Tetrahedron Letters, Vol. 33, No. 43, pp. 6411-6414, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Synthesis of All Four Isomers of Disparlure Using Osmium-Catalyzed Asymmetric Dihydroxylation.

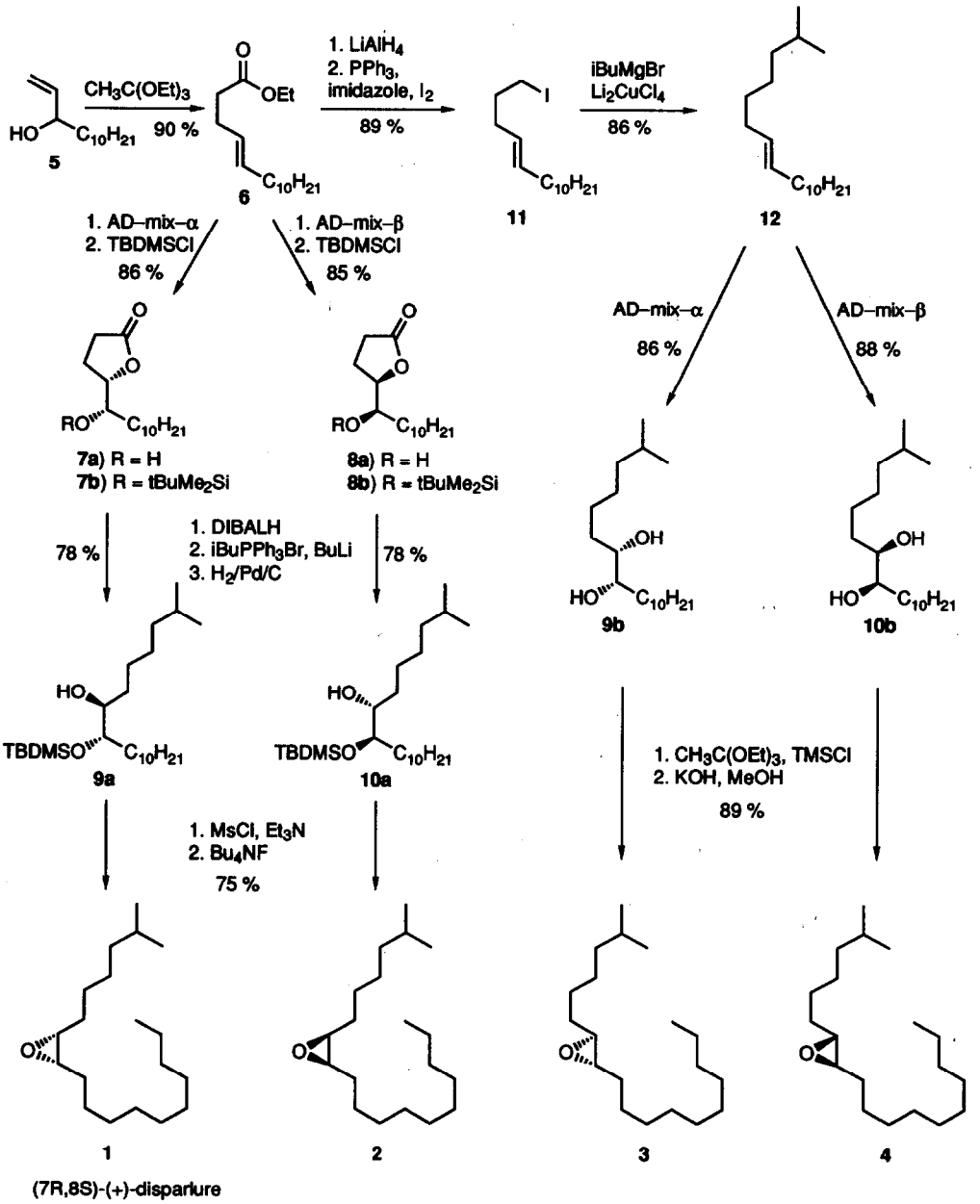
Ehud Keinan*#a Subhash C. Sinha[a], Anjana Sinha-Bagchi[a],
Zhi-Min Wang, Xiu-Lian Zhang and K. Barry Sharpless

Departments of Chemistry and Molecular Biology[a], The Scripps Research Institute,
10666 N. Torrey Pines Road, La Jolla, CA 92037, U.S.A.

Abstract: (+)-Disparlure, the sex attractant emitted by the female gypsy moth, *Porthetria dispar* (L.), and its (-)-enantiomer were synthesized in 43% yield and >99% ee, starting from undecanal and using the asymmetric dihydroxylation (AD) reaction. Similarly, the two trans-isomers of disparlure were synthesized in 51% yield and 95% ee.

The structure of disparlure, the sex attractant emitted by the female gypsy moth, *Porthetria dispar* (L.), has been established as (+)-(7R,8S)-cis-7,8-epoxy-2-methyloctadecane (**1**).[1,2] Because of the important role played by this pheromone in pest control, many syntheses of (+)-disparlure have been reported.[3] The classical approaches employ enantiopure natural products as starting materials. For example, both enantiomers of disparlure (**1** and **2**) as well as their trans isomers (**3** and **4**) were synthesized from L-glutamic acid in 11 or 13 steps.[2] Other useful starting materials include L-(+)-tartaric acid,[4] D-(+)-glyceraldehyde,[5] D-glucose,[6] D-ribose,[7] as well as enantiomerically pure sulfoxides.[8] An efficient method for the synthesis of **1** is based on the asymmetric epoxidation reaction (AE) using achiral starting materials.[9]

We report here highly selective and efficient syntheses of all four disparlure isomers (**1-4**) using the asymmetric dihydroxylation reaction (AD) and employing undecanal as starting material. Reaction of the latter with vinylmagnesium bromide (2 equiv) at 0 °C in THF afforded tridec-1-en-3-ol (**5**[10]) in 95% yield. Heating with triethylorthoacetate and catalytic amount of propionic acid, gave the corresponding Johnson-Claisen[11] rearrangement product, (E)-ethyl pentadec-4-enoate (**6**[12]). Asymmetric dihydroxylation of the latter with either AD-mix-α or AD-mix-β and methane-sulfonamide under the conditions described in our accompanying paper,[13] afforded hydroxylactones **7a**[14] or **8a**, respectively. The enantiomeric purity of these two products (95% and 96% ee, respectively) was easily increased to essentially 100% ee by a single recrystallization from pentane-ether, as was determined by HPLC (using Pirkle 1-A chiral column with hexane:isopropanol, 95:5) and by ^{1}H NMR of their Mosher's esters.[15]



Protection of the free hydroxyl group in **7a** or **8a** with *t*-butyldimethyl-silyl chloride afforded the corresponding silyl ethers **7b** and **8b**[16]. These were converted to compounds **9a** and **10b**,[17] respectively, via a three step sequence. First, partial reduction of the lactone to lactol using diisobutylaluminum hydride in THF at -78 °C,[2] then Wittig reaction with isobutyltriphenylphosphonium ylid in THF at room temperature, and finally,

hydrogenation of the resultant olefin (1 atm H_2, 10% Pd/C, THF, room temperature, 24 h). (+)-Disparlure (**1**) and (-)-disparlure (**2**) were obtained from **9a** and **10a**, respectively in two steps: first, mesylation of the free alcohol, using methanesulfonyl chloride in methylene chloride and triethylamine, and then desilation of the silyl ether with tetrabutylammonium fluoride in THF.[5b] Our synthetic **1** and **2** were found to be identical (by ^{1}H NMR, ^{13}C NMR, IR, $[\alpha]_D$ and MS) to the reported data.[1-9]

The two trans epoxides **3** and **4** were prepared from diols **9b** and **10b**, respectively. The latter are also readily available by desilation of **9a** and **10a** (six steps from **6**). We found that **9b** and **10b** can be prepared by an alternative, four-step route from **6**. Reduction with $LiAlH_4$ in ether at 0 °C afforded the corresponding primary alcohol.[18] Treatment of the latter with triphenylphosphine, imidazole and iodine (1.25 equiv of each) in toluene at 60 °C for 3 h afforded (E)-1-iodo-pentadec-4-ene **11**.[19] Cross-coupling of **11** with isobutylmagnesium bromide (2.5 equiv), in the presence of Li_2CuCl_4 (10 mol %) in THF at 0 °C for 16 h, gave (E)-2-methyloctadec-7-ene (**12**[20]). AD reaction of this olefin with either AD-mix-α or AD-mix-β afforded diols **9b** or **10b**,[21] in 95 and 97 % ee, respectively, as determined by both HPLC (using Pirkle 1-A chiral column) and ^{1}H NMR of their Mosher's esters.[15] Using the recently improved methodology[22] for conversion of vicinal diols into epoxides, compounds **9a** and **10b** were treated with chlorotrimethylsilane and triethyl orthoacetate in methylene chloride (0 °C, 2 h) and then with 0.5M methanolic KOH (0 °C, 1 h), to produce **3** and **4**, respectively. Epoxides **3** ($[\alpha]_D$ = -26.96° (c = 3.13, CCl_4), lit.[2] -26.6° (c = 0.5, CCl_4)) and **4** ($[\alpha]_D$ = +27.03° (c = 5.18, CCl_4), lit.[2] +27.5° (c = 0.5, CCl_4)) were found to be identical (by ^{1}H NMR, IR, and MS) to the reported compounds.[2]

Acknowledgment: EK thanks the United States-Israel Binational Science Foundation (090-00427) and KBS thanks the National Institute of Health (GM-28384) for financial support.

References and notes

#) Permanent address: Department of Chemistry, Technion - Israel Institute of Technology, Technion City, Haifa 32000, Israel.

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10. Tridec-1-en-3-ol (**5**): **^{1}H NMR**: 5.84 (ddd, J = 17.2, 10.4, 6.4, 1H), 5.19 (d, J = 17.2, 1H), 5.07 (d, J=10.4, 1H), 4.06 (q, J = 6.4, 1H), 1.76 (br s, 1H), 1.49 (m, 1H), 1.24 (m, 17H), 0.86 (t, J = 6.4, 3H). **^{13}C NMR**: 141.33, 114.44, 73.23, 37.08, 31.88, 29.71, 29.26, 25.35, 22.66, 14.07. **MS (FIB)**: 221 (M+Na$^+$).

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12. (E)-Ethyl pentadec-4-enoate (**6**): **^{1}H NMR**: 5.39 (m, 2H), 4.09 (q, J = 7.2, 2H), 2.31 (m, 4H), 1.93 (q, J = 6.6, 2H), 1.25 (m, 19H), 0.85 (t, J = 7.2, 3H). **^{13}C NMR**: 173.18, 131.78, 127.84, 60.13, 34.38, 32.47, 31.88, 29.59, 29.48, 29.41, 29.31, 29.09, 22.65, 14.20. **MS (FIB)**: 269 (M+H$^+$).

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14. 5-Hydroxypentadecan-1,4-olide (**7a**): **m.p.** 66 °C (lit.[2] 66 °C). **Anal.** Calc. for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01. Found: C, 70.31; H, 11.00. $[\alpha]_D$ = +24.95° (c = 5.01, $CHCl_3$), lit.[2] +29.2° (c = 1.2, $CHCl_3$). **8a**: $[\alpha]_D$ = -25.29° (c = 5.1, $CHCl_3$).

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16. 5-(t-Butyldimethylsiloxy)pentadecan-1,4-olide (**7b** and **8b**): **^{1}H NMR**: 4.48 (m, 1H), 3.66 (dt, J= 6.0,4.4, 1H), 2.50 (m, 2H), 2.20 (m, 1H), 2.03 (m, 1H), 1.58 (m, 1H), 1.46-1.20 (br s, 17H), 0.88 (s, 9H), 0.87 (t, J = 7.2, 3H), 0.08 (s, 3H), 0.07 (s, 3H). **^{13}C NMR**: 177.35, 81.63, 74.19, 32.68, 31.86, 29.69, 29.53, 29.48, 29.29, 28.56, 25.78, 25.20, 23.62, 22.65, 18.03, 14.08, -4.48.

17. 2-Methyl-8-(*t*-butyldimethylsiloxy)octadecan-7-ol (**9** and **10**): **^{1}H NMR**: 3.49 (dt, J = 6.2, 4.4, 1H), 3.42 (m, 1H), 1.70-1.15 (br s, 27H), 0.90 (s, 9H), 0.88 (t, J = 7.0, 3H), 0.86 (d, J = 6.7, 6H), 0.08 (s, 3H), 0.07 (s, 3H).

18. (E)-Pentadec-4-en-1-ol: **^{1}H NMR**: 5.41 (m, 2H), 3.63 (t, J = 6.8, 2H), 2.06 (q, J = 7.6, 2H), 1.95 (q, J = 7.2, 2H), 1.61 (quintet, J = 6.8, 2H), 1.36-1.20 (br s, 16H), 0.87 (t, J = 7.2, 3H). **^{13}C NMR**: 131.27, 129.30, 62.54, 32.54, 32.43, 31.89, 29.61, 29.55, 29.50, 29.32, 29.16, 28.90, 22.66, 14.09.

19. (E)-1-Iodopentadec-4-ene (**11**): **^{1}H NMR**: 5.47 (dt, J = 15.2, 6.8, 1H), 5.31 (dt, J = 15.2, 8.4, 1H), 3.17 (t, J = 7.0, 2H), 2.08 (q, J = 7.0, 2H), 1.96 (q, J = 6.7, 2H), 1.86 (quintet, J = 6.8, 2H), 1.34-1.20 (br s, 16H), 0.87 (t, J = 7.2, 3H). **^{13}C NMR**: 132.31, 127.61, 33.09, 32.57, 31.90, 29.62, 29.52, 29.33, 29.15, 22.68, 14.11, 6.65. **GC/MS**: 336 (M$^+$).

20. (E)-2-Methyl octadec-7-ene (**12**): **^{1}H NMR**: 5.38 (t, J = 5.2, 2H), 1.96 (br s, 4H), 1.50 (sepstet, J = 6.6, 1H), 1.40-1.10 (m, 22H), 0.88 (t, J = 6.6, 3H), 0.86 (d, J = 6.6, 6H). **^{13}C NMR**: 130.36, 38.87, 32.61, 31.91, 29.88, 29.65, 29.53, 29.35, 29.16, 27.93, 26.88, 22.68, 14.09. **Anal.** Calc. for $C_{19}H_{38}$: C, 85.63; H, 14.37. Found: C, 85.42; H, 14.49.

21. (S,S)- and (R,R)-2-Methyl-7,8-dihydroxyoctadecane (**13** and **14**): **m.p.** 58 °C. **^{1}H NMR**: 3.40 (br s, 2H), 1.60-1.12 (m, 27H), 0.87 (t, J = 6.8, 3H), 0.86 (d, J = 6.6, 6H). **^{13}C NMR**: 74.60, 38.93, 33.55, 33.47, 31.89, 29.72, 29.63, 29.33, 27.91, 27.45, 25.95, 25.71, 22.60, 14.06. **Anal.** Calc. for $C_{19}H_{40}O_2$: C, 75.94; H, 13.42. Found: C, 75.99; H, 13.46. **13**: $[\alpha]_D$ = -19.96° (c = 2.45, $CHCl_3$). **14**: $[\alpha]_D$ = +20.16° (c = 5.00, $CHCl_3$).

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(Received in USA 12 June 1992; accepted 3 August 1992)