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SEMIOCHEMICALS VIA EPOXIDE INVERSION

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Abstract—A sequence of reactions is presented for inverting the configurations of both epoxide carbons in 1,2-disubstituted epoxides. As examples, (+)-disparlure was converted to its enantiomer, (−)-disparlure, and *exo-endo* conversion of a cyclohexene oxide was demonstrated.

Key Words—Enantiomer, chirality, pheromone, disparlure.

INTRODUCTION

(+)-Disparlure **1** [(7*R*,8*S*)-2-methyl-7,8-epoxyoctadecane] (Figure 1), the sex pheromone of the gypsy moth, *Lymantria dispar* L., (Bierl et al., 1970) is a chiral biomolecule whose performance in trapping experiments has been found to be very sensitive to the presence of even small amounts of the (−) enantiomer (Plimmer et al., 1977). We recently developed an analytical procedure for determining the chirality of **1** that involved conversion, with two inversions of configuration, to *N*-(α-methylbenzyl)aziridines (Oliver and Waters, 1995). This procedure involved epoxide opening with α-methylbenzylamine (stereoselective with inversion, but not regioselective), mesylation of the OH, and intramolecular displacement of the mesylate (stereoselective with inversion). It occurred to us that a similar sequence, but using an appropriate oxygen nucleophile, ought to be applicable to an epoxide–epoxide enantiomeric conversion that would complement the formal *cis–trans* inversions of disparlure developed in our labora-

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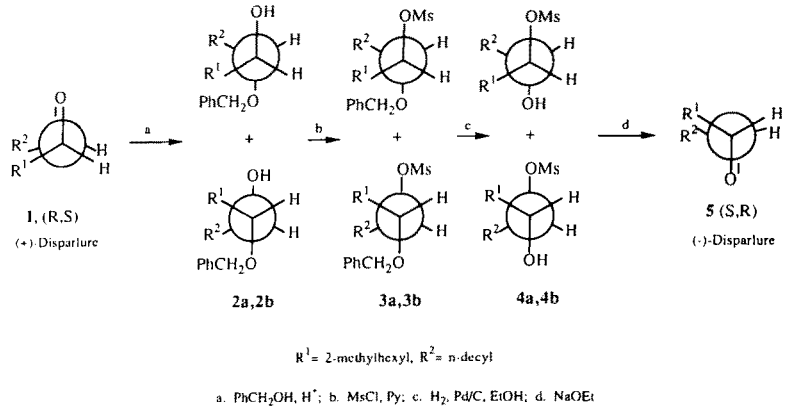


FIG. 1. Conversion of (+)-disparlure to (−)-disparlure.

tories a number of years ago (Sonnet and Oliver, 1976a,b). Here we report the application of epoxide inversion to the synthesis of (−)-disparlure and an unrelated epoxide of semiochemical interest.

METHODS AND MATERIALS

Gas chromatography was performed on Shimadzu 9A and 14A instruments, equipped with 15-m DB-5 and 60-m SPB 608 capillary columns, respectively. The former was generally used for following the progress of reactions and flash chromatography, whereas the latter, operated isothermally at 240°C, was employed for disparlure chirality analyses (Oliver and Waters, 1995) and also for attempted separations of positional isomers derived from epoxide opening of disparlure (e.g., **2a, 2b** and **3a, 3b**). ^{1}H NMR spectra were obtained with a General Electric QE-300 spectrometer on deuteriochloroform or deuteriobenzene solutions. Mass spectra were recorded on a Finnigan model 4510 GC-MS. (Mention of a proprietary product or company does not imply endorsement by the U.S. Department of Agriculture.)

Inversion of (+)-Disparlure to (−)-Disparlure. A mixture of (+)-disparlure (170 mg), benzyl alcohol (466 mg), and 2 Nafion beads (Aldrich, ca. 10 mg) was allowed to stand at room temperature for four days, then was thoroughly partitioned between pentane and water. Flash chromatography (2.5% then 5% EtOAc in cyclohexane) provided separation from rearrangement products and gave 155 mg (66%) of a mixture of regioisomeric benzyloxy alcohols **2a** and **2b.** [No GC separation of the ketonic rearrangement products was realized;

chemical ionization mass spectrometry confirmed molecular weight 282 (isomeric to **1**); the electron impact spectrum contained the four expected acyl ions for 2-methyloctadecan-7-one and 2-methyloctadecan-8-one (*m/z* 127, 141, 169, 183) but the predicted McClafferty rearrangement ions (*m/z* 142, 156, 184, 198) although visible, were too weak to be very diagnostic: m/z(%), 183 (13), 169 (16), 127 (10), 123 (10), 109 (23), 96 (14), 95 (19), 85 (18), 83 (15), 82 (100), 71 (57), 67 (11), 59 (13), 58 (39), 57 (73), 55 (34). Its infrared spectrum (neat, 1712 cm^{-1}) indicated ketone(s), as did the lack of a deshielded signal in the ^1H NMR spectrum indicative of an aldehyde.] The entire sample of **2a** and **2b** in pyridine (2 ml) was treated with methanesulfonyl chloride (100 μl) in a nitrogen atmosphere, and the solution was allowed to stand overnight at room temperature. It was then partitioned between cold, dilute HCl and pentane, and the pentane was rinsed with water and with aqueous sodium carbonate. Removal of solvent provided 203 mg of **3a** + **3b** as a clear oil that was not purified (TLC yielded a single spot, R_f = 0.43, 5% EtOAc/toluene), but was hydrogenated (1 atm, 10% Pd on charcoal) in absolute ethanol—see below. No gas chromatographic resolution was achieved between regioisomers **2a, 2b,** or **3a, 3b,** and detailed characterization was not attempted. Mass and ^1H NMR spectra were recorded on mixtures of the isomers: Mass spectrum **2a** + **2b** (GS introduction; mol wt 390 confirmed by chemical ionization with both methane and ammonia reagent gases) electron ionization m/z (%) 390 (0.03, M^+), 127 (6), 92 (14), 91 (100), 83 (5), 69 (10), 57 (6), 55 (7). Mass spectrum of **3a** + **3b** (probe introduction): m/z (%), 468 (0.1, M^+), 127 (6), 111 (8), 107 (10), 97 (9), 92 (7), 91 (100), 83 (10), 69 (17), 57 (10), 55 (10).

Following hydrogenation of **3a, 3b,** filtration and evaporation of solvent gave 111 mg of **4a** + **4b** as a glassy residue. Addition of methanol (2 ml) followed by 0.25 ml of 2.9 M sodium methoxide in methanol resulted in the almost immediate precipitation of a white solid. After 1.75 hr the solvent was concentrated, and the residue was partitioned between water and pentane. Flash chromatography of the pentane-soluble product (hexane followed by 2.5% and finally 5% ethyl acetate in hexanes) gave 67 mg of (−)-disparlure **5** indistinguishable from the starting material except for its chirality (Oliver and Waters, 1995—see text). Mass spectrum of **5** (e. i., m/z (%)]: 282, M^+ (0.2), 183 (8), 111 (17), 110 (17), 109 (10), 97 (42), 95 (17), 85 (9), 84 (11), 83 (27), 82 (58), 71 (17), 70 (22), 71 (17), 70 (22), 69 (100), 67 (25), 57 (38), 56 (39), 55 (64).

Opening of Ethyl-trans-4-Methyl-7-oxabicyclo[4.1.0]heptane-3-cis-Carboxylate **6**. A mixture of **6** (racemic, 7.36 g), benzyl alcohol (30 ml), and Nafion (0.5 g) was allowed to stand at room temperature for 12 days (this reaction could also be conducted at elevated temperatures if desired). The product was partitioned between pentane and water, and then, after evaporation of

the pentane, between cyclohexane and water. Alternatively, the bulk of the excess benzyl alcohol could be removed by distillation *in vacuo* prior to partitioning. Removal of solvent gave 9.87 g of a clear oil that contained **8** plus its positional isomer and very little benzyl alcohol. Mass spectrum of **8:** m/z (%), 168 (8), 155 (8), 137 (6), 111 (13), 109 (10), 94 (12), 92 (15), 91 (100), 85 (8), 83 (6), 81 (20), 71 (14), 65 (10), 55 (9).

Benzyloxymesylate **9.** The preceding sample, dissolved in a mixture of pyridine (15 ml) and dichloromethane (30 ml), was stirred and cooled in a nitrogen atmosphere while a solution of methanesulfonyl chloride (3.5 ml) in dichloromethane (10 ml) was added dropwise. After 2.5 hr at 0°C the ice bath was removed, and after an additional hour 0.5 ml of methanesulfonyl choride was added slowly. After stirring at room temperature one more hour, ice was added and the mixture was partitioned between water and ether–hexane (1 : 1). The solution was rinsed with water, twice with 2 N HCl, again with water, and finally with 1 M Na_2CO_3. The solution was dried and concentrated, and the residue (12 g) was passed through a short silica gel column with 10% followed by 20% ethyl acetate in hexanes. Evaporation of solvent gave 10.46 g (84%) of **9** plus its regioisomeric benzyloxy mesylate. A sample of the major isomer **9** was isolated by flash chromatography (ca. 20% ethyl acetate in hexanes). Mass spectrum of **9:** m/z (%), 370 (1, M^+), 168 (17), 122 (6), 95 (6), 94 (38), 92 (8), 91 (100), 81 (7), 65 (6). ^1H NMR of **9** ($CDCl_3$) 0.94 (d, J = 6.6, 6-Me), 1.24 (t, J = 7.2, $C\underline{H}_3CH_2$), 1.73 (m, H-$5_{a,b}$), 1.96 (m, H-2), ca. 2.05 (m, H-6), 2.40 (dt, J = 5.4 and 10.2 H-1), 2.98 (s, $C\underline{H}_3SO_3$), 3.79 (app. d, H-3), 4.15 (q, J = 7.2, $CH_3C\underline{H}_2$), 4.55 (d, J = 11.7, $PhC\underline{H}_2$), 4.62 (d, J = 11.7, $PhC\underline{H}_2$), 4.84 (app. d, J = 3.0, H-4), 7.34 (phenyl).

Hydrogenolysis. A solution of 1.47 g of **9** in absolute ethanol (20 ml) plus 0.17 g 10% Pd on C was hydrogenated at one atmosphere. No reaction occurred, and eventually the mixture was filtered and the catalyst was replaced with ca. 0.2 g of PtO_2. Three drops of conc. HCl were added, but no hydrogenation occurred until the solution was again filtered and the catalyst replaced with 0.25 g of fresh PtO_2. After two more hours, GC indicated the disappearance of **9** and the appearance of two products, **10** and **11,** with the **10** predominating by about 2 : 1. The mixture was filtered through Celite, and the filtrate was treated with 2 ml of 3 N NaOEt in ethanol. After 0.5 hr the mixture was partitioned between aqueous ammonium chloride and 8 : 2 hexane–ethyl acetate. Removal of solvent gave 0.63 g of an oil that was flash chromatographed (10%, 20%, and 30% EtOAc in hexanes) to give 277 mg of epoxide **7** and 215 mg of cyclohexanemethanol derivative **11.** The epoxide **7** was identical to **7** produced along with **6** upon epoxidation of the corresponding olefin. Epoxide **7:** m/z (%) 184 (0.7, M^+), 139 (32), 138 (10), 114 (14), 112 (12), 111 (34), 110 (100), 101 (21), 95 (24), 93 (53), 91 (10), 86 (10), 85 (14), 84 (34), 83 (24), 82 (15),

81 (41), 79 (13), 77 (11), 73 (18), 72 (19), 71 (10), 70 (25), 69 (25), 68 (13), 67 (33), 56 (13), 55 (71), 53 (15). ^{1}H NMR ($CDCl_3$) 0.84 (d, J = 6, 6-Me), 1.25 (t, J = 7.2, $C\underline{H}_3CH_2O$), 1.52 (m, H-$5_{a,b}$), 1.66 (m, H-6), 2.01 (m, H-$2_{a,b}$), 2.13 (m, H-$5_{b,a}$), 2.23 (m, H-1), 2.27 (m, H-$2_{a,b}$), 3.14 (app. t, H-4), 3.22 (br s, H-3), 4.13 (dq, J = 1.2 and 6.9, $CH_3C\underline{H}_2O$). Compound **11** was identified by its mass and NMR spectra: m/z (%) 331 (6), 207 (10), 185 (45), 183 (30), 155 9260, 139 (12), 138 (8), 137 (22), 111 (55), 109 (11), 97 (62), 96 (13), 95 (16), 94 (17), 93 (25), 81 (22), 79 (17), 65 (11), 63 (13), 55 (100), ^{1}H NMR ($CDCl_3$) 0.92 (d, J = 6.6, 6-Me), 1.27 (t, J = 6.9, $C\underline{H}_3CH_2$), 1.65 (m, H-$5_{a,b}$), 1.85 (m, H-$5_{a,b}$), 1.92 (m, H-2), 2.32 (dt, J = 4.8 and 10.2, H-1), 3.04 (s, CH_3SO_2), 3.24 (dd, J = 6.6 and 9.0) and 3.31 (dd, J = 6.6 and 8.7), $C\underline{H}_2$-cyclohexyl, 3.62 (br d, H-3), 4.15 (q, J = 7.2, $CH_3C\underline{H}_2O$) 4.81 (br, H-4).

*Confirmation of Cyclohexanemethanol Derivative **11**.* A solution of **6** (166 mg) and pyridinium *p*-toluenesulfonate (23 mg) in cyclohexanemethanol (1 ml) was heated as 110°C under nitrogen ca. 20 hr. Part of the cyclohexanemethanol was removed in vacuo, and the residue was thoroughly partitioned between pentane and water. To about 90% of the crude product was added benzene (2 ml), pyridine (0.5 ml), and methanesulfonyl chloride (0.5 ml). After 3 hr at room temperature the mixture was partitioned between water and ether–hexane (1 : 1). The organic phase was rinsed with dilute HCl, with water, and with aqueous Na_2CO_3, and then dried and concentrated. Flash chromatography (20–25% EtOAc–hexane gave a total of 90 mg of **11**, part of which was crystallized from hexane, mp 60–61. This material was identical to **11** isolated from the above reaction.

RESULTS AND DISCUSSION

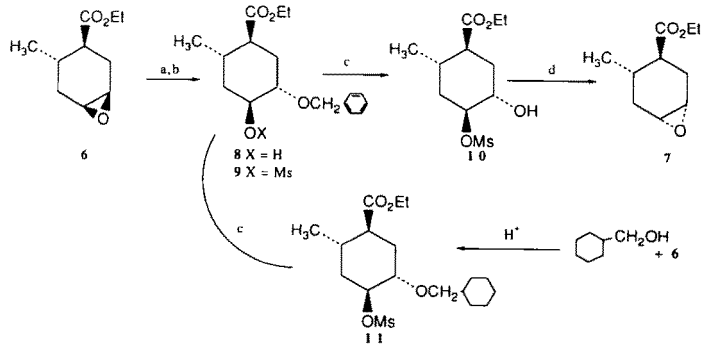
We had noted (Oliver and Waters, 1995) that disparlure (**1**) was very resistant to ring opening under nonacidic conditions, but that anhydrous neutral alumina (Posner and Rogers, 1977) satisfactorily catalyzed ring opening with α-methylbenzylamine at 145°C. Under similar conditions (sealed tube), alumina catalyzed epoxide opening with benzyl alcohol. Rearrangement (the rearrangement of **1** is assumed to proceed more or less equally to two regioisomeric ketones, but like other regioisomers in the disparlure series, no gas chromatographic resolution was achieved—see Methods and Materials) competed with opening, but the products were readily separated by flash chromatography and **2a, 2b** were isolated in 34% yield. Other catalysts were also investigated: a trace of sulfuric acid quickly catalyzed rapid opening of **1** in benzyl alcohol at room temperature, but considerable self-condensation of benzyl alcohol also

occurred [product(s) not investigated] Nafion-catalyzed opening (Olah et al., 1981) with benzyl alcohol as solvent was slow (four to seven days at room temperature for complete reaction), but epoxide rearrangement was minimized ($\leq 15\%$), and **2a, 2b** were obtained in 66% yield after chromatography. Pyridinium toluenesulfonate seemed quite similar to Nafion as a catalyst, although a systematic comparison was not made.

Mesylation of regioisomers **2a, 2b** proceeded without incident, as did hydrogenolysis (EtOH, Pd on C, 1 atm) of the benzyloxymesylates **3a, 3b.** Treatment of the resulting hydroxymesylates **4a, 4b** with sodium ethoxide resulted in rapid conversion to expoxide **5** (7*S*,8*R*), indistinguishable from **1** by gas chromatography or mass spectrometry. The yield of **5,** after flash chromatography, from **3a, 3b** was 81% (Figure 1).

For successful conversion of **1** to **5,** both the epoxide opening and closing reactions have to occur with inversion. If one of the two were to occur with retention, the result would be *trans*-disparlure (7*R*,8*R*) or (7*S*,8*S*). *trans*-Disparlure is separable from **1** and **5** by GC or even column chromatography, and, in fact, ca. 0.6% of the *trans* epoxide was detectable (by GC) in at least one conversion of **1** to **5.** The starting material for this sequence had been 97.3% **1** and 2.7% **5,** and the product analyzed for 2.2% **1** and 97.8% **5.** It is uncertain whether this 0.5% difference is outside of experimental error, but in any event, the stereoefficiency was very high.

Another example of epoxide inversion involved **6** and **7** (Figure 2). These had long ago been found to be attractive to Mediterranean fruit flies (Valega and Beroza, 1967), but only a mixture of *exo* and *endo* epoxides is available upon epoxidation of *trans*-6-methyl-3-cyclohexenecarboxylic acid or its esters. In contrast, the *exo*-epoxide **6** is readily available via an iodolactone (see, for



a. $PhCH_2OH$, H^+; b. CH_3SO_2Cl, Py; c. H_2, Pt, EtOH; d. NaOEt

FIG. 2. The *exo-endo* epoxide inversion.

example, Ogliaruso and Wolfe, 1993), but comparison of the attractiveness of pure **6** and the mixture of **6** and **7** suggested that the activity lay with the latter (R.T. Cunningham and J.W. Avery, unpublished results). Epoxide **6** (in this case racemic) was less subject to rearrangement than disparlure, and ring opening could conveniently be carried out at 100–110°C with either pyridinium toluenesulfonate or Nafion in benzyl alcohol. In this case the opening was somewhat regioselective, and after treatment of the crude product with methanesulfonyl chloride, mesylate **9** could be isolated as a solid. Benzyloxymesylate **9** was more resistant to hydrogenation than **3a, 3b.** No reaction was observed with palladium on carbon in ethanol (1 atm), whereas addition of a trace of HCl and replacement of the catalyst with platinum oxide permitted a very slow reduction to occur (in some cases requiring two or more days to reach completion at one atmosphere). The major product was evidently the expected alcohol **10,** since treatment of the ethanol solution with sodium ethoxide rapidly gave the desired epoxide **7.** No isomers of **7** were detected, although a minor product was observed from the conversion of **9** to **7.** After isolation by flash chromatography, it was identified by mass spectrometry and NMR spectroscopy as the cyclohexylmethyl ether **11,** i.e., the product of aromatic ring reduction instead of hydrogenolysis. Platinum-catalyzed ring saturation of benzyl ethers, although generally unanticipated, is not without precedent (see Rylander, 1979). The structure of **11** was confirmed by opening **6** with cyclohexanemethanol instead of with benzyl alcohol, then treating the ether–alcohol with methanesulfonyl chloride.

In summary, a straightforward procedure for the inversion of certain 1,2-disubstituted epoxides is reported. Although asymmetric epoxidation procedures can often be applied to either enantiomer, particularly of acyclic epoxides, many cyclic epoxides, naturally occurring epoxides, or epoxides prepared by microbial- or enzyme-mediated sequences, may be more available as one enantiomer than the other (Besse et al., 1994), and the current method may prove useful in such cases. We have not investigated inversions of trisubstituted epoxides, anticipating that epoxide rearrangements as well as difficulties with tertiary mesylates could present competing pathways. Unsaturated substrates subject to catalytic hydrogenation would present another limitation of the sequence described, but alternative oxygen nucleophiles convertible to OH by other means, such as *p*-methoxyphenol (Corey and Link, 1992), or masked OH nucleophiles (Fleming, 1988) might also find application. Ironically, an initial objective of the project was to invert the configuration of (+)-diethylepoxyfumarate. We were unable to effect ring opening of that epoxide with benzyl alcohol under a variety of acidic or alkaline conditions; only very slow (over several weeks) transesterification occurred under the conditions described above for the opening of **1** or **7,** and the corresponding dibenzyl ester (examined separately) failed to react at all.

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