Metalated Nitriles: Diastereoselective Internal Asymmetric Induction

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Compound	Procedure	¹ H NMR	¹³ C NMR	X-ray
10	S8	S41	S42
10	S8	S43	S44
12a	S9	S45	S46
12b	S10	S47	S48
12bi	S10	S49	S50	S51 (CCDC#297964)
12c	S11	S52	S53
12d	S12	S54	S55
12e	S12	S56	S57
12f	S13	S58	S59
12g	S14	S60	S61
12h	S14	S62	S63

S14	S64	S65
S15	S66	S67	S68
S15	S69	S70
S15	S71	S72
S16	S73	S74
S16	S75	S76
S17	S77	S78
S18	S79	S80	S81 (CCDC#297965)
S18	S82	S83
S19	S84	S85
S19	S86	S87
S19	S88	S89
S20	S90	S91
S21	S92	S93

19	S21	S94	S95
S22	S96	S97
viii	S22	S98	S99
21a	S23	S100	S101
21b	S24	S102	S103
24a	S24	S104	S105
23a	S24	S104	S105
24a	S24	S104	S105
ix	S25	S106	S107
x	S25	S108	S109
23b	S26	S110	S111
24b	S26	S112	S113
23b	S26	S112	S113
i	S26	S114	S115
xi	S26	S114	S115
25	S27	S116	S117
26	S27	S118	S119
28	S28	S120	S121
			S122 (CCDC#633730)

xii	S28	S123	S124	S125 (CCDC#633729)
29	S29	S126	S127
30a	S29	S128	S129
xiii	S30	S130	S131
xiv	S30	S132	S133	S134 (CCD#667708)
30b	S31	S135	S136
30c	S31	S137	S138
xv	S32	S139	S140
30d	S32	S141	S142
30e	S33	S143	S144
30f	S33	S145	S146
30g	S34	S147	S148
30h	S34	S149	S150
30i	S34	S151	S152
xvi	S35	S153	S154

S35	S155	S156
S36	S157	S158
S36	S159	S160
S37	S161	S162
S37	S163	S164
S38	S165	S166
S38	S167	S168
S39	S169	S170
S39	S171	S172
S39	S173	S174
S40	S175	S176
S40	S177	S178
References	S179		

Reaction schemes for chemical Correlations:

Scheme 1: Preparation of Nitrile **36**.

Scheme 2: Chemical Correlation for the Configurational Assignment of Alkylated Nitriles **12c**, **12e**, and **12f**.

Scheme 3: Preparation of Ester **21a** and the Chemical Correlation for the Configurational Assignment of Ester **23a**.

Scheme 4: Preparation of Ester **21b** and the Chemical Correlation of **24b** with **12a**.

Scheme 5: Synthesis of Nitrile **31**

General Nitrile Bromination Procedure. Neat bromine (1.1 equiv) and nitrile (1 equiv) were sequentially added to ice-cooled PBr₃ (1.1 equiv). The ice bath was removed and the reaction was then heated to 60 °C. After 5 h the mixture was poured onto ice, extracted with ether (3x), and then the crude extracts were washed with saturated, aqueous NaHCO₃ (3x), and water, and then dried (MgSO₄). Concentration and purification of the crude product by radial chromatography afforded analytically pure material.

(2*R, 3*S**) and (2*R**, 3*R**) 2-Bromo-2-methyl-3-phenylbutanenitrile (10):** The general bromination procedure was employed with a 1:1 diastereomeric mixture of **14a** (2.10 g, 13.2 mmol), Br₂ (2.24 g, 14 mmol) and PBr₃ (3.78 g, 14 mmol) to afford, after purification by radial chromatography (1: 60 to 1: 30 EtOAc/hexanes), 2.28 g (73%) of **10** as an oily 1:1 mixture of diastereomers. For one diastereomer: IR (film) 2234, 1602, 1380 cm⁻¹; ¹H NMR: δ 1.72 (d, *J* = 5.9 Hz, 3H), 1.88 (s, 3H), 3.17-3.23 (m, 1H), 7.26 – 7.35 (m, 5H); ¹³C NMR: δ 17.9, 29.7, 49.8, 51.5, 120.0, 128.1, 128.1, 129.0, 138.4; HRMS(EI) calcd for (M⁺), C₁₁H₁₂BrN⁺ 237.0148, found 237.0141. For the other diastereomer: IR (film) 2232 cm⁻¹; ¹H NMR: δ 1.63 (d, *J* = 7.3 Hz, 3H), 1.98 (s, 3H), 3.14 – 3.21 (m, 1H), 7.26 – 7.35 (m, 5H); ¹³C NMR: δ 18.5, 30.3, 50.4, 50.8, 120.6, 128.6, 128.7, 129.5, 139.0 ; HRMS(EI) calcd for (M⁺), C₁₁H₁₂BrN⁺ 237.0148, found 237.0141.

Standard *in situ* Exchange - Alkylation Procedure A: A THF solution of *i*-PrMgBr (1.05 equiv) was added to a -78 °C, THF solution of the bromonitrile (1.0 equiv) and the electrophile (1.05 equiv). After 3 h at -78 °C saturated, aqueous NH₄Cl was added, the

crude product was extracted with EtOAc, dried (MgSO₄), concentrated, and purified by radial chromatography to afford analytically pure material.

Standard Deprotonation – Alkylation Procedure B: A THF solution of the nitrile (1.0 equiv) was added to a -78 °C, THF solution of LDA, generated from butyllithium (1.05 equiv) and diisopropylamine (1.15 equiv). After 50 min at -78 °C, neat electrophile (1.2 equiv) was added. After 3 h at -78 °C, saturated, aqueous NH₄Cl was added, the crude product was extracted with EtOAc, dried (MgSO₄), concentrated, and purified by radial chromatography to afford analytically pure material.

General Bromine-Copper Exchange Procedure: A THF solution of the bromonitrile (1.0 equiv) was added to a 0 °C, ether solution of Me₂CuLi [generated by adding methyllithium (2.2 equiv) to copper iodide (1.2 equiv)]. After 1 h, the electrophile (1.3 equiv) was added neat and, after a further 2 h at 0 °C, saturated, aqueous NH₄Cl solution was then added. The mixture was stirred vigorously with exposure to air for 30 min, the crude product was extracted with ether and was then dried (MgSO₄). Concentration of the crude product and purification by radial chromatography afforded analytically pure material.

(2S*, 3S*)-Methyl 2-cyano-2-methyl-3-phenylbutanoate (12a): The exchange procedure (A) was employed with **10** (61.6 mg, 0.26 mmol) and methyl cyanoformate (23.2 mg, 0.27 mmol) to afford, after purification by radial chromatography (stepped gradient 1:19, 1:9 EtOAc/hexanes), 42.3 mg (75%) of **12a** as an oil: IR (film) 2245, 1745

cm⁻¹; ¹H NMR: δ 1.36 (s, 3H), 1.46 (d, *J* = 6.8 Hz, 3H), 3.26 (q, *J* = 6.8 Hz, 1H), 3.87 (s, 3H), 7.30 – 7.36 (m, 5H); ¹³C NMR: δ 17.6, 22.5, 45.6, 49.7, 53.4, 118.8, 127.8, 128.4, 138.9, 170.1; HRMS(EI) calcd for (M+Na⁺), C₁₃H₁₅NO₂Na⁺ 240.0995, found 240.1004. Employing the deprotonation procedure B with **14a** (58.9 mg, 0.37 mmol) and methyl cyanoformate (37.8 mg, 0.44 mmol) afforded after purification by radial chromatography (1:39 to 1:19 EtOAc/hexanes), 65.9 mg (82%) of **12a** as an oil.

(2S*, 3S*)-and (2R*, 3S*)-(2-(1-Hydroxycyclohexyl)-2-methyl-3-phenylbutanenitrile (12b and 12bi): The exchange procedure (A) was employed with **10** (142 mg, 0.60 mmol) and cyclohexanone (61.7 mg, 0.63 mmol) to afford, after purification by radial chromatography (1:4 EtOAc/hexanes), 99 mg (66%) of **12b** as an oil: IR (film) 3473, 2230, 1602 cm⁻¹; ¹H NMR: δ 1.22 (s, 3H), 1.43 - 1.91 (m, 11H), 1.61 (d, *J* = 6.5 Hz, 3H), 3.24 (q, *J* = 6.5 Hz, 1H), 7.23 - 7.35 (m, 5H); ¹³C NMR: δ 18.2, 21.1, 21.6, 25.3, 31.7, 33.6, 42.2, 51.4, 75.6, 123.5, 127.2, 128.6, 143.1; HRMS(EI) calcd for (M+Na⁺), C₁₇H₂₃NONa⁺ 280.1672, found 280.1690. The diastereomer **12bi** was generated by the exchange procedure (A) with **10** (616 mg, 2.60 mmol), but after 3 h at -78 °C, the reaction temperature was allowed to rise to room temperature for 2 h, which afforded 582 mg (87%) of a 1:6 mixture of **12bi** and **12b**. After purification by radial chromatography (stepped gradient 1:19, 1:4 EtOAc/hexanes), pure **12bi** was obtained as a white crystalline solid whose structure was determined by x – ray crystallography (m.p. 104 - 107 °C): IR (film) 3463, 2232, 1604 cm⁻¹; ¹H NMR: δ 1.47 (d, *J* = 6.8 Hz, 3H), 1.48 (s, 3H), 1.26 - 1.65 (m, 9H), 1.74 – 1.76 (m, 1H), 1.85 – 1.87 (m, 1H), 3.15 (q, *J* = 6.8 Hz, 1H), 7.26 – 7.42 (m, 5H); ¹³C NMR: δ 18.0, 18.9, 21.4, 25.2, 32.4, 42.5, 51.5, 75.4, 123.1,

127.2, 128.4, 128.5, 143.7; HRMS(EI) calcd for $(M+N_a^+)$, $C_{17}H_{23}NO_2N_a^+$ 280.1672, found 280.1676. Employing the deprotonation procedure (B) with **14a** (33.4 mg, 0.21 mmol) and cyclohexanone (24.5 mg, 0.25 mmol) afforded 38.8 mg (72%) of **12b** as an oil.

(2*S,3*S**)-2-(1'-*R*'-Hydroxy-phenyl-methyl)-2-methyl-3-phenyl-butyronitrile and (2*S**,3*S**)-2-(1'-*S*'-Hydroxy-phenyl-methyl)-2-methyl-3-phenyl-butyronitrile (**12c**):**

The exchange procedure (A) was employed with **10** (143 mg, 0.60 mmol) and benzaldehyde (66.8 mg, 0.63 mmol) to afford, after purification by radial chromatography (1:7 EtOAc/hexanes), 82.8 mg (52%) of **12c** as a 1:1 oily mixture: IR (film) 3450, 2236 cm^{-1} . Diastereomer a: 1H NMR: δ 0.78 (s, 3H), 1.46 (d, $J = 7.3$ Hz, 3H), 2.57 (s, 1H), 3.44 (q, $J = 7.3$ Hz, 1H), 4.16 (s, 1H), 7.14 – 7.38 (m, 10H); ^{13}C NMR: δ 16.2, 17.3, 41.8, 47.9, 74.0, 122.5, 127.3, 127.5, 128.0, 128.2, 128.3, 128.7, 129.1, 139.4, 139.7; MS (CI) m/e 266 ($M + H^+$). Diastereomer b: 1H NMR: δ 0.85 (s, 3H), 1.48 (d, $J = 7.0$ Hz, 3H), 2.69 (s, 1H), 3.14 (q, $J = 7.0$ Hz, 1H), 4.93 (s, 1H), 7.14 – 7.38 (m, 10H); ^{13}C NMR: δ 16.9, 17.2, 43.0, 47.4, 75.4, 121.9, 127.1, 127.5, 127.5, 128.0, 128.2, 128.3, 128.3, 128.6, 139.2, 142.1; MS (CI) m/e 266 ($M + H^+$). Employing the deprotonation procedure (B) with **14a** (95.4 mg, 0.60 mmol) and benzaldehyde (80.7 mg, 0.76 mmol) afforded after purification by radial chromatography (1:7 EtOAc/hexanes), 124 mg (78%) of 1:1 mixtures of **12c**. For chemical correlation, a cyclohexane/ether solution (0.10 mL) of phenyllithium (0.15 mmol) was added dropwise to a -78 °C, THF solution (5 mL) of **vi** (28.1 mg, 0.15 mmol). After 2 h, saturated, aqueous NH_4Cl was added, and then the crude product was extracted with EtOAc, dried ($MgSO_4$), concentrated and purified by

radial chromatography (1:7 EtOAc/hexanes) to afford 23.9 mg (60%, 2:1 mixture) of **12c** as an oil.

2-(S*)-Methyl-3-phenyl-2-(S*)-(trimethylsilyl)butanenitrile (12d): The exchange procedure (A) was employed with **10** (85.3 mg, 0.36 mmol) and chlorotrimethylsilane (40.8 mg, 0.38 mmol) to afford, after purification by radial chromatography (1:30 EtOAc/hexanes), 48.2 mg (58%) of **12d** as an oil: IR (film) 2211, 1254, 852 cm^{-1} ; ^1H NMR: δ 0.28 (s, 9H), 1.14 (s, 3H), 1.56 (d, $J = 7.4$ Hz, 3H), 2.86 (q, $J = 7.4$ Hz, 1H), 7.30 – 7.44 (m, 5H); ^{13}C NMR: δ -2.7, 18.7, 20.0, 28.3, 43.4, 124.2, 127.1, 128.2, 128.4, 143.0; HRMS(EI) calcd for (M^+), $\text{C}_{14}\text{H}_{21}\text{NSi}^+$ 231.1438, found 231.1453. Employing the deprotonation procedure (B) with **14a** (47.7 mg, 0.30 mmol) and chlorotrimethylsilane (38.9 mg, 0.36 mmol) afforded after purification by radial chromatography (1:30 EtOAc/hexanes), 54.8 mg (79%) of **12d** as an oil.

R*-2-Methyl-5-phenyl-2-(S*)-1-phenylethylpent-E-4-enenitrile (12e): The exchange procedure (A) was employed with **10** (85.3 mg, 0.36 mmol) and 3-bromoprop-1-*E*-(enyl)benzene (74.5 mg, 0.38 mmol) to afford, after purification by radial chromatography (1:25 EtOAc/hexanes), 78.3 mg (79%) of **12e** as an oil: IR (film) 2231, 1600 cm^{-1} ; ^1H NMR: δ 1.16 (s, 3H), 1.55 (d, $J = 7.3$ Hz, 3H), 2.30-2.37 (m, 1H), 2.67 - 2.74 (m, 1H), 2.86 (q, $J = 7.3$ Hz, 1H), 6.22 – 6.32 (m, 1H), 6.48 – 6.53 (m, 1H), 7.25 – 7.41 (m, 10H); ^{13}C NMR: δ 17.3, 21.7, 41.7, 46.2, 123.3, 123.5, 126.3, 127.4, 127.7, 128.4, 128.6, 128.6, 134.9, 136.7, 141.0; HRMS(EI) calcd for ($\text{M}+\text{Na}^+$), $\text{C}_{20}\text{H}_{21}\text{NNa}^+$ 298.1566, found 298.1572. Employing procedure (B) with **14a** (47.7 mg, 0.30 mmol) and

(*E*)-(3-bromoprop-1-enyl)benzene (74.5 mg, 0.38 mmol) afforded, after purification by radial chromatography (1:25 EtOAc/hexanes), 72.6 mg (88%) of **12e**.

(*R*^{*})-2-Methyl-2-(*S*^{*})-1-phenylethyl)pent-4-enenitrile (12f): The exchange procedure A was employed with **10** (142 mg, 0.60 mmol) and 3-bromoprop-1-ene (75.6 mg, 0.63 mmol), except that after 3 h at -78 °C the reaction was allowed to reach room temperature over 2 h. After purification of the crude product by radial chromatography (1:40 EtOAc/hexanes), 94.4 mg (79%) of **12f** was obtained as an oil: IR (film) 2231, 1641, 1602 cm⁻¹; ¹H NMR: δ 0.85 – 1.81 (m, 4H), 1.12 (s, 3H), 1.50 (d, *J* = 7.4 Hz, 3H), 2.06 – 2.13 (m, 2H), 2.76 – 2.83 (m, 1H), 4.97 – 5.06 (m, 2H), 5.72 – 5.86 (m, 1H), 7.26 – 7.37 (m, 5H); ¹³C NMR: δ 17.1, 21.5, 24.0, 33.5, 37.5, 41.3, 46.4, 115.1, 123.6, 127.1, 128.2, 128.5, 137.6, 141.1; HRMS(EI) calcd for (M+Na⁺), C₁₆H₂₁NNa⁺ 250.1566, found 250.1586. Employing the deprotonation procedure (B) with **14** (79.5 mg, 0.50 mmol) and 3-bromoprop-1-ene (72.0 mg, 0.60 mmol), except after 3 h at -78 °C allowing the reaction to reach room temperature over 2 h, afforded after purification of the crude product by radial chromatography (1:40 EtOAc/hexanes), 78.7 mg (79%) of **12f**. Preparation of **12f** from **iv** (Scheme 2): A THF solution of allylmagnesium chloride (0.21 mmol, 0.18 mL) was added dropwise to a THF – *N*-methyl-pyrrolidinone (4:1, 2.5 mL)] solution of **iv** (62.6 mg, 0.2 mmol), CuCl₂ (2.7 mg, 0.02 mmol) and anhydrous LiCl (1 mg, 0.02 mmol). After 1 h and the reaction mixture was cooled to -10 °C, and then aqueous hydrochloric acid (1N, 3 mL) was added. The aqueous layer was extracted twice with ether and then the combined organic phase was washed with saturated brine. After drying (MgSO₄), the crude product was concentrated and purified by radial

chromatography (1:60 to 1:30 EtOAc/hexanes) to afford 40.7 mg (65%) of **iv** and 4.8 mg (12%) of **12f**.

(2R*, 3S*)- Methyl 2-cyano-2,3-diphenylbutanoate (12g): The deprotonation procedure (B) was employed with **14b** (86.9 mg, 0.37 mmol) and methyl cyanoformate (37.8 mg, 0.44 mmol) to afford, after purification by radial chromatography (1:40 EtOAc/hexanes), 88.8 mg (86%) of **12g** as an oil: IR (film) 2245, 1746 cm^{-1} ; ^1H NMR: δ 1.65 (d, $J = 7.3$ Hz, 3H), 3.84 (s, 3H), 7.00 – 7.36 (m, 10H); ^{13}C NMR: δ 18.3, 47.3, 53.9, 60.7, 117.1, 126.3, 127.8, 128.4, 128.5, 128.5, 133.2, 138.6, 168.0; MS (CI) m/e 280 ($M + \text{H}^+$).

(2S*, 3S*)-2-Methyl-2,3-diphenyl-butyronitrile (12h): The deprotonation procedure (B) was employed with **14b** (86.9 mg, 0.37 mmol) and methyl iodide (62.5 mg, 0.44 mmol) to afford, after purification by radial chromatography (1:40 EtOAc/hexanes), 73.7 mg (80%) of **12h** as an oil: IR (film) 2235 cm^{-1} ; ^1H NMR: δ 1.52 (d, $J = 6.8$ Hz, 3H), 1.81 (s, 3H), 3.13 (q, $J = 6.8$ Hz, 1H), 6.90 – 7.24 (m, 10H); ^{13}C NMR: δ 16.9, 24.9, 47.6, 49.8, 122.8, 126.5, 127.1, 127.6, 127.7, 128.1, 128.6, 138.2, 140.5; MS (CI) m/e 236 ($M + \text{H}^+$).

2-S*-Phenyl-2-(1-S*-phenyl-ethyl)-pent-4-enenitrile (12i): The deprotonation procedure (B) was employed with **14b** (86.9 mg, 0.37 mmol) and allyl bromide (53.2 mg, 0.44 mmol) to afford, after purification by radial chromatography (1:40 EtOAc/hexanes), 83.6 mg (81%) of **12i** as an oil: IR (film) 2235, 1641 cm^{-1} ; ^1H NMR: δ 1.63 (d, $J = 7.0$ Hz, 3H), 2.84 – 2.89 (m, 1H), 2.97 – 3.02 (m, 1H), 3.28 (q, $J = 7.0$ Hz, 1H), 5.12 (d, $J =$

10.3 Hz, 1H), 5.20 – 5.25 (m, 1H), 5.57 – 5.68 (m, 1H), 6.93 – 7.28 (m, 10H); ^{13}C NMR: δ 17.4, 41.7, 48.7, 53.4, 119.7, 121.4, 126.9, 127.3, 127.5, 127.6, 128.0, 128.7, 132.0, 135.8, 140.2; MS (CI) m/e 262 ($\text{M} + \text{H}^+$).

(2*R, 3*S**)-2,3-Diphenyl-2-phenylsulfanyl-butyronitrile (12j)**: The deprotonation procedure (B) was employed with **14b** (86.9 mg, 0.37 mmol) and S-phenyl benzenethiosulfonate (110.1 mg, 0.44 mmol) to afford, after purification by radial chromatography (1:20 EtOAc/hexanes), 99.8 mg (82%) of **12j** as a crystalline solid (m.p. 95 - 98 °C) whose structure was determined by x - ray crystallography: IR (film) 2227, 698 cm^{-1} ; ^1H NMR: δ 1.89 (d, $J = 7.0$ Hz, 3H), 3.62 (q, $J = 7.0$ Hz, 1H), 7.04 – 7.28 (m, 15H); ^{13}C NMR: δ 18.7, 49.2, 61.3, 119.0, 127.2, 127.7, 127.9, 128.0, 128.5, 128.7, 129.8, 129.8, 136.3, 136.4, 140.0; MS (CI) m/e 330 ($\text{M} + \text{H}^+$).

(2*R, 3*S**)- and (2*R**, 3*R**)- 2-Methyl-3-phenylbutanenitrile (14a)**: Neat propionitrile (826 mg, 15.0 mmol) was added dropwise to a -78 °C, THF solution (35 mL) of LDA, generated from butyllithium (15.0 mmol, 2.5 M solution) and diisopropylamine (16.0 mmol). After 50 min at -78 °C, neat (1-bromoethyl)-benzene (2.96 g, 16.0 mmol) was added quickly in one portion, the cooling bath was removed, and then the mixture was allowed to warm to room temperature. After 2 h, saturated, aqueous NH_4Cl was added, and then the crude product was extracted with EtOAc, dried (MgSO_4), concentrated and purified by radial chromatography (1:50 to 1:30 EtOAc/hexanes) to afford 1.62 g (68%) of **14a**¹ as an oily mixture of diastereomers (1:1). For one diastereomer: IR (film) 2239 cm^{-1} ; ^1H NMR: δ 1.21 (d, $J = 7.4$ Hz, 3H), 1.45 (d, $J = 5.8$ Hz, 3H), 2.28-2.99 (m, 2H),

7.27-7.38 (m, 5H); ^{13}C NMR: δ 16.9, 19.2, 33.1, 43.2, 122.1, 127.1, 127.3, 128.8, 142.5; HRMS(EI) calcd for (M^+), $\text{C}_{11}\text{H}_{13}\text{N}^+$ 159.1043, found 159.1032. For the other diastereomer: IR (film) 2239 cm^{-1} ; ^1H NMR: δ 1.21 (d, $J = 7.4\text{ Hz}$, 3H), 1.45 (d, $J = 5.8\text{ Hz}$, 3H), 2.84-2.99 (m, 2H), 7.27-7.38 (m, 5H); ^{13}C NMR: δ 15.6, 18.5, 32.7, 42.2, 121.9, 127.3, 127.7, 128.6, 141.4; HRMS(EI) calcd for (M^+), $\text{C}_{11}\text{H}_{13}\text{N}^+$ 159.1043, found 159.1032.

(2*S, 3*R**)- and (2*R**, 3*R**)- 2,3-Diphenylbutanenitrile (14b):** Neat 2-phenylacetonitrile (527 mg, 4.5 mmol) was added to a $-78\text{ }^\circ\text{C}$, THF solution (15 mL) of LDA, generated from butyllithium (4.6 mmol) and diisopropylamine (4.8 mmol). After 50 min at $-78\text{ }^\circ\text{C}$, neat (1-bromoethyl)benzene (4.8 mmol, 888 mg) was added, the cooling bath was removed, and then the mixture was allowed to warm to room temperature. After 2 h, saturated, aqueous NH_4Cl was added, and then the crude product was extracted with EtOAc, dried (MgSO_4), concentrated, and purified by radial chromatography (1:30 EtOAc/hexanes) to afford 751 mg (71%, 1.8:1 mixture) of **14b**² as an oil. For **(2*S**, 3*R**)-2,3-Diphenylbutanenitrile**: IR (film) 2239.1 cm^{-1} ; ^1H NMR: δ 1.29 (d, $J = 7.3\text{ Hz}$, 3H), 3.15 (pentet, $J = 7.3\text{ Hz}$, 1H), 3.87 (d, $J = 7.3\text{ Hz}$, 1H), 7.01 – 7.30 (m, 10H); ^{13}C NMR: δ 18.8, 44.8, 45.4, 119.9, 127.4, 127.7, 128.0, 128.1, 128.3, 128.6, 134.2, 140.9; HRMS(EI) calcd for (M^+), $\text{C}_{16}\text{H}_{15}\text{N}^+$ 221.1199, found 221.1214. For **(2*R**, 3*R**)- 2,3-Diphenylbutanenitrile**: IR (film) 2239.5 cm^{-1} ; ^1H NMR: δ 1.48 (d, $J = 6.8\text{ Hz}$, 3H), 3.20 (pentet, $J = 6.8\text{ Hz}$, 1H), 3.96 (d, $J = 6.8\text{ Hz}$, 1H), 7.16 – 7.31 (m, 10H); ^{13}C NMR: δ 17.3, 45.1, 45.9, 119.7, 127.3, 127.4, 127.9, 128.0, 128.6, 128.7, 134.7, 141.8; HRMS(EI) calcd for (M^+), $\text{C}_{16}\text{H}_{15}\text{N}^+$ 221.1199, found 221.1214.

(2*S,3*S**)-2-(hydroxymethyl)-2-methyl-3-phenylbutanenitrile (i)**: Solid LiBH₄ (183 mg, 8.4 mmol) was added to a THF solution (15 mL) of **12a** (130 mg, 0.6 mmol). After 18 h, saturated, aqueous NaHCO₃ (5mL) was added, the mixture was stirred for 15 min and then the phases were separated. The aqueous phase was extracted with ether (3x) and the combined organic extract was dried (MgSO₄), filtered, and concentrated under reduced pressure and the residue was purified by radial chromatography (1:5 EtOAc/hexanes) to afford 93 mg (82%) of **i** as an oil: IR (film) 3467, 2236, 1603 cm⁻¹; ¹H NMR: δ 1.18 (s, 3H), 1.54 (d, *J* = 8.5 Hz, 3H), 2.36 - 2.40 (m, 1H), 3.10 – 3.17 (m, 1H), 3.58 – 3.71 (m, 2H), 7.33 – 7.36 (m, 5H); ¹³C NMR: δ 16.9, 18.4, 42.0, 44.1, 66.4, 123.0, 127.3, 128.3, 128.4, 128.6, 140.3; HRMS(EI) calcd for (M+Na⁺), C₁₂H₁₅NONa⁺ 212.1046, found 202.1047. From **vi** for chemical correlation: solid NaBH₄ (45.4 mg, 1.2 mmol) was added to a methanolic solution (10 mL) of **vi** (112 mg, 0.6 mmol). After 4 h, an aqueous solution of HCl (1M, 2 mL) was added, and after 15 min, the layers were separated, and the aqueous phase was extracted with ether (3x). The combined organic phase was dried (MgSO₄), filtered, concentrated under reduced pressure and the residue was then purified by radial chromatography (1:5 EtOAc/hexanes) to afford 76 mg (67%) of **i** as an oil.

(2*S, 3*S**)-2-cyano-2-methyl-3-phenylbutyl 4-nitrobenzoate (16)**: A hexanes solution of butyllithium (0.55 mmol, 1.3 mL) was added to a -78 °C, THF solution (5 mL) of **i** (94.6 mg, 0.5 mmol), followed after 10 min, by neat p-nitrobenzoyl chloride (97.4 mg, 0.53 mmol). The resulting solution was allowed to warm to room temperature and stirred

for 1 h before the addition of water. Extraction with EtOAc (3x), drying (MgSO₄), concentration and radial chromatography (1:8 EtOAc/hexanes) provided 154 mg (91%) of **16** as a crystalline solid (m.p. 84-86 °C) whose structure was solved by x-ray diffraction: IR (film) 2235, 1721 cm⁻¹; ¹H NMR: δ 1.34 (s, 3H), 1.63 (d, *J* = 7.3 Hz, 3H), 3.16 (q, *J* = 7.3 Hz, 1H), 4.31 – 4.43 (m, 2H), 7.28 – 7.40 (m, 5H), 8.26 – 8.37 (m, 4H); ¹³C NMR: δ 17.0, 19.1, 41.8, 43.6, 68.4, 121.4, 123.6, 127.8, 128.5, 128.6, 130.8, 134.5, 139.3, 150.7, 163.8; MS (CI) *m/e* 339 (*M* + H⁺).

(*R)-2-methyl-4-oxo-2-((*S**)-1-phenylethyl)butanenitrile (ii):** A stream of ozone was passed through a dichloromethane solution (4 mL) of **12e** (140 mg, 0.51 mmol) until the distinctive of blue color of ozone was clearly observed. Ozonolysis was then terminated, the excess ozone was displaced by passing a stream of nitrogen through the solution, and then neat Me₂S (5 mL) was added slowly. The resultant solution was stirred overnight. The reaction mixture was concentrated and purified by radial chromatography (1:10 EtOAc/hexanes) to provide 58.4 mg (57%) of **ii**: IR (film) 2739, 2235, 1728 cm⁻¹; ¹H NMR: δ 1.30 (s, 3H), 1.54 (d, *J* = 5.9 Hz, 3H), 2.48-2.82 (m, 2H), 3.01 - 3.08 (m, 1H), 7.25 – 7.37 (m, 5H), 9.83 (s, 1H); ¹³C NMR: δ 16.8, 21.8, 37.9, 46.0, 50.3, 122.3, 127.8, 128.6, 128.7, 139.7, 198.2.

(*S)-4-hydroxy-2-methyl-2-((*S**)-1-phenylethyl)butanenitrile (iii):** Solid LiBH₄ (183 mg, 8.4 mmol) was added to a THF solution (15 mL) of **ii** (121 mg, 0.6 mmol). After 18 h, saturated aqueous NaHCO₃ was added, and after 15 min, the layers were separated, and the aqueous phase was then extracted with ether (3x). The combined organic phase

was dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue was purified by radial chromatography (1:5 EtOAc/hexanes) to afford 100 mg (82%) of **iii** as oil: IR (film) 3442, 2230 cm⁻¹; ¹H NMR: δ 1.20 (s, 3H), 1.52 (d, *J* = 7.3 Hz, 3H), 1.65 – 1.71 (m, 1H), 2.06 – 2.12 (m, 1H), 2.83 – 2.89 (m, 1H), 3.86 – 3.97 (m, 2H), 7.26 – 7.34 (m, 5H); ¹³C NMR: δ 17.1, 21.9, 39.8, 40.2, 47.1, 59.5, 123.6, 127.4, 128.4, 128.7, 140.8; HRMS(EI) calcd for (M⁺), C₁₃H₁₇NO⁺ 203.1305, found 203.1315.

(*R)-4-iodo-2-methyl-2-((*S**)-1-phenylethyl)butanenitrile (iv)**: Solid PPh₃ (124 mg, 0.47 mmol), imidazole (64 mg, 0.94 mmol), and iodine (120 mg, 0.47 mmol) were added to a THF solution (8 mL) of **iii** (96 mg, 0.47 mmol). After 4 h, the solvent was removed and the crude iodide was purified by radial chromatography (1:30 EtOAc/hexanes) to afford 119 mg (81%) of **iv** as oil: IR (film) 2230 cm⁻¹; ¹H NMR: δ 1.16 (s, 3H), 1.52 (d, *J* = 6.8 Hz, 3H), 1.95 – 2.01 (m, 1H), 2.38 – 2.44 (m, 1H), 2.82 (q, *J* = 7.3 Hz, 1H), 3.20 – 3.25 (m, 2H), 7.24 – 7.35 (m, 5H); ¹³C NMR: δ 17.1, 20.9, 24.1, 42.9, 43.5, 46.5, 122.4, 127.6, 128.5, 128.5, 140.2; HRMS(EI) calcd for (M⁺), C₁₃H₁₆IN⁺ 313.0322, found 313.0344.

(*R)-2-methyl-2-((*S**)-1-phenylethyl)but-3-enenitrile (v)**: Solid t-BuOK (64.5 mg, 0.57 mmol) was added to a THF solution (5 mL) of **iv** (60 mg, 0.19 mmol). After 6 h, saturated aqueous NH₄Cl was added, and after 5 min, the layers were separated, and the aqueous phase was then extracted with ether (3x). The combined organic phase was dried (MgSO₄), filtered, and concentrated under reduced pressure. The crude alkene was then purified by radial chromatography (1:50 EtOAc/hexanes) to afford 31.3 mg (89%) of **v** as

oil: IR (film) 2238, 1636 cm^{-1} ; ^1H NMR: δ 1.21 (s, 3H), 1.43 (d, $J = 7.0$ Hz, 3H), 2.82 (q, $J = 7.0$ Hz, 1H), 5.30 (dd, $J = 9.7, 0.9$ Hz, 1H), 5.55 (dd, $J = 7.1, 0.9$ Hz, 1H), 5.61 – 5.68 (m, 1H), 7.26 – 7.34 (m, 5H); ^{13}C NMR: δ 17.5, 24.8, 46.2, 47.4, 116.3, 121.3, 127.5, 128.4, 128.5, 138.3, 140.7; HRMS(EI) calcd for (M^+), $\text{C}_{13}\text{H}_{15}\text{N}^+$ 185.1199, found 185.1183.

(2*R,3*S**)-2-formyl-2-methyl-3-phenylbutanenitrile (vi):** A stream of ozone was passed through a -78 °C dichloromethane solution (3 mL) of **v** (29.6 mg, 0.16 mmol) until the distinctive of blue color of ozone was clearly observed. Ozonolysis was then terminated, the excess ozone was displaced by passing a stream of nitrogen through the solution, and then neat Me_2S (2 mL) was added slowly. The resultant solution was stirred overnight. The reaction mixture was concentrated and the crude aldehyde was purified by radial chromatography (1:30 EtOAc/hexanes) to provide 18.8 mg (63%) of **vi**: IR (film) 2731, 2244, 1737 cm^{-1} ; ^1H NMR: δ 1.25 (s, 3H), 1.48 (d, $J = 6.8$ Hz, 3H), 3.14 (q, $J = 6.8$ Hz, 1H), 7.31 – 7.38 (m, 5H), 9.54 (s, 1H); ^{13}C NMR: δ 17.7, 18.9, 43.3, 54.1, 118.4, 128.1, 128.4, 128.8, 138.8, 194.3; HRMS(EI) calcd for (M^+), $\text{C}_{12}\text{H}_{13}\text{NO}^+$ 187.0992, found 187.0976.

(2*S, 3*S**)-Cyano-2-methyl-3-phenyl-butyric acid (vii):** An aqueous solution of sodium hydroxide (0.6 mmol, 0.6 mL) was added to a 1:1 THF: H_2O solution (5 mL) of ester **12a** (109 mg, 0.5 mmol). After 19 h at room temperature, the solvent was removed, the residue was acidified to pH 2 and then extracted with EtOAc (20 mL). The organic extract was concentrated to give 96 mg, (94%) of **vii** as a white powder: IR (film) 2936,

1715 cm^{-1} ; ^1H NMR: δ 1.42 (s, 3H), 1.55 (d, $J = 7.0$ Hz, 3H), 3.28 (q, $J = 7.0$ Hz, 1H), 7.25 – 7.38 (m, 5H), 10.80 (s, 1H); ^{13}C NMR: δ 17.8, 22.5, 45.4, 50.2, 118.2, 128.1, 128.5, 128.6, 138.5, 175.3.

(1*S, 2*S**)-(1-Cyano-1-methyl-2-phenyl-propyl)-carbamic acid benzyl ester (19):**

Neat triethylamine (0.067 mL, 0.48 mmol) and solid diphenyl phosphorazidate (0.10 mL, 0.48 mmol) were added to a toluene solution (3 mL) of **viii** (81mg, 0.4 mmol) and the reaction was heated to reflux. After 1 h, neat benzoyl alcohol (0.1ml) was added to the mixture, the mixture heated to reflux and after 22 h, the solvent was removed in vacuo, and the residue was dissolved in ethyl acetate. The crude carbamate was washed sequentially with 1M HCl, water, saturated aqueous NaHCO_3 , saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. Purification of the crude carbamate by radial chromatography (chloroform-methanol-isopropylamine 45:5:1) afforded 55.7 mg (80%) of **19** as an oil: IR (film) 3321, 2238, 1703 cm^{-1} ; ^1H NMR: δ 1.49 (s, 3H), 1.55 (d, $J = 7.2$ Hz, 3H), 3.55 – 3.61 (m, 1H), 4.76 (s, 1H), 5.00 (d, $J = 12$ Hz, 1H), 5.23 (d, $J = 12$ Hz, 1H), 7.15 – 7.40 (m, 10H); ^{13}C NMR: δ 16.0, 21.5, 30.9, 54.9, 67.3, 119.9, 127.9, 128.5, 128.5, 128.5, 128.6, 129.0, 135.8, 138.1, 154.1; MS (CI) m/e 309 ($\text{M} + \text{H}^+$).

2-Methyl-3-phenylbutanoic acid (viii): A diethylene glycol solution (15 mL) of a 1:1 mixture of **14a** (191 mg, 1.2 mmol), NaOH (3 g, 75 mmol) and water (0.5 ml) was heated at 170 $^\circ\text{C}$ for 16 h, and then heated to reflux for 6 h. After cooling, the mixture was acidified with HCl (5M) to pH 3, and extracted with ether. The combined organic extract was dried (Na_2SO_4), concentrated and purified by radial chromatography (stepped

gradient pure CH₂Cl₂, 1:49 MeOH/ CH₂Cl₂, 1:24 MeOH/CH₂Cl₂) to afford 175 mg (82%) of a 1.5:1 ratio of diastereomeric acids **viii**³ as an oil: IR (film) 2964, 1694 cm⁻¹; ¹H NMR: δ 1.00 (d, *J* = 6.9 Hz, 3H) and 1.20 (d, *J* = 6.8 Hz, 3H), 1.30 (d, *J* = 6.8 Hz, 3H) and 1.34 (d, *J* = 6.8 Hz, 3H), 2.58 – 2.66 (m, 1H), 2.72 – 2.75 (m, 1H), 2.91 – 2.93 (m, 1H), 3.15 – 3.20 (m, 1H), 7.19 – 7.34 (m, 5H each), 11.2 (s, 1H each); ¹³C NMR: δ 13.5, (16.2), 17.0, (20.8), 41.7, (43.2), 46.4, (46.9), 126.4, (126.6), 127.4, (127.5), 128.3, (128.5), 144.0, (144.6), 197.7, (197.7); MS (CI) *m/e* 179 (*M* + H⁺).

Methyl 2-methyl-3-phenylbutanoate (21a): Solid K₂CO₃ (0.48 g, 3.47 mmol) and neat MeI (0.72 mL, 11.6 mmol) were added to a room temperature DMF solution (15 mL) of **viii** (137 mg, 0.77 mmol). After 8 h, the solution was filtered, the filtrate was evaporated, and the residual DMF was removed by Kugelrohr distillation (≤ 30 °C/0.05 mmHg). The residue was partitioned between H₂O (50 mL) and EtOAc (50 mL), the aqueous layer separated and extracted with EtOAc (2x), and then the combined organic layers were washed with 5% Na₂S₂O₃, saturated NaHCO₃, brine and then dried (Na₂SO₄). Concentration afforded the crude ester that was purified by radial chromatography (1:20 EtOAc/hexanes) to afford 132 mg (89%) of **21a**⁴ as an oily mixture of diastereomers: IR (film) 1733 cm⁻¹; ¹H NMR: δ 0.96 (d, *J* = 7.3 Hz, 6H) and 1.19 (d, *J* = 6.8 Hz, 3H), 1.27 (d, *J* = 6.8 Hz, 6H) and 1.29 (d, *J* = 6.8 Hz, 3H), 2.60 – 2.72 (m, 1H each), 2.90 – 2.96 (m, 1H) and 3.06 – 3.12 (m, 1H), 3.48 (s, 3H) and 3.73 (s, 3H), 7.17 – 7.33 (m, 5H each); ¹³C NMR: δ 14.0, (16.1), 17.4, (20.6), 42.3, (43.4), (46.7), 51.4, 126.3, (126.4), 127.2, (127.4), 128.1, (128.4), (144.2), 144.8, 175.9, (176.7); MS (CI) *m/e* 193 (*M* + H⁺).

Ethyl 2-cyano-3-phenylbutanoate (21b): A DMF solution (5 mL) of (1-bromoethyl)benzene (185 mg, 1.0 mmol), ethyl 2-cyanoacetate (113 mg, 1.0 mmol) and anhydrous potassium carbonate (276 mg, 2.0 mmol) was maintained at room temperature for 8 h. The reaction mixture was then poured into water and extracted with ether (30 mL). The combined organic phase was then washed with water (3x5 mL), dried (MgSO₄), concentrated, and purified by radial chromatography (1:20 EtOAc/hexanes) to afford 157 mg (72%) of a diastereomeric mixture of **21b** as an oil: IR (film) 2249, 1746 cm⁻¹; ¹H NMR: δ 1.15 (t, *J* = 7.4 Hz, 3H) and 1.19 (t, *J* = 7.3 Hz, 3H), 1.49 (s, 3H) and 1.50 (s, 3H), 3.48 – 3.57 (m, 2H), 3.67 (d, *J* = 5.8 Hz, 1H) and 3.72 (d, *J* = 7.4 Hz, 1H), 4.09 – 4.20 (m, 2H each), 7.26 – 7.36 (m, 5H each); ¹³C NMR: δ 13.6, 17.4, (19.1), (40.1), 40.2, (45.5), 45.7, 62.3, (62.5), 115.3, 127.0, (127.3), 127.6, (127.7), 128.5, (128.6), (139.9), 140.7, 165.1, (165.2); MS (CI) *m/e* 218 (*M* + H⁺).

(*S,*E*)-methyl 2-methyl-5-phenyl-2-((*S**)-1-phenylethyl)pent-4-enoate and (*R**,*E*)-methyl 2-methyl-5-phenyl-2-((*S**)-1-phenylethyl)pent-4-enoate (23a and 24a):** A THF solution (8 mL) of a 1:1 mixture of **21a** (192 mg, 1 mmol) was added to a -78 °C, THF solution of LDA, generated from butyllithium (1.1 mmol, 2.35 M in hexanes) and diisopropylamine (121 mg, 1.2 mmol). After 50 min at -78 °C, *E*-(3-bromoprop-1-enyl)benzene (245 mg, 1.25 mmol) was added. After 3 h, saturated, aqueous NH₄Cl was added, the phase were separated and the aqueous phase was extracted with EtOAc. The combined organic extract was dried (MgSO₄), concentrated, and purified by radial chromatography (1:20 EtOAc/hexanes) to afford to afford 191 mg (62%) of a 6:1 mixture of **23a** and **24a**. For **23a**: IR (film) 1723, 1600 1494 cm⁻¹; ¹H NMR: δ 1.12 (s,

3H), 1.33 (d, $J = 7.3$ Hz, 3H), 2.28 (dd, $J = 14, 7.7$ Hz, 1H), 2.74 (dd, $J = 14, 6.7$ Hz, 1H), 3.21 (q, $J = 7.3$ Hz, 1H), 3.56 (s, 1H), 6.07 – 6.14 (m, 1H), 6.39 (d, $J = 15.6$ Hz), 7.16 – 7.32 (m, 10H); ^{13}C NMR: δ 15.2, 17.5, 40.8, 46.8, 51.0, 51.3, 126.1, 126.4, 126.6, 127.1, 127.8, 128.4, 128.8, 133.1, 137.5, 142.7, 176.3; MS (CI) m/e 309 ($M + H^+$). A pure sample of **24a** was prepared by esterifying **x**: Solid K_2CO_3 (0.40 g, 2.93 mmol) and neat MeI (0.60 mL, 9.7 mmol) were added to a room temperature DMF solution (10 mL) of **x** (191 mg, 0.65 mmol). After 8 h, the solution was filtered, the filtrate was evaporated, and the residual DMF was removed by Kugelrohr distillation (≤ 30 °C/0.05 mmHg). The residue was partitioned between H_2O (20 mL) and EtOAc (20 mL), the aqueous layer separated and extracted with EtOAc (2x), and then the combined organic layers were washed with 5% $\text{Na}_2\text{S}_2\text{O}_3$, saturated NaHCO_3 , and brine. The crude ester was dried (Na_2SO_4), concentrated and purified by radial chromatography (1:20 EtOAc/hexanes) to afford 164 mg (82%) of **24a**: IR (film) 1732, 1600 cm^{-1} ; ^1H NMR: δ 1.11 (s, 3H), 1.28 (d, $J = 7.4$ Hz, 3H), 1.91-1.98 (m, 1H), 2.63 - 2.70 (m, 1H), 3.21 (q, $J = 7.4$ Hz, 1H), 3.70 (s, 3H), 5.93 – 6.03 (m, 1H), 6.31 (d, $J = 15.6$ Hz, 1H), 7.16 – 7.33 (m, 10H); ^{13}C NMR: δ 16.2, 16.5, 42.5, 46.9, 51.0, 51.6, 125.9, 126.1, 126.7, 127.1, 127.8, 128.4, 129.4, 133.1, 137.5, 142.1, 176.8; MS (CI) m/e 309 ($M + H^+$).

(*S^,*E*)-2-methyl-5-phenyl-2-((*S^**)-1-phenylethyl)pent-4-enal (ix)**: A hexanes solution (0.97 mL, 1.2 mmol, 25% w/w) of $i\text{-Bu}_2\text{AlH}$ was added dropwise over 10 min to a 0 °C, THF solution (5 mL) of **12e** (220 mg, 0.8 mmol). The cooling bath was removed and the mixture was allowed to warm to room temperature. After 4 h, the reaction was poured into a 5:2 water – ether solution (7 mL) containing tartaric acid (5 mmol). The crude

product was extracted with Et₂O, dried (MgSO₄), concentrated, and purified by radial chromatography (1:30 EtOAc/hexanes) to afford 200 mg (90%) of **ix** as an oil: IR (film) 2704, 1726, 1600 cm⁻¹; ¹H NMR: δ 1.07 (s, 3H), 1.28 (d, *J* = 7.4 Hz, 3H), 2.07 -2.15 (m, 1H), 2.47 - 2.53 (m, 1H), 3.07 (q, *J* = 7.3 Hz, 1H), 5.90 – 6.00 (m, 1H), 6.31 (d, *J* = 16.2 Hz, 1H), 7.18 – 7.32 (m, 10H), 9.62 (s, 1H); ¹³C NMR: δ 14.8, 16.3, 38.9, 44.5, 52.9, 124.7, 126.1, 126.9, 127.3, 128.1, 128.5, 129.1, 133.6, 137.1, 141.6, 206.4; MS (CI) *m/e* 279 (M + H⁺).

(*S,*E*)-2-methyl-5-phenyl-2-((*S**)-1-phenylethyl)pent-4-enoic acid (**x**):** Solid NaClO₂ (90.4 mg, 1 mmol) and NaH₂PO₄·H₂O (138 mmol, 1 mmol) were added to a 2:1 THF-H₂O solution (4 mL) of **ix** (97.3 mg, 0.35 mmol) and 2-methyl-2-butene (102 mg, 1.5 mmol). After 2 h the crude material was dissolved in ethyl acetate and washed with aqueous NaOH solution (1 M, 3 mL), and then HCl (1 M, 3.3 mL). The crude product was dried (MgSO₄), concentrated, and purified by radial chromatography (1:40 EtOAc/hexanes, then 1:4 EtOAc/hexanes) to afford 20 mg (21%) of **ix** and 54 mg (52%) of **x** as an oil: IR (film) 2977, 1697, 1600 cm⁻¹; ¹H NMR: δ 1.15 (s, 3H), 1.36 (d, *J* = 5.9 Hz, 3H), 1.98-2.07 (m, 1H), 2.68 - 2.75 (m, 1H), 3.25 - 3.31 (m, 1H), 6.03 – 6.14 (m, 1H), 6.38 (d, *J* = 16.2 Hz, 1H), 7.20 – 7.34 (m, 10H); ¹³C NMR: δ 15.8, 16.4, 42.2, 46.7, 50.8, 125.5, 126.1, 126.8, 127.1, 127.9, 128.4, 129.4, 137.4, 141.7, 182.9; MS (CI) *m/e* 294 (M + H⁺).

(2*R, 3*S**)-ethyl 2-cyano-2-methyl-3-phenylbutanoate and (2*R**, 3*R**)-ethyl 2-cyano-2-methyl-3-phenylbutanoate (**23b** and **24b**)** : The deprotonation procedure (B) was

employed with a 1:1 mixture of diastereomers of **21b** (174 mg, 0.8 mmol) and iodomethane (136 mg, 0.96 mmol) to afford, after purification by radial chromatography (1:25 EtOAc/hexanes), 152 mg (82%), a 6:1 mixture of **23b** (oil) (major isomer) and **24b** (oil) (minor isomer). For **23b**: IR (film) 2242, 1737 cm^{-1} ; ^1H NMR: δ 0.98 (t, $J = 7$ Hz, 3H), 1.52 (d, $J = 7.3$ Hz, 3H), 1.68 (s, 3H), 3.19 (q, $J = 7.3$ Hz, 1H), 3.96 (q, $J = 7$ Hz, 2H), 7.26 – 7.33 (m, 5H); ^{13}C NMR: δ 13.6, 16.1, 22.3, 46.2, 50.2, 62.3, 119.1, 127.8, 128.0, 128.4, 140.3, 168.9; MS (CI) m/e 232 ($\text{M} + \text{H}^+$), $\text{C}_{10}\text{H}_{15}\text{N}^+$ 149.1199, found 149.1182. For **24b**: IR (film) 2243, 1737 cm^{-1} ; ^1H NMR: δ 1.35 (s, 3H), 1.36 (t, $J = 7.2$ Hz, 3H), 1.47 (d, $J = 7.3$ Hz, 3H), 3.25 (q, $J = 7.3$ Hz, 1H), 4.25 – 4.36 (m, 2H), 7.25 – 7.36 (m, 5H); ^{13}C NMR: δ 14.0, 17.7, 22.6, 45.7, 49.9, 62.9, 119.0, 127.9, 128.5, 128.6, 139.2, 169.7; MS (CI) m/e 232 ($\text{M} + \text{H}^+$).

(2R*, 3R*)-2-(hydroxymethyl)-2-methyl-3-phenylbutanenitrile (i and xi): Solid LiBH_4 (183 mg, 8.4 mmol) was added to a THF solution (15 mL) of a 1:3 diastereomeric mixture of **23b** and **24b** (139 mg, 0.6 mmol). After 18 h, saturated aqueous NaHCO_3 was added, and after 15 min, the layers were separated, and the aqueous phase was extracted with ether (3x). The combined organic phase was dried (MgSO_4), filtered, and concentrated under reduced pressure and the residue was purified by radial chromatography (1:20 to 1:5 EtOAc/hexanes) to afford 88.5 mg (78%) of a 1:3 diastereomeric mixture of **i** and **xi** as an oil. For **xi**: IR (film) 3452, 2237 cm^{-1} ; ^1H NMR: δ 1.43 (s, 3H), 1.47 (d, $J = 7.3$ Hz, 3H), 2.27 (br s, 1H), 2.89 (q, $J = 7.3$ Hz, 1H), 3.37 (d, $J = 11$ Hz, 1H), 3.52 (d, $J = 11$ Hz, 1H), 7.25-7.33 (m, 5H); ^{13}C NMR: δ 16.6, 20.1, 43.6, 44.3, 66.6, 122.4, 127.4, 128.1, 128.5, 141.1; MS (CI) m/e 304 ($\text{M} + \text{H}^+$).

(E)-3-Methylpent-3-en-2-ol (25): A THF solution (10 mL) of MeMgCl (5.7 mL, 17.2 mmol) was added to a -78 °C, THF solution (25 mL) of (E)-2-methylbut-2-enal (1.0 g, 11.5 mmol). After 1 h saturated, aqueous NH₄Cl was added the crude reaction mixture was extracted (ether), dried (Na₂SO₄), concentrated to afford 880 mg (88%) of pure **25** product as a colorless oil: IR (film) 3354, 1671 cm⁻¹; ¹H NMR δ 1.30 (d, *J* = 6.0 Hz, 3H), 1.66 (d, *J* = 8.3 Hz, 3H), 1.67 (s, 3H), 4.26 (q, *J* = 6.0 Hz, 1H), 5.51- 5.58 (m, 1H); ¹³C NMR δ 11.1, 13.0, 21.6, 73.2, 119.0, 139.4; GCMS *m/e* 100 (M⁺).

(E)-3-Methylpent-3-en-2-yl propionate (26): Freshly distilled propionyl chloride (1.3 mL, 1.3 mmol) was added neat to a 0 ° C, CH₂Cl₂ solution (25 mL) of **25** (1 g, 10 mmol) and pyridine (1.2 mL, 1.3 mmol.). After 2 h at 0° C aqueous NaHCO₃ was added, the crude reaction mixture was extracted with ether, and the combined extracts were washed with a saturated, aqueous solution of NaCl, and dried (Na₂SO₄). Concentration of the crude product and purification by radial chromatography (1:5 ether/ pentane) afforded 850 mg (85 %) of **26** as a colorless oil: IR (film) 1733, 1674 cm⁻¹; ¹H NMR δ 1.12 (t, *J* = 7 Hz, 3H), 1.27 (d, *J* = 6.7 Hz, 3H), 1.59 (d, *J* = 7.9 Hz, 3H), 1.61 (s, 3H), 2.30 (q, *J* = 7 Hz, 1H), 5.23- 5.30 (m, 2H), 5.47- 5.57 (m, 1H); ¹³C NMR δ 9.3, 11.7, 13.3, 19.3, 28.1, 75.4, 121.6, 135.3, 174.0; GCMS *m/e* 156 (M⁺).

(2R*, 3S*), (E)- 4-Trimethylhex-4-enoic acid (28): A THF solution (5 mL) of **26** (1 g, 6.4 mmol) was added dropwise to a -78 °C THF solution (20 mL) of TMSCl (1.14 mL, 8.9 mmol) and LDA prepared from butyllithium (1.05 equiv.) and diisopropylamine (1.1

equiv.). The reaction mixture was allowed to warm to room temperature and after 16 h, an aqueous solution of HCl (10%) was added. The crude reaction mixture was extracted (EtOAc), dried (Na₂SO₄), concentrated and purified by radial chromatography (1:10, 1:5, EtOAc/ hexanes) to afford 700 mg (70 %) of **28** as a pure, crystalline solid (m.p. 42-44 °C) whose structure was unequivocally assigned by x – ray crystallography: IR (film) 2929, 1708, 1666 cm⁻¹; ¹H NMR δ 1.00 (d, *J*= 7.3 Hz, 6H), 1.45 (s, 3H), 1.54 (d, *J*= 5.9 Hz, 3H), 2.16- 2.44 (m, 2H), 5.25-5.32 (m, 1H); ¹³C NMR δ 11.4, 13.3, 16.5, 18.2, 43.8, 46.6, 121.2, 136.6, 184.1: GCMS *m/e* 157 (M+H).

(2R*, 3S*), (E)- 4-Trimethylhex-4-enamide (xii): Freshly distilled DMF (2 drops) was added to a 0 °C, CH₂Cl₂ solution (20 mL) of **28** (700 mg, 6.7 mmol) followed by oxalyl chloride (0.61 mL, 6.7 mmol). After 1 h the reaction mixture was concentrated, dissolved in CH₂Cl₂ (30 mL), and re-concentrated. The dissolution-concentration sequence was repeated two additional times and then saturated, aqueous ammonia (20 mL) was added at 0° C. After 1 h the crude product was extracted (ether), dried (Na₂SO₄) and concentrated to afford 588 mg (84%) of pure **xii** as a white crystalline solid (m.p. 188-190 °C) whose structure was unequivocally assigned by x – ray crystallography: IR (film) 3385, 1692, 1634⁻¹; ¹H NMR δ 1.02 (d, *J*= 5.9 Hz, 3H), 1.50 (s, 3H), 1.58 (d, *J*= 5.8 Hz, 3H), 2.09-2.32 (m, 2H), 5.30-5.37 (m, 1H), 5.55 (br s, 1H), 5.78 (br s, 1H); ¹³C NMR δ 14.3, 16.0, 19.7, 20.7, 47.5, 49.3, 123.6, 139.6, 181.7; HRMS (ESI) calcd for (M+Na⁺) C₉H₁₇NONa 178.1207, found 178.1198.

(2R*,3S*), (E)- 4-Trimethylhex-4-enenitrile (29): A THF solution (5 mL) of **xii** (588 mg, 3.79 mmol) was added, dropwise, to a 0 °C, THF solution (10 mL) of trifluoroacetic anhydride (6.61 mL, 9.48 mmol). After 2 h saturated aqueous NaHCO₃ was added, the crude reaction mixture was extracted (ether), dried (Na₂SO₄), and passed through a 1 inch pad of silica gel (230-400 mesh) eluting with 1:10 ether/pentanes. The purified product was concentrated to afford 482 mg (82%) of pure **29** as a pale yellow oil: IR (film) 2240, 1671 cm⁻¹; ¹H NMR δ 1.26 (d, *J*= 6.7 Hz, 6H), 1.57 (s, 3H), 1.65 (d, *J*= 6.7 Hz), 2.22-2.32 (m, 1H), 2.54-2.64 (m, 1H), 5.38-5.45 (m, 1H); ¹³C NMR δ 12.0, 13.5, 17.2, 17.6, 30.0, 46.6, 122.1, 122.9, 135.4; GCMS *m/e* 138 (M+H).

(2S*, 3R*), (E)-Methyl 2-cyano-4-trimethylhex-4-enoate (30a): Performing the general procedure with a THF solution (5 mL) of **29** (25 mg, 0.18 mmol) and methyl cyanoformate (17 mg, 0.20 mmol), provided, after purification by radial chromatography (1:20 EtOAc/hexanes) 18.5 mg (74%) of pure **30a** as an oil: IR (film) 2244, 1746, 1622 cm⁻¹; ¹H NMR δ 1.24 (d, *J*= 7.0 Hz, 6H), 1.52 (s, 3H), 1.68 (d, *J*= 7.6 Hz, 3H), 1.74 (s, 3H), 2.71 (q, *J*= 7.0 Hz, 1H), 3.87 (s, 3H), 5.48-5.54 (m, 1H); ¹³C NMR δ 13.2, 16.4, 22.8, 48.1, 49.2, 53.7, 120.1, 125.2, 134.0, 170.9; GCMS *m/e* 196 (M+H).

(2S*, 3R*), (E), 2-(hydroxymethyl)-2,3,4-trimethylhex-4-enenitrile (xiii): Solid LiBH₄ (153 mg, 4.12 mmol) was added to a 0 °C, THF solution (5 mL) of **30a** (100 mg, 0.51 mmol) and after 8 h, saturated, aqueous, NH₄Cl was added. The crude reaction mixture was separated, the aqueous phase extracted with ether, and then the combined organic phases were dried (Na₂SO₄), and purified using radial chromatography (1:6

EtOAc/hexanes) to give 92 mg of **xiii** as a pure oil: IR (film) 3453, 2236, 1659 cm^{-1} ; ^1H NMR δ 1.20 (s, 3H), 1.22 (d, $J = 8$, 3H), 1.57 (d, $J = 7.6$ Hz, 3H), 1.64 (s, 3H), 1.93 (br s, 1H), 2.25-2.32 (m, 1H), 3.50 (d, $J = 11$ Hz, 1H), 3.75 (d, $J = 11$ Hz, 1H), 5.30-5.37 (m, 1H); ^{13}C δ 13.5, 15.9, 19.9, 42.9, 46.0, 67.6, 123.6, 128.4, 135.6, 160.2; GCMS m/e 168 (M+H).

(2S*, 3R*), (E), 4-Nitro-benzoic acid 2-cyano-2,3,4-trimethyl-hex-4-enyl ester (xiv):

A THF solution (3 mL) of LDA, generated from BuLi (1.05 equiv.) and diisopropylamine (1.1 equiv.) was added to a 0 °C, THF solution (8 mL) of **xiii** (55 mg, 0.33 mmol). After 20 min a THF solution (5 mL) of p-nitrobenzoylchloride (104 mg, 0.36 mmol) was added and then the reaction mixture was allowed to warm to room temperature. After 16 h saturated, aqueous, NH_4Cl was added and then the phases were separated. The aqueous phase was extracted with EtOAc, and the combined extracts were dried (Na_2SO_4), and purified using radial chromatography (1:10 EtOAc/hexanes) to give 70 mg (73 %) of **xiv** as a light yellow solid (m.p. 75 - 77 °C), whose structure was determined by x-ray crystallography: IR (film) 2242, 1714, 1604 cm^{-1} ; ^1H NMR: δ 1.35 (d, $J = 6.8$ Hz, 3H), 1.39 (s, 3H), 1.62 (d, $J = 5.8$ Hz, 3H), 1.72 (s, 3H), 2.43 (q, $J = 6.8$ Hz, 1H), 4.30 (d, $J = 10.8$ Hz, 1H), 4.48 (d, $J = 10.8$ Hz, 1H), 5.42 (q, $J = 5.8$ Hz, 1H), 8.25-8.33 (m, 4H); ^{13}C NMR: δ 13.3, 13.5, 15.7, 20.3, 40.5, 46.9, 68.9, 121.8, 123.7, 124.4, 130.8, 134.3, 134.6, 150.8, 164.0; MS (CI) m/e 317 (M + H^+).

(2S*, 3R*), (E)-2-(1-Hydroxycyclohexyl)-2,3,4-trimethylhex-4-enenitrile (30b):

Performing the general procedure with a THF solution (5 mL) of **29** (25 mg, 0.18 mmol)

and cyclohexanone (19mg, 0.19 mmol), provided, after purification by radial chromatography (1:5 EtOAc/hexanes) 18.5 mg (74%) of **30b** as an oil: IR (film) 3478, 2231, 1678 cm^{-1} ; ^1H NMR δ 1.15-1.80 (m, 8H), 1.37 (s, 3H), 1.38 (d, J = 7.0 Hz, 3H), 1.64 (d, J = 6.8 Hz, 3H), 1.70 (s, 3H), 1.82-1.97 (m, 3H), 2.83 (q, J = 7.0, 1H), 5.47 (q, J = 6.2 Hz, 1H); ^{13}C NMR δ 13.6, 17.3, 18.4, 21.9, 25.6, 32.5, 33.2, 45.0, 50.0, 76.1, 124.0, 124.3, 138.7; HRMS (ESI) calcd for ($\text{M} + \text{Na}^+$) $\text{C}_{15}\text{H}_{25}\text{ONNa}$ 258.1833, found 258.1895.

(2S*, 3R*), (E)-2-(Cyclohexyl(hydroxy)methyl)-2,3,4-trimethylhex-4-enenitrile (30c):

Performing the general procedure with a THF solution (5 mL) of **29** (25 mg, 0.18 mmol) and cyclohexanecarboxaldehyde (30 mg, 0.19 mmol), provided, after purification by radial chromatography (1:4 EtOAc/hexanes) 21 mg (84 %) of **30c** as a 1:1 mixture of inseparable diastereomers as a pure oil: IR (film) 3451, 2234, 1672 cm^{-1} ; ^1H NMR δ 1.18-2.10 (m, 40H), 2.60 (q, J = 7.1 Hz, 1H), 2.77 (q, J = 7.1 Hz, 1H), 3.40-3.50 (m, 1H), 3.53- 3.62 (m, 1H), 5.38- 5.54 (m, 2H); ^{13}C δ 13.5, 13.6, 13.6, 14.3, 14.4, 15.8, 16.0, 17.4, 25.9, 26.3, 26.3, 26.4, 26.7, 27.0, 28.2, 30.0, 32.5, 32.7, 39.8, 40.7, 41.4, 44.3, 46.0, 46.2, 46.8, 47.0, 123.8, 124.5, 128.6, 135.6, 136.5; GCMS m/e 249 ($\text{M}+\text{H}$).

(2S*, 3R*, E)-2-(Cyclohexanecarbonyl)-2,3,4-trimethylhex-4-enenitrile (xv): Solid

TPAP (0.05 equiv.) was added to a room temperature, CH_2Cl_2 solution (8 mL) of **30c** (21 mg, 0.08 mmol), N-methyl morpholine N-oxide (49 mg, 0.42 mmol) and activated 4Å molecular sieves. After 2 h saturated aqueous NH_4Cl was added, the phases were separated, and the aqueous phase was extracted with ether. The combined organic extracts were dried (Na_2SO_4), and purified, to provide 16 mg (77 %) of ketone **xv** as a

colorless oil: IR (film) 2232, 1718 cm^{-1} ; ^1H NMR: δ 1.09 (d, J = 6.8 Hz, 3H), 1.22-1.43 (m, 6H), 1.30 (s, 3H), 1.61-1.63 (m, 3H), 1.70-1.71 (m, 3H), 1.73 – 1.93 (m, 4H), 2.66 (q, J = 6.8 Hz, 1H), 3.01-3.07 (tt, J = 11.0, 3.2 Hz, 1H), 5.43-5.47 (m, 1H); ^{13}C NMR: δ 13.1, 13.3, 16.6, 23.0, 25.2, 25.4, 25.6, 28.5, 29.6, 48.0, 48.9, 52.4, 121.7, 124.5, 134.4, 208.6; GCMS m/e 248 (M+H).

(2S*, 3R*), (E)-2,3,4-trimethyl-2-(phenylthio)hex-4-enenitrile (30d): Performing the general procedure with a THF solution (5 mL) of **29** (25 mg, 0.18 mmol) and S-phenyl benzenethio-sulfonate (59 mg, 0.23 mmol), provided, after purification by radial chromatography (1:5 EtOAc/hexanes) 20 mg of **30d** (79 %) as a pure oil: IR (film) 2226, 1659, 1582 cm^{-1} ; ^1H NMR δ 1.34 (s, 3H), 1.45 (d, J = 7 Hz, 3H), 1.60 (d, J = 6.7 Hz, 3H), 1.69 (s, 3H), 2.43 (q, J = 7 Hz, 1H), 5.42 (q, J = 6.7 Hz, 1H), 7.64-7.67 (m, 2H), 7.39-7.44 (m, 3H); ^{13}C δ 13.3, 13.5, 16.8, 25.7, 51.5, 121.7, 124.3, 128.4, 129.4, 130.4, 135.5, 137.6; GCMS m/e 246 (M+H).

(2S*, 3R*), (4E)-2-Cinnamyl-2,3,4-trimethylhex-4-enenitrile (30e): Performing the general procedure with a THF solution (5 mL) of **29** (30 mg, 0.22 mmol) and cinnamyl bromide (48 mg, 0.24 mmol), provided, after purification by radial chromatography (1:20 EtOAc/hexanes) 23.4 mg (78%) of **30e** as an oil: IR (film): 2232, 1679 cm^{-1} ; ^1H NMR δ 1.29 (s, 3H), 1.35 (d, J = 7.1 Hz, 3H), 1.32-1.87 (m, 6H), 2.25 (q, J = 7.1 Hz, 1H), 2.35 (dd, J = 8.6, 5.2 Hz, 1H), 2.76 (dd, J = 7.6, 6.2 Hz, 1H), 5.00-5.21 (m, 2H), 5.41 (q, J = 6.0, 1H), 7.25-7.50 (m, 5H); ^{13}C NMR δ 13.5, 15.9, 22.6, 40.1, 42.4, 49.8, 123.4, 123.8, 124.4,

126.5, 127.8, 128.9, 135.0, 136.1, 137.1; HRMS (ESI) calcd for (M+Na⁺) C₁₈H₂₃N Na 253.1830, found 253.1827.

(2S*, 3R*), (E)-2,3,4-trimethyl-2-(3-phenylprop-2-ynyl)hex-4-enenitrile (30f):

Performing the general procedure with a THF solution (5 mL) of **29** (30 mg, 0.22 mmol) and 1-(3-bromoprop-1-ynyl)benzene (55 mg, 0.28 mmol), provided, after purification by radial chromatography (1:5 EtOAc/hexanes) 23.4 mg (78 %) of **30f** as a pure oil: IR (film) 2237, 1662, 1586 cm⁻¹; ¹H NMR δ 1.25 (d, *J*= 7 Hz, 3H), 1.36 (s, 3H), 1.45-1.78 (m, 6, 1H), 2.70 d, *J*= 16.8 Hz, 1H), 2.81 (d, *J*= 16.8 Hz, 1H), 5.35-5.41 (m, 1H), 7.30-7.42 (m, 5H); ¹³C NMR δ 13.3, 14.1, 15.6, 22.8, 30.0, 31.6, 48.2, 83.7, 84.5, 123.0, 123.5, 123.5, 128.2, 128.3, 131.7, 135.4; GCMS *m/e* 252 (M+H).

(2S*, 3R*), (E)-4-Trimethyl-2-propylhex-4-enenitrile (30g):

Performing the general procedure with a THF solution (5 mL) of **29** (25 mg, 0.18 mmol) and PrI (34 mg, 0.20 mmol), provided, after purification by radial chromatography (1:20 EtOAc/hexanes) 18.0 mg (72%) of pure **30g** as an oil; IR (film) 2230· 1732 cm⁻¹; ¹H NMR δ 0.83 (t, *J*= 7.2 Hz, 3H), 1.07 (s, 3H), 1.11 (d, *J*= 7.0 Hz, 3H), 1.48 (d, *J*= 7.6 Hz, 3H), 1.55-1.57 (m, 3H), 2.01 (q, *J*= 7.0 Hz, 1H), 5.17-5.24 (m, 1H); ¹³C NMR δ 13.5, 14.5, 15.8, 18.3, 22.4, 29.9, 40.0, 41.0, 50.2, 123.1, 124.7, 136.4; GCMS *m/e* 180 (M+H).

(2S*, 3R*), 2-Methyl-2-((E)-3-methylpent-3-en-2-yl)hept-6-enenitrile (30h):

Performing the general procedure with a THF solution (5 mL) of **29** (30 mg, 0.22 mmol) and 5-bromopentene (39 mg, 0.24 mmol), provided, after purification by radial

chromatography (1:20 EtOAc/ hexanes) 24.6 mg (82%) of **30h** as an oil: IR (film) 2231, 1684 cm^{-1} ; ^1H NMR δ 1.25 (s, 3H), 1.28 (d, J = 7 Hz, 3H), 1.65 (d, J = 7.6 Hz, 3H), 1.73 (s, 3H), 2.10- 2.30 (m, 1H), 5.34- 5.41 (m, 1H), 5.78- 5.98 (m, 1H); ^{13}C NMR δ 13.4, 13.6, 15.8, 22.4, 24.2, 33.9, 38.2, 40.0, 50.1, 115.4, 123.1, 124.6, 136.3, 138.1; GCMS m/e 205 (M^+).

(2S*, 3R*), (E)-2-Isopropyl-2,3,4-trimethylhex-4-enenitrile (30i): Performing the general procedure with a THF solution (5 mL) of **29** (30 mg, 0.22 mmol) and 2-iodopropane (41 mg, 0.24 mmol), provided, after purification by radial chromatography (1:20 EtOAc/hexanes) 15.6 mg (52%) of pure **30i** as an oil: IR (film) 2232, 1651 cm^{-1} ; ^1H NMR δ 0.86 (d, J = 7.0 Hz, 3H), 1.03 (s, 3H), 1.10 (d, J = 6.7 Hz, 3H), 1.17 (d, J = 6.7 Hz, 3H), 1.57 (d, J = 5.5 Hz, 3H), 1.65 (s, 3H), 1.95-2.05 (m, 1H), 2.27 (q, J = 7.0 Hz, 1H), 5.27-5.31 (m, 1H); ^{13}C 6.1, 13.5, 15.6, 16.1, 17.0, 19.4, 32.1, 47.0, 123.1, 124.7, 136.5; GCMS m/e 180 ($\text{M}+\text{H}$).

(E)-Pent-3-en-2-yl propionate (xvi): Freshly distilled propionyl chloride (1.4 mL, 1.3 mmol) was added neat to a 0 ° C, CH_2Cl_2 solution (25 mL) of commercially available (E)-pent-3-en-2-ol (1 g, 11.6 mmol) and pyridine (1.3 mL, 1.3 mmol.). After 2 h at 0° C aqueous NaHCO_3 was added, the crude reaction mixture was extracted with ether, and the combined extracts were washed with a saturated, aqueous solution of NaCl, and dried (Na_2SO_4). Concentration of the crude product and purification by radial chromatography (1:5 ether/ pentane) afforded 1.3 g (78 %) of **xvi** as a colorless oil: IR (film) 1737, 1678 cm^{-1} ; ^1H NMR δ 1.15 (t, J = 7.8 Hz, 3H), 1.30 (d, J = 6.4 Hz, 3H), 1.71 (d, J = 6.4 Hz, 3H),

2.28-2.36 (m, 2H), 5.29- 5.38 (m, 1H), 5.45- 5.53 (m, 1H), 5.68-5.79 (m, 1H); ^{13}C NMR δ 9.3, 17.9, 20.5, 28.1, 71.1, 128.2, 131.1, 174.0; GCMS m/e 143 (M^+).

(2R*, 3S*), (E), 2,3,4-Trimethylhex-4-enoic acid (xvii): A THF solution (5 mL) of **xvi** (1 g, 7.0 mmol) was added dropwise to a $-78\text{ }^{\circ}\text{C}$, THF solution (20 mL) of TMSCl (1.25 mL, 9.8 mmol) and LDA, prepared from butyllithium (1.05 equiv.) and diisopropylamine (1.1 equiv.). The reaction mixture was allowed to warm to room temperature and after 16 h, an aqueous solution of HCl (10%) was added. The crude reaction mixture was extracted (EtOAc), dried (Na_2SO_4), concentrated and purified by radial chromatography (1:10, 1:5, EtOAc/ hexanes) to afford 700 mg (70 %) of **xvii** as a pure dense oil: IR (film) 2979, 1709, 1650 cm^{-1} ; ^1H NMR δ 1.06 (d, $J= 6.4$ Hz, 3H), 1.13 (d, $J= 6.8$, 3H), 1.69 (d, $J= 6.1$ Hz, 3H), 2.29- 2.46 (m, 2H), 5.23-5.53 (m, 2H); ^{13}C NMR δ 14.6, 18.1, 19.2, 40.1, 45.6, 126.1, 133.3, 183.4; GCMS m/e 143 ($\text{M}+\text{H}$).

(2R*, 3R*), (E), 2,3-Dimethylhex-4-enamide (xviii): Freshly distilled DMF (2 drops) was added to a $0\text{ }^{\circ}\text{C}$, CH_2Cl_2 solution (20 mL) of **xvii** (500 mg, 3.5 mmol) followed by oxalyl chloride (0.44 mL, 4.9 mmol). After 1 h the reaction mixture was concentrated, dissolved in CH_2Cl_2 (30 mL), and re-concentrated. The dissolution-concentration sequence was repeated two additional times and then saturated aqueous ammonia (20 mL) was added at 0°C . After 1 h the crude product was extracted (ether), dried (Na_2SO_4) and concentrated to afford 415 mg (84%) of pure **xviii** as a white crystalline solid (m.p. $166\text{--}169\text{ }^{\circ}\text{C}$): IR (film) 3360, 1658, 1630 cm^{-1} ; ^1H NMR δ 1.07 (d, $J= 6.7$ Hz, 3H), 1.16 (d, $J= 7$ Hz, 3H), 1.72 (d, $J= 7.9\text{Hz}$, 3H), 2.06-2.41 (m, 2H), 5.27-5.35 (m, 1H), 5.49-5.58 (m,

1H): ^{13}C NMR δ 16.0, 18.2, 19.2, 40.5, 46.9, 126.0, 134.2, 178.9; GCMS m/e 142 (M+H).

(2R*, 3R*), (E), 2,3-Dimethylhex-4-enenitrile (31): A THF solution (5 mL) of **xviii** (500 mg, 3.54 mmol) was added, dropwise, to a 0 °C, THF solution (10 mL) of trifluoroacetic anhydride (0.69 mL, 4.96 mmol). After 2 h saturated aqueous NaHCO_3 was added, the crude reaction mixture was extracted (ether), dried (Na_2SO_4), and passed through a 1 inch pad of silica gel (230-400 mesh) eluting with 1:10 ether/pentanes. The purified product was concentrated to afford 358 mg (82%) of pure **31** as a pale yellow oil: IR (film) 2239, 1641 cm^{-1} ; ^1H NMR δ 1.12 (d, J = 6.7 Hz, 6H), 1.23 (d, J = 7.3 Hz), 1.65 (d, J =7.4, 3H), 2.20-2.52 (m, 1H), 5.23-5.26 (m, 2H); ^{13}C NMR δ 15.8, 17.5, 17.8, 31.6, 40.0, 122.1, 127.0, 132.3; GCMS m/e 123 (M+H).

(2S*, 3R*, E)-2,3-Dimethyl-2-propylhex-4-enenitrile (33a) and (2R*, 3R*, E)-2,3-Dimethyl-2-propylhex-4-enenitrile (33b): Performing the general procedure with a THF solution (5 mL) of **31** (25 mg, 0.21 mmol) and PrI (44 mg, 0.29 mmol), provided, after purification by radial chromatography (1:20 EtOAc/hexanes) 18.0 mg (72%) of pure **33** as an inseparable mixture of diastereomers in the ratio of 1:4⁵ as an oil: IR (film) 2232 cm^{-1} , 1730 cm^{-1} ; ^1H NMR δ 0.95 (t, J = 7.5 Hz, 3H), 1.10 (d, J = 8.3, 3H), 1.15 (d, J = 6.8 Hz, 3H), 1.21 (s, 3H), 1.23-1.74 (m, 17H), 1.25 (s, 3H), 1.69 (d, J = 6.4 Hz, 3H), 2.19-2.28 (m, 1H), 5.28-5.55 (m, 2H); ^{13}C NMR δ 14.5, (16.1), 16.9, 18.2, 18.3, (18.4), 21.0, (21.6), (29.9), (39.2), 39.8, 40.8, (40.9), 43.9, (44.4), (124.3), 124.5, (127.9), 128.1, 130.8, (131.5); GCMS m/e 166 (M+H).

2,3,7-Trimethyloct-6-enenitrile (34): Performing the general procedure with a THF solution (5 mL) of 3,7-dimethyloct-6-enenitrile^{1a} (25 mg, 0.17 mmol) and MeI (35 mg, 0.22 mmol) provided, after purification by radial chromatography (1:20 EtOAc/hexanes) 21 mg (85%) of **34** as a 1.3:1⁶ inseparable mixture of diastereomers as an oil: IR (film) 2246, 1692, 1666 cm⁻¹; ¹H NMR δ 1.05 (d, J = 6.8 Hz, 3H), 1.28 (d, J = 7.3, 3H), 1.31 (d, J = 7.3, 3H), 1.63 (s, 3H), 1.71 (s, 3H), 1.94-2.13 (m, 1H), 2.56-2.62 (m, 2H), 2.65-2.70 (m, 2H), 5.07-5.15 (m, 1H); ¹³C δ 14.7, (14.8), 15.8, (16.1), 17.0, (17.9), 25.5, (25.9), 31.2, (31.5), 33.3, 35.2, 35.6, (35.9), 122.0, (122.8), 123.8, (123.8), 128.5, 132.4; GCMS m/e 165 (M+H).

(2S*, 3R*), 2,3,7-Trimethyl-2-propyloct-6-enenitrile (35): Performing the general procedure with a THF solution (5 mL) of **34** (25 mg, 0.15 mmol) and PrI (33 mg, 0.19 mmol) provided, after purification by radial chromatography (1:20 EtOAc/hexanes) 20 mg (80%) of **35** as a 1.8:1⁷ inseparable diastereomeric mixture of pure oil; IR(film) 2247, 1691, 1666 cm⁻¹; ¹H NMR δ 0.98 (t, J = 6.8 Hz, 3H), 1.06 (d, J = 6.9 Hz, 3H), 1.24 (d, J = 6.3 Hz, 3H), 1.63 (s, 3H), 1.71 (s, 3H), 1.90-1.99 (m, 2H), 2.09-2.22 (m, 3H), 5.11 (q, J = 8 Hz, 1H); ¹³C δ (13.7), 14.5, 15.0, (17.9), 18.4, 20.7, 20.9, (25.9), 26.3, 26.4, (31.3), 32.6, 38.9, 39.0, (39.3), 41.4, 123.9, (124.1), 124.9, 132.4, (132.5); GCMS m/e 208 (M+H).

3-Phenylbutanenitrile (36): Neat acetonitrile (616 mg, 15.0 mmol) was added dropwise to a -78 °C, THF solution (35 mL) of LDA, generated from butyllithium (15.0 mmol) and diisopropylamine (16.0 mmol). After 50 min at -78 °C, neat (1-bromoethyl)benzene (2.96

g, 16.0 mmol) was added, the cooling bath was removed, and then the mixture was allowed to warm to room temperature. After 2 h, saturated, aqueous NH_4Cl was added, and then the aqueous phase was separated and extracted with EtOAc. The combined extracts were dried (MgSO_4), concentrated and purified by radial chromatography (1:50 to 1:30 EtOAc/hexanes) to afford 1.31 g (60%) of **36** as an oil: IR (film) 2246, 1601 cm^{-1} ; ^1H NMR: δ 1.47 (d, $J = 7.4$ Hz, 3H), 2.54 - 2.65 (m, 2H), 3.14 – 3.21 (m, 1H), 7.25-7.38 (m, 5H); ^{13}C NMR: δ 20.6, 26.3, 36.5, 118.5, 126.5, 127.2, 128.8, 143.1; MS (CI) m/e 146 ($\text{M} + \text{H}^+$).

2-(1-Phenyl-ethyl)-pent-4-enenitrile (38): The deprotonation procedure (B) was employed with **36** (122 mg, 0.84 mmol) and allylbromide (121 mg, 1.0 mmol) to afford, after purification by radial chromatography (1:30 EtOAc/hexanes), 125 mg (80%) of **38** as a oily 1:2 mixture of diastereomers: IR (film) 2237, 1643, 1603 cm^{-1} ; For the major isomer : ^1H NMR: δ 1.41 (d, $J = 6.7$ Hz, 3H), 2.12 – 2.19 (m, 2H), 2.67- 2.72 (m, 1H), 2.84 – 2.90 (m, 1H), 5.04 – 5.10 (m, 2H), 5.69 – 5.77 (m, 1H), 7.12 – 7.27 (m, 5H); ^{13}C NMR: δ 19.3, 34.8, 39.3, 41.0, 118.9, 120.7, 127.1, 127.7, 128.8, 133.0, 142.5; MS (CI) m/e 304 ($\text{M} + \text{H}^+$). For the minor isomer: ^1H NMR: δ 1.39 (d, $J = 8.3$ Hz, 3H), 2.12 – 2.19 (m, 2H), 2.73- 2.77 (m, 1H), 2.90 – 2.96 (m, 1H), 5.04 – 5.10 (m, 2H), 5.69 – 5.77 (m, 1H), 7.12 – 7.27 (m, 5H); ^{13}C NMR: δ 19.3, 34.3, 39.1, 40.6, 118.7, 120.5, 127.3, 127.4, 128.6, 133.3, 141.3; MS (CI) m/e 186 ($\text{M} + \text{H}^+$). Employing the bromine-copper exchange procedure with **39** (134mg, 0.60 mmol) and allylbromide (90.7 mg, 0.75 mmol) afforded, after purification by radial chromatography (1:30 EtOAc/hexanes), 58.8 mg (53%) of **38** as a 1:1 mixture of diastereomers.

(2*R, 3*S**) and (2*R**, 3*R**) 2-Bromo-3-phenylbutanenitrile (39):** The bromination procedure was employed with 3-phenylbutanenitrile (1.92 g, 13.2 mmol), Br₂ (2.24 g, 14 mmol) and PBr₃ (3.78 g, 14 mmol) to afford, after purification by radial chromatography (1: 60 to 1: 30 EtOAc/hexanes), 2.46 g (83%, 1:1 mixture) of **39** as an oil. For one diastereomer: IR (film) 2241, 703 cm⁻¹; ¹H NMR: δ 1.63 (d, *J* = 7.3 Hz, 3H), 3.31 – 3.36 (m, 1H), 4.44 (d, *J* = 5.4 Hz, 1H), 7.26-7.39 (m, 5H); ¹³C NMR: δ 16.9, 33.8, 45.0, 116.1, 127.5, 128.3, 129.0, 139.7; HRMS(EI) calcd for (M⁺), C₁₀H₁₀BrN⁺ 222.9991, found 222.9976. For the other diastereomer: IR (film) 2242, 702 cm⁻¹; ¹H NMR: δ 1.57 (d, *J* = 7.3 Hz, 3H), 3.29 – 3.35 (m, 1H), 4.41 (d, *J* = 6.8 Hz, 1H), 7.25-7.40 (m, 5H); ¹³C NMR: δ 18.2, 34.9, 44.4, 116.6, 127.7, 128.3, 128.8, 139.3 MS (CI) m/e 224 (M + H⁺).

(2*R,3*R**)-2-(1-hydroxycyclohexyl)-3-phenylbutanenitrile and (2*S**, 3*R**)-2-(1-hydroxycyclohexyl)-3-phenylbutanenitrile (41):** The deprotonation procedure (B) was employed with **36** (95.4 mg, 0.60 mmol) and cyclohexanone (61.7 mg, 0.63 mmol) to afford, after purification by radial chromatography (stepped gradient 1:19, 1:4 EtOAc/hexanes), 111 mg (76%) of **41** as a 1:3.6 mixture of diastereomers (oil). For the major diastereomer (which elutes first in the separation): IR (film) 3463, 2238 cm⁻¹; ¹H NMR: δ 1.23 – 1.82 (m, 10H), 1.54 (d, *J* = 7.3 Hz, 3H), 2.86 (d, *J* = 3.9 Hz, 1H), 3.30 (dq, *J* = 7.3, 3.9 Hz, 1H), 7.23-7.35 (m, 5H); ¹³C NMR: δ 19.7, 21.6, 21.6, 25.2, 35.5, 36.1, 36.3, 51.6, 72.8, 119.3, 126.9, 127.0, 128.9, 145.3; MS (CI) m/e 244 (M + H⁺). For the minor diastereomer: IR (film) 3531, 2234 cm⁻¹; ¹H NMR: δ 1.14 – 1.68 (m, 10H), 1.50 (d, *J* = 6.9 Hz, 3H), 2.89 (d, *J* = 4.4 Hz, 1H), 3.29 (dq, *J* = 6.9, 4.4 Hz, 1H), 7.26-

7.47 (m, 5H); ^{13}C NMR: δ 21.4, 21.7, 23.0, 25.2, 35.9, 36.0, 36.6, 51.0, 72.6, 120.0, 127.6, 128.1, 128.9, 142.3; MS (CI) m/e 244 ($\text{M} + \text{H}^+$). Employing the exchange procedure (A) with **39** (71.4 mg, 0.30 mmol) and cyclohexenone (37.2 mg, 0.38 mmol) afforded 61.3 mg (84%) of **41** as a mixture of diastereomers in a 3.4:1 ratio.

Chloroform-d

PPM

FFWL0202.010
DATE 2-2-4

SF	75.475
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RD	3.000
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RG	200
NS	1416
TE	297
FW	22400
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DP	20H BB
LB	0.0
GB	0.0
CX	25.00
CY	15.00
F1	220.014P
F2	.024P
HZ/CM	664.150
PPM/CM	8.800
SR	-1394.66

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128.432

127.846

118.815

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76.976

76.560

53.402

49.671

45.637

22.467

17.644

PPM

FFWL0924.488
DATE 21-10-99

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SM 16384
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TE 297

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PPM/CM 8.800
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WANG

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PPM

CARBON.000
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TE 297

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GB 0.0
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CY 14.00
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F2 -.004P
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PPM/CM 8.800
SR -1392.48

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128.180
127.139
123.647

115.126

77.409
76.998
76.56646.354
41.330
37.476
33.47123.970
21.481
17.095

200 180 160 140 120 100 80 60 40 20

Chloroform-d

PPM
198.215

FFWL0401.401
DATE 1-4-4

SF 75.469
SY 75.0
O1 6147.202
SI 16384
TD 16384
SM 17857.143
HZ/PT 2.180

PW 4.0
RO 3.000
AQ .459
RG 200
NS 16260
TE 297

FW 22400
O2 4004.452
DP 20H BB

LB 0.0
GB 0.0
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CY 14.00
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F2 -.004P
HZ/CM 664.150
PPM/CM 8.800
SR -1403.38

139.679

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128.558
127.778
122.347

77.426
76.999
76.567

50.284

46.005

37.891

21.803

16.780

FFWL0915.401
DATE 13-10-99

PR
Q

7 37015
3535
34147
32778

3.13095

460
2511
2448

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SY 210.0
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SI 8192
TD 8192
SW 6024.096
HZ/PT 1.471

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AQ .680
RG 8
NS 8
TE 297

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CY 12.50
F1 10.001P
F2 .196P
HZ/CM 122.423
PPM/CM .408
SR 3367.50

25

25

alcoholcarbon

Propionyl ester(proton).tnt

The structure of **28** is disordered showing two crystallographically independent conformers stacked on top of each other looking down a diagonal bisecting the *a c* axes in the P-1 unit cell. The conformers reside in groups of two hydrogen-bonded dimers, where $Z = 2$. Refinement constraints allowed the evaluation of the percentage of each conformer in the unit cell: conformer A, 64 %; conformer B, 36 %. Structure B is less well resolved with more elongated thermal ellipsoids.

The structure of **xii** is disordered showing two crystallographically independent conformers stacked on top of each other looking down *c* axis in the P2(1)/c unit cell. The conformers reside in pairs, where $Z = 4$, *i.e.*, two pairs, Refinement constraints allowed the evaluation of the percentage of each conformer in the unit cell: conformer A, 72 %; conformer B, 28 %. Structure B is less well resolved with more elongated thermal ellipsoids.

46.97
46.81
46.15
45.99
44.33

41.43
40.70
39.77

32.74
32.53

29.78
28.23
26.92
26.65
26.36
26.30
26.27
25.92

17.36
15.97
15.81
14.43
14.29
13.62
13.58
13.48

30i

34

34

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- ⁵ The ratio was determined by ¹H NMR integration of the methyl doublets centered on δ = 1.10 and 1.15
- ⁶ The ratio was determined by ¹H NMR integration of the nitrile-bearing methine signals that were clearly distinguishable in the region δ = 2.5-2.7
- ⁷ The ratio was determined by ¹H NMR integration of the methyl doublets centered on δ = 1.06 and 1.24