated utility of these compounds as building blocks for the rapid and stereoselective synthesis of heterocycles, and the fact that optically active α-chloroaldehydes are readily available through organocatalysis, these methods should find use in the synthesis of various natural products. The efficiency of these processes was also demonstrated in a short synthesis of the C4–C15 fragment of haterumalide NA and biselide A, that incorporates the functionalized tetrahydrofuran core and (*Z*)-vinyl chloride functionalities found in both natural products.



Scheme 4 Synthesis of the C4–C15 fragment of haterumalide NA (**8**) and biselide A (**9**)

All reactions were performed under an atmosphere of dry argon using oven-dried glassware unless otherwise specified. All commercially obtained reagents were used as received without further purification unless otherwise noted. Reactions performed at r.t. were at approximately 22 °C. Flash chromatography was carried out with 230–400 mesh ASTM silica gel (E. Merck, Silica Gel 60). THF was freshly distilled from sodium/benzophenone and CH_2Cl_2 was distilled from CaH_2 prior to use. Concentration and removal of trace solvents was performed via a Büchi rotary evaporator using an acetone/dry ice condenser and a Welch vacuum pump. NMR spectra were recorded using $CDCl_3$, CD_3OD, or C_6D_6 as the solvent. Signal positions (δ) are given in parts per million from tetramethylsilane (δ = 0) and were measured relative to the signal of the solvent ($CDCl_3$: δ = 7.26, ^{1}H NMR; δ = 77.16, ^{13}C NMR; CD_3OD: δ = 3.31, ^{1}H NMR; δ = 49.0, ^{13}C NMR; C_6D_6: δ = 7.16, ^{1}H NMR; δ = 128.06, ^{13}C NMR). Coupling constants (*J* values) are given in hertz (Hz) and are reported to the nearest 0.1 Hz. ^{1}H NMR spectral data are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet), coupling constants, number of protons, assignment (where possible). NMR spectra were recorded on a Bruker Avance 600 equipped with a QNP or TCI cryoprobe (600 MHz) or Bruker 400 (400 MHz). Assignments of ^{1}H and ^{13}C NMR spectra are based on analysis of ^{1}H-^{1}H COSY, HMBC, HSQC, TOCSY, and 1D NOESY spectra. IR spectra were recorded on a MB-series Bomem/Hartman & Braun Fourier transform spectrophotometer with NaCl plates. Only selected, characteristic absorption data are provided for each compound. Chemical ionization (CI) mass spectra were recorded on a Varian 4000 GC/MS/MS mass spectrometer. High-resolution mass spectra were performed on an Agilent 6210 TOF LC/MS mass spectrometer.

1,2-*anti* β-Ketochlorohydrins; General Procedure

To a cold (0 °C) stirred solution of *i*-Pr_2NH (1.2 equiv) in THF (0.1 M) was added *n*-BuLi in hexanes (2.5 M, 1.2 equiv) and the mixture was stirred at 0 °C for 30 min, then cooled to –78 °C and the ketone (1 equiv) was added slowly in one portion. The resulting solution was stirred for an additional 30 minutes at –78 °C. After this time, a solution of α-chloroaldehyde[25] (1.2 equiv) in THF (1.0 M) was added dropwise over 15 min at –78 °C, and the resulting mixture was stirred for an additional 30 minutes. Sat. aq NH_4Cl (25 mL) was then added, and the mixture was allowed to warm to r.t. The reaction mixture was then diluted with EtOAc (10 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 15 mL) and the combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, hexanes–EtOAc) yielded the pure 1,2-*anti* β-ketochlorohydrin.[15]

(1*E*,5*S**,6*R**)-6-Chloro-5-hydroxy-1-phenylundec-1-en-3-one (3)

Isolated as a white solid (93% yield); mp 51–53 °C.

IR (thin film): 3424, 2950, 2923, 2860, 1659, 1177, 1073 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 16.1 Hz, 1 H), 7.57 (m, 2 H), 7.41 (m, 3 H), 6.76 (d, *J* = 16.1 Hz,1 H), 4.21 (m, 1 H), 3.98 (ddd, *J* = 3.1, 6.2, 9.4 Hz, 1 H), 3.52 (d, *J* = 4.8 Hz, 1 H), 3.12 (dd, *J* = 2.8, 17.4 Hz, 1 H), 3.03 (dd, *J* = 8.5, 17.4 Hz, 1 H,) 1.95 (m, 1 H), 1.70 (m, 1 H), 1.63 (m, 1 H), 1.42 (m, 1 H), 1.33 (m, 4 H), 0.90 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 200.5, 144.3, 134.3, 131.1, 129.3, 128.7, 126.4, 71.4, 66.3, 43.0, 34.1, 31.5, 26.2, 22.7, 14.2.

HRMS: *m*/*z* calcd for $C_{17}H_{24}ClO_2$: 295.1465 (M + H); found: 295.1468 (M + H).

(5*R**,6*S**)-6-Chloro-5-hydroxy-1-phenylnonan-3-one (11)

Isolated as a colorless solid (80% yield); mp 41–45 °C.

IR (thin film): 3463, 3028, 2964, 2875, 1708, 1614, 1048, 755 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.32 (m, 2 H), 7.15–7.23 (m, 3 H), 4.06–4.13 (m, 1 H), 3.88–3.94 (m, 1 H), 3.18 (d, *J* = 5.1 Hz, 1

H), 2.88–2.95 (m, 2 H), 2.73–2.85 (m, 4 H), 1.78–1.87 (m, 1 H), 1.58–1.68 (m, 1 H), 1.38–1.45 (m, 1 H), 0.95 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.5, 140.6, 128.6, 128.3, 126.3, 70.9, 65.8, 45.19, 45.17, 35.8, 29.5, 19.6, 13.5.

HRMS: *m*/*z* calcd for $C_{15}H_{21}ClO_2$: 291.1122 (M + Na); found: 291.1131 (M + Na).

(5*R,6*S**)-6-Chloro-5-hydroxy-7-methyl-1-phenyloctan-3-one (12)**
Isolated as a colorless solid (90% yield); mp 30–35 °C.

IR (thin film): 3943, 3688, 2685, 1704, 1421 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.36 (m, 2 H), 7.17–7.27 (m, 3 H), 4.09–4.19 (m, 1 H), 3.77 (dd, *J* = 3.6, 8.4 Hz, 1 H), 3.40 (d, *J* = 5.4 Hz, 1 H), 3.02–2.80 (m, 5 H), 2.73 (dd, *J* = 8.4, 17.8 Hz, 1 H), 2.36 (m, 1 H), 1.03 (d, *J* = 6.8 Hz, 3 H), 0.98 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.3, 140.5, 128.5, 128.2, 126.2, 71.4, 69.0, 46.0, 45.1, 29.4, 29.1, 20.6, 15.8.

HRMS: *m*/*z* calcd for $C_{15}H_{21}ClO_2$: 291.1119 (M + Na); found: 291.1122 (M + Na).

(5*R,6*S**)-6-Chloro-5-hydroxy-1,7-diphenylheptan-3-one (13)**
Isolated as a colorless solid (75% yield); mp 56–60 °C.

IR (thin film): 3463, 3028, 2924, 2360, 1704, 1491, 1455, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.16 (m, 10 H), 4.15–4.07 (m, 2 H), 3.41 (d, *J* = 4.7 Hz, 1 H), 3.30 (dd, *J* = 3.8, 15 Hz, 1 H), 2.98–2.75 (m, 7 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.7, 129.5, 128.6, 128.4, 128.3, 126.9, 126.3, 70.5, 65.5, 45.2, 45.1, 40.0, 29.5.

HRMS: *m*/*z* calcd for $C_{19}H_{21}ClO_2$: 317.1300 (M + H); found: 317.1303 (M + H).

(3*R,4*S**)-4-Chloro-3-hydroxy-5-methyl-1-phenylhexan-1-one (14)**
Isolated as a colorless solid (77% yield); mp 110–115 °C.

IR (thin film): 3507, 3066, 2930, 1968, 1663 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.0 (d, *J* = 8.0 Hz, 2 H), 7.62 (tt, *J* = 1.2, 7.4 Hz, 1 H), 7.51 (t, *J* = 8.4 Hz, 2 H), 4.31 (ddt, *J* = 2.5, 4.9, 8.6 Hz, 1 H), 3.91 (dd, *J* = 3.5, 8.0 Hz, 1 H), 3.64 (d, *J* = 4.9 Hz, 1 H), 3.61 (dd, *J* = 2.5, 17.9 Hz, 1 H), 3.25 (dd, *J* = 8.4, 17.9 Hz, 1 H), 2.52–2.44 (m, 1 H), 1.07 (d, *J* = 6.8 Hz, 3 H), 1.03 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.1, 136.6, 133.8, 128.7, 128.2, 71.5, 69.3, 42.0, 29.0, 20.7, 15.7.

HRMS: *m*/*z* calcd for $C_{13}H_{17}ClO_2$: 263.0809 (M + Na); found: 263.0809 (M + Na).

(3*R,4*S**)-4-Chloro-3-hydroxy-1-phenylheptan-1-one (15)**
Isolated as a white solid (96% yield); mp 54–55 °C.

IR (thin film): 2962, 2954, 2922, 1681, 1597, 1449, 1377 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.4 Hz, 2 H), 7.61 (tt, *J* = 1.3, 7.4 Hz, 1 H), 7.49 (dt, *J* = 1.3, 7.4 Hz, 2 H), 4.30 (m, 1 H), 4.05 (ddd, *J* = 3.6, 6.6, 9.6 Hz, 1 H), 3.49 (d, *J* = 4.8 Hz, 1 H), 3.42 (dd, *J* = 2.4, 17.4 Hz, 1 H), 3.31 (dd, *J* = 9.0, 17.4 Hz, 1 H), 1.94 (m, 1 H), 1.76–1.63 (m, 2 H), 1.47 (m, 1 H), 0.97 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 200.4, 136.6, 133.7, 128.7, 128.2, 71.1, 65.8, 41.1, 36.0, 19.6, 13.5.

HRMS: *m*/*z* calcd for $C_{13}H_{18}ClO_2$: 241.0995 (M – H_2O + H); found: 241.1010 (M – H_2O + H).

(3*S,4*R**)-3-Chloro-4-hydroxy-2-methylpentadecan-6-one (16)**
Isolated as a colorless solid (76% yield); mp 45–50 °C.

IR (thin film): 3688, 3054, 2685, 1694 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.14–4.06 (m, 1 H), 3.78 (dd, *J* = 3.7, 8.7 Hz, 1 H), 3.49 (d, *J* = 5.2 Hz, 1 H), 2.99 (dd, *J* = 2.4, 17.8 Hz, 1 H), 2.71 (dd, *J* = 8.4, 17.8 Hz, 1 H), 2.47 (t, *J* = 7.5 Hz, 2 H), 2.43–2.33 (m, 1 H), 1.64–1.55 (m, 2 H), 1.34–1.22 (m, 12 H), 1.03 (d, *J* = 6.6 Hz, 3 H), 0.98 (d, *J* = 6.6 Hz, 3 H), 0.89 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.9, 71.4, 69.1, 45.6, 43.8, 31.8 29.4, 29.3, 29.2, 29.1, 29.0, 23.6, 22.6, 20.7, 15.7, 14.1.

HRMS: *m*/*z* calcd for $C_{16}H_{31}ClO_2$: 291.2083 (M + H); found: 291.2085 (M + H).

(4*S,5*R**)-4-Chloro-5-hydroxyhexadecan-7-one (17)**
Isolated as a white solid (74% yield); mp 35–38 °C.

IR (thin film): 3435, 2923, 2859, 1708, 1458, 1374, 1068, 754 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.10 (m, 1 H), 3.92 (m, 1 H), 3.32 (d, *J* = 4.8 Hz, 1 H), 2.82 (dd, *J* = 2.9, 17.6 Hz, 1 H), 2.75 (dd, *J* = 8.5, 17.6 Hz, 1 H), 2.46 (t, *J* = 7.5 Hz, 2 H), 1.85 (m, 1 H), 1.68–1.55 (m, 4 H), 1.42 (m, 1 H), 1.33–1.21 (m, 12 H), 0.94 (t, *J* = 7.3 Hz, 3 H), 0.88 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 212.3, 71.2, 65.9, 45.0, 44.1, 36.1, 32.1, 29.6, 29.6, 29.5, 29.3, 23.8, 22.9, 19.8, 14.3, 13.7.

HRMS: *m*/*z* calcd for $C_{16}H_{31}ClO_2$: 313.1905 (M + Na); found: 313.1901 (M + Na).

(2*S,3*R**)-2-Chloro-3-hydroxy-1-phenyltetradecan-5-one (18)**
Isolated as a white solid (63% yield); mp 60.5–61.0 °C.

IR (thin film): 3349, 2916, 2849, 1698, 698 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.34–7.30 (m, 2 H), 7.27–7.24 (m, 3 H), 4.12–4.07 (m, 2 H), 3.52 (d, *J* = 4.8 Hz, 1 H), 3.32 (dd, *J* = 3.1, 14.4 Hz, 1 H), 2.95 (dd, *J* = 8.6, 14.4 Hz, 1 H), 2.91 (dd, *J* = 2.1, 17.8 Hz, 1 H), 2.78 (dd, *J* = 8.1, 17.8 Hz, 1 H), 2.45 (t, *J* = 7.4 Hz, 2 H), 1.58 (m, 2 H), 0.88 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 212.5, 137.5, 129.8, 128.6, 127.1, 70.8, 65.8, 45.0, 44.1, 40.3, 32.1, 29.6, 29.6, 29.5, 29.3, 23.8, 22.9, 14.3.

HRMS: *m*/*z* calcd for $C_{20}H_{31}ClO_2$: 339.2085 (M + H); found: 339.2077 (M + H).

(6*S,7*R**)-6-Chloro-7-hydroxynonadec-18-en-9-one (19)**
Isolated as a white solid (88% yield); mp 30 °C.

IR (thin film): 3416, 2921, 2852, 1698, 1087 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.80 (tdd, *J* = 6.5, 10.5, 17.5 Hz, 1 H), 4.98 (dd, *J* = 1.5, 17.5 Hz, 1 H), 4.92 (dd, *J* = 1.5, 10.5 Hz, 1 H), 4.09 (m, 1 H), 3.90 (ddd, *J* = 3.0, 6.0, 9.5 Hz, 1 H), 3.31 (d, *J* = 5.5 Hz, 1 H), 2.81 (dd, *J* = 3.0, 9.5 Hz, 1 H), 2.74 (dd, *J* = 8.5, 9.5 Hz, 1 H), 2.45 (t, *J* = 7.5 Hz, 2 H), 1.99 (dd, *J* = 7.0, 15.0 Hz, 2 H), 1.88 (m, 1 H), 1.67–1.57 (m, 4 H), 1.46–1.23 (m, 15 H), 0.89 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 212.0, 139.1, 114.1, 70.9, 66.0, 44.8, 43.8, 33.81, 33.77, 31.2, 29.29, 29.26, 29.1, 29.0, 28.9, 26.0, 23.5, 22.5, 14.0.

HRMS: *m*/*z* calcd for $C_{19}H_{36}ClO_2$: 331.2404 (M + H); found: 331.2402 (M + H).

(6*R,7*S**)-1-(*tert*-Butyldimethylsilyloxy)-7-chloro-6-hydroxy-8-phenyloctan-4-one (20)**
Isolated as a clear, colorless oil (57% yield).

IR (neat): 3446, 2952, 2927, 2851, 2356, 1708, 1249, 698 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.34–7.30 (m, 2 H), 7.28–7.24 (m, 3 H), 4.14–4.08 (m, 2 H), 3.62 (t, *J* = 6.0 Hz, 2 H), 3.54 (d, *J* = 4.5 Hz, 1 H), 3.23 (dd, *J* = 3.7, 14.7 Hz, 1 H), 2.97–2.91 (m, 2 H), 2.80 (dd, *J* = 8.1, 17.7 Hz, 1 H), 2.58–2.54 (t, *J* = 7.2 Hz, 2 H), 1.83–1.77 (m, 2 H), 0.89 (s, 9 H), 0.04 (s, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 212.0, 137.5, 129.7, 128.6, 127.0, 70.7, 65.8, 62.2, 45.2, 40.4, 40.3, 26.7, 26.1, 18.5, –5.2.

HRMS: *m*/*z* calcd for $C_{20}H_{33}ClO_3Si$: 385.1960 (M + H); found: 385.1976 (M + H).

(2*S)-2-[(1′*R**,2′*S**)-2-Chloro-1-hydroxypentyl]cyclohexanone (21)**

Isolated as a colorless oil (76% yield).

IR (thin film): 3463, 3305, 2979, 1740, 1651, 1373 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.07 (dt, *J* = 2.6, 8.9 Hz, 1 H), 3.46–3.32 (m, 2 H), 3.05–2.96 (m, 1 H), 2.4–2.3 (m, 2 H), 2.17–1.55 (m, 9 H), 1.42 (m, 1 H), 0.93 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 215.8, 76.9, 64.1, 51.5, 43.1, 35.8, 32.6, 28.2, 25.1, 19.2, 13.5.

HRMS: *m*/*z* calcd for $C_{11}H_{19}ClO_2$: 241.0967 (M + Na); found: 241.0966 (M + Na).

(2*S)-2-[(1′*R**,2′*S**)-2-Chloro-1-hydroxy-3-phenylpropyl]cyclohexanone (22)**

Isolated as a colorless oil (61% yield).

IR (thin film): 3689, 3054, 1694, 1421 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.24 (m, 5 H), 4.34 (dt, *J* = 3.1, 8.8 Hz, 1 H), 3.56–3.45 (m, 3 H), 2.96 (dd, *J* = 8.8, 14.5 Hz, 1 H), 3.03–3.10 (m, 1 H), 2.43–2.35 (m, 2 H), 2.18–2.05 (m, 2 H), 1.99–1.91 (m, 2 H), 1.79–1.62 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 216.1, 137.6, 129.7, 128.2, 126.6, 76.7, 64.2, 51.2, 43.2, 40.1, 32.8, 28.3, 25.2.

HRMS: *m*/*z* calcd for $C_{15}H_{19}ClO_2$: 267.1142 (M + H); found: 267.1146 (M + H).

(3*R,4*S**)-4-Chloro-3-hydroxy-*N*,*N*-dimethylnonanamide (23)**

Isolated as a white solid (80% yield); mp 54–55 °C.

IR (thin film): 3347, 2961, 2874, 2772, 2447, 1771, 1709, 1643, 1467, 1171 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.80 (d, *J* = 4.4 Hz, 1 H), 4.00 (m, 1 H), 3.93 (m, 1 H), 3.03 (s, 3 H), 2.97 (s, 3 H), 2.76 (dd, *J* = 2.8, 16.4 Hz, 1 H), 2.64 (dd, *J* = 7.8, 16.4 Hz, 1 H), 2.02 (m, 1 H), 1.71–1.60 (m, 2 H), 1.44–1.27 (m, 6 H), 0.90 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4, 71.7, 65.7, 37.2, 35.23, 35.19, 34.2, 31.3, 25.9, 22.5, 14.0.

HRMS: *m*/*z* s calcd for $C_{11}H_{23}ClNO_2$: 236.1412 (M + H); found: 236.1404 (M + H).

(1*R,2*R**)-2-[(1′*R**,2′*S**)-2′-Chloro-1′-hydroxy-3-phenylpropyl]cyclohexan-1-ol (24) and (1*S**,2*R**)-2-[(1′*R**,2′*S**)-2′-Chloro-1′-hydroxy-3-phenylpropyl]cyclohexan-1-ol (25)**

To a cold (0 °C) stirred solution of **22** (68 mg, 0.25 mmol) in MeOH (2.5 mL) was added $NaBH_4$ (19 mg, 0.5 mmol) and the reaction mixture was stirred at 0 °C for 3 h. After this time, H_2O (5 mL) was added and the resulting mixture was then extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and concentrated to provide a colorless oil. Purification of the crude product by flash chromatography (silica gel, 4:1 hexanes–EtOAc) afforded **24** (36 mg, 54%) and **25** (12 mg, 18%).

24

Isolated as a clear, colorless oil.

IR (thin film): 3689, 3054, 2936, 1421 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.36–7.31 (m, 2 H), 7.30–7.22 (m, 3 H), 4.40 (dt, *J* = 2.8, 10.8 Hz, 1 H), 4.05–3.94 (m, 1 H), 3.66–3.57 (m, 1 H), 3.45 (d, *J* = 1.7 Hz, 1 H), 3.20 (dd, *J* = 2.8, 14.9 Hz, 1 H), 3.00 (dd, *J* = 10.8, 14.9 Hz, 1 H), 2.08–2.00 (m, 1 H), 1.81–1.62 (m, 3 H), 1.39–1.18 (m, 3 H), 1.14–1.01 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.9, 129.3, 128.4, 126.8, 81.2, 75.2, 66.9, 45.9, 36.7, 34.9, 27.3, 25.1, 24.2.

HRMS: *m*/*z* calcd for $C_{15}H_{21}ClO_2$: 269.1302 (M + H); found: 269.1303 (M + H).

25

IR (thin film): 3603, 3449, 2935, 2935, 2858, 1732, 1496 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.23 (m, 5 H), 4.43–4.39 (m, 1 H), 4.18 (dt, *J* = 2.8, 8.8 Hz, 1 H), 3.76 (d, *J* = 7.8 Hz, 1 H), 3.64 (dt, *J* = 4.1, 8.2 Hz, 1 H), 3.55 (dd, *J* = 2.8, 14.5 Hz, 1 H), 2.95 (dd, *J* = 9.5, 14.5 Hz, 1 H), 2.06–1.98 (m, 1 H), 1.95–1.74 (m, 4 H), 1.66–1.43 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.2, 129.7, 128.2, 126.6, 77.8, 67.9, 64.6, 40.6, 39.9, 33.7, 25.6, 24.3, 19.9.

HRMS: *m*/*z* calcd for $C_{15}H_{21}ClO_2$: 269.1302 (M + H); found: 269.1303 (M + H).

Tetrahydrofuran Formation; General Procedure

A stirred solution of the diol **24** or **25** in H_2O (0.1 M) was heated at reflux for 12 h. After this time, the solution was diluted with Et_2O and the Et_2O layer was washed with brine, dried ($MgSO_4$), and concentrated to provide a white solid, which was purified via flash chromatography (silica gel, hexanes–EtOAc).

(1*R,6*S**,7*R**,8*R**)-8-Benzyl-7-hydroxy-9-oxabicyclo[4.3.0]nonane (26)**

Isolated as a white solid (91% yield); mp 85–88 °C.

IR (thin film): 3608, 3053, 2937, 1265 cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6): δ = 7.30 (d, *J* = 7.5 Hz, 2 H), 7.20–7.14 (m, 2 H), 7.12–7.07 (m, 1 H), 4.19–4.14 (dt, *J* = 3.7, 7.2 Hz, 1 H), 3.67 (dt, *J* = 3.7, 10.9 Hz, 1 H), 3.57–3.53 (m, 1 H), 3.11–3.06 (dd, *J* = 7.2, 13.7 Hz, 1 H), 3.03–2.96 (dd, *J* = 7.2, 13.7 Hz, 1 H), 2.20–2.14 (m, 1 H), 1.57–1.48 (m, 2 H), 1.48–1.41 (m, 1 H), 1.32–0.81 (m, 6 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 129.4, 128.2, 128.0, 125.9, 83.8, 78.9, 72.8, 51.0, 36.3, 32.4, 25.5, 24.1, 23.8.

HRMS: *m*/*z* calcd for $C_{15}H_{20}O_2$: 233.1535 (M + H); found: 233.1536 (M + H).

(1*S,6*S**,7*R**,8*R**)-8-Benzyl-7-hydroxy-9-oxabicyclo[4.3.0]nonane (27)**

Isolated as a white solid (86% yield); mp 78–83 °C.

IR (thin film): 3609, 3054, 2934, 1421, 1265 cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6): δ = 7.30 (d, *J* = 7.2 Hz, 2 H), 7.20–7.16 (m, 2 H), 7.10–7.06 (m, 1 H), 3.93–3.89 (m, 1 H), 3.79–3.76 (t, *J* = 6.0 Hz, 1 H), 3.65–3.61 (m, 1 H), 3.02–2.93 (m, 2 H), 1.86–1.78 (m, 1 H), 1.76–1.67 (m, 1 H), 1.62–0.71 (m, 8 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 140.0, 129.5, 128.3, 126.0, 82.2, 75.2, 42.1, 37.1, 29.8, 29.7, 23.8, 22.1, 21.2.

HRMS: *m*/*z* calcd for $C_{15}H_{20}O_2$: 233.1536 (M + H); found: 233.1536 (M + H).

(*Z*)-5-Chlorononа-5,8-dien-2-one (31)

To a stirred solution of allyl chloride (4.05 mL, 50.0 mmol) in THF (60 mL) at r.t. was added sequentially bis(benzonitrile)palladium(II) chloride (115 mg, 0.3 mmol) and propargyl bromide (**29**; 1.1 g, 10 mmol) dropwise over 30 min. The reaction mixture was stirred for 2 h. After this time, the mixture was filtered over Celite, the filtrate was concentrated to provide the crude allyl bromide **30**, which was used directly in the next step without further purification. To a cold (–10 °C) stirred solution of NaH (0.55 g, 13.8 mmol) in THF (25 mL) was added ethyl acetoacetate (1.8 mL, 13.8 mmol) dropwise over 20 min. After this time, the freshly prepared allyl bromide **30** was added in one portion and the reaction mixture was allowed to warm to r.t. and the stirring was continued for 18 h. The resulting mixture was quenched with aq 1 N HCl (5 mL), diluted with Et_2O (20 mL), and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 15 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), and concentrated to provide a crude yellow oil. To this oil was added aq 5% NaOH (10 mL) and the mixture was heated at reflux for 2 h. The mixture was then acidified to pH 4 with concd HCl, diluted with Et_2O (20 mL), and the Et_2O layer was washed with sat. aq $NaHCO_3$ (15 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 15 mL) and the combined organic phases were washed with brine (25 mL), dried ($MgSO_4$), and concentrated to provide a yellow oil. Purification of the crude product by flash chromatography (silica gel, 6:1 hexanes–EtOAc) afforded **31** (1.2 g, 70%) as a clear oil.

IR (neat): 3080, 2979, 2920, 2229, 1718, 1432, 1362, 1162 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.78 (m, 1 H), 5.56 (t, *J* = 6.4 Hz, 1 H), 5.08–4.99 (m, 2 H), 2.91 (t, *J* = 6.4 Hz, 2 H), 2.71 (m, 2 H), 2.62 (m, 2 H), 2.17 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.5, 135.0, 134.1, 123.8, 115.4, 41.4, 33.5, 32.7, 30.1.

HRMS: *m/z* calcd for $C_9H_{13}ClO$: 173.0733 (M + H); found: 173.0732 (M + H).

(*S)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-chloropropanal (33)**

To a cold (0 °C) stirred solution of 3-[(*tert*-butyldimethylsilyl)oxy]propanal (**32**;[24] 1.88 g, 10.0 mmol) in CH_2Cl_2 (20 mL) was added D-proline (115 mg, 1.0 mmol) and *N*-chlorosuccinimide (1.33 g, 10 mmol). The reaction mixture was stirred for 18 h. After this time, the mixture was diluted with pentane (20 mL), cooled (–78 °C), filtered through a fritted funnel, and concentrated on a rotary evaporator in an ice water bath. The resulting oil was dissolved in pentane (20 mL), cooled (–78 °C), filtered through a fritted funnel, and concentrated on a rotary evaporator in an ice-water bath to give **33** (1.9 g, 86% yield) as a clear oil.

IR (neat): 2955, 2930, 2857, 1710, 1632, 1471, 1256 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.52 (d, *J* = 2.4 Hz, 1 H), 4.19 (ddd, *J* = 2.4, 4.8, 6.0 Hz, 1 H), 4.05 (m, 2 H), 0.88 (s, 9 H), 0.08 (s, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 195.0, 69.8, 63.3, 35.6, 25.6, –5.6.

HRMS: *m/z* calcd for $C_9H_{19}ClO_2Si$: 223.0921 (M + H); found: 223.0916 (M + H).

(2*S,3*R**,8*Z*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2,8-dichloro-3-hydroxydodeca-8,11-dien-5-one (34)**

To a cold (–78 °C) stirred solution of *i*-Pr_2NH (0.37 mL, 2.7 mmol) in THF (22 mL) was added *n*-BuLi (2.5 M in hexane, 0.97 mL, 2.4 mmol). The resulting solution was stirred at –78 °C for 30 min, then warmed to 0 °C, and stirred for an additional 15 min. After this time, the slightly yellow solution was cooled to –78 °C and (*Z*)-5-chlorononа-5,8-dien-2-one (**31**; 0.39 g, 2.2 mmol) was added in one portion. The reaction mixture was then stirred for 30 min. A solution of (*S*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-chloropropanal (**33**; 0.59 g, 2.7 mmol) in THF (2.0 mL) was then added dropwise over 5 min at –78 °C and the resulting mixture was stirred for an additional 30 min. Sat. aq NH_4Cl (10 mL) was then added, the mixture was diluted with EtOAc (20 mL), and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 15 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 6:1 hexanes–EtOAc) afforded **34** (0.80 g, 93%) as a yellow oil.

IR (neat): 3583, 3001, 2957, 2904, 2863, 2275, 1723, 1613, 1464, 1092 cm^{-1}

^1H NMR (600 MHz, $CDCl_3$): δ = 5.77 (m, 1 H), 5.56 (t, *J* = 6.6 Hz, 1 H), 5.07–5.00 (m, 2 H), 3.97–3.85 (m, 4 H), 2.92–2.60 (m, 6 H), 0.91 (s, 9 H), 0.09 (s, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 209.2, 135.3, 135.2, 123.1, 115.3, 75.7, 71.0, 65.9, 39.8, 35.6, 35.4, 32.9, 25.8, 25.7, –5.6.

HRMS: *m/z* calcd for $C_{18}H_{32}Cl_2O_3Si$: 395.1596 (M + H); found: 395.1601 (M + H).

(2*S,3*R**,5*R**,8*Z*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2,8-dichlorododeca-8,11-diene-3,5-diol (35)**

To a cold (–78 °C) solution of **34** (325 mg, 0.82 mmol) in THF (15 mL) was added DIBAL-H (1.0 M in THF, 2.0 mL, 2.0 mmol) and the reaction mixture was stirred for 4 h. After this time, a solution of aq 1 M HCl (5 mL) was added, the mixture was diluted with Et_2O (20 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (15 mL), and the combined organic phases were washed with H_2O (3 × 10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated to provide an oil. Purification of the crude product by flash chromatography (silica gel, 4:1 hexanes–EtOAc) afforded an inseparable 4:1 mixture of **35** and the C-5 epimer (278 mg, 91%) as a clear oil.

35 (Major Diastereomer)

IR (neat): 3525, 3003, 2957, 2906, 2862, 2837, 1513, 1248, 1098 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.78 (m, 1 H), 5.56 (t, *J* = 6.8 Hz, 1 H), 5.10–5.00 (m, 2 H), 4.07–3.82 (m, 5 H), 2.93 (m, 2 H), 2.63–2.40 (m, 4 H), 1.84–1.58 (m, 2 H), 0.91 (s, 9 H), 0.11 (s, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 135.7, 128.9, 123.3, 115.4, 75.8, 70.7, 66.1, 63.1, 39.7, 35.6, 35.4, 32.5, 25.8, 25.7, –5.1.

HRMS: *m/z* calcd for $C_{18}H_{34}Cl_2O_3Si$: 419.1552 (M + Na); found: 419.1555 (M + Na).

(2*R,3*R**,5*R**)-5-[(3′*Z*)-3′-Chlorohepta-3′,6′-dien-1′-yl]-2-(hydroxymethyl)tetrahydrofuran-3-ol (36)**

A 4:1 mixture of **35** and the C-5 epimer (100 mg, 0.25 mmol) were placed in a 10 mL vial, deionized H_2O (2 mL) was then added, and the vial was sealed in a CEM Discover LabMate microwave. The reaction mixture was then heated to 120 °C (as monitored by a vertically focused IR temperature sensor) and maintained at this temperature for 20 min. After this time, the mixture was diluted with EtOAc (10 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 15 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), and concentrated. Purification of the crude product by flash chromatography (silica gel, 2:1 hexanes–EtOAc) afforded **36** (43 mg, 70%) as a clear oil.

IR (neat): 3453, 2952, 2857, 1658, 1639, 1430, 1255, 1087 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 5.80 (m, 1 H), 5.61 (t, *J* = 6.8 Hz, 1 H), 5.08–4.97 (m, 2 H), 4.38 (m, 1 H), 4.21 (m, 1 H), 3.92 (m, 1 H), 3.81–3.67 (m, 2 H), 2.92 (m, 2 H), 2.58–2.32 (m, 3 H), 2.04 (dd, *J* = 6.0, 13.2 Hz, 1 H) 1.73–1.84 (m, 2 H).

^{13}C NMR (150 MHz, CD_3OD): δ = 136.4, 136.3, 124.3, 115.8, 83.7, 77.9, 73.5, 62.1, 42.5, 37.1, 35.1, 33.7.

HRMS: *m/z* calcd for $C_{12}H_{19}ClO_3$: 247.1101 (M + H); found: 247.1111 (M + H).

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