Total Synthesis of the Gypsy Moth Pheromones (+)- and (−)-Disparlure from a Single Nonracemic α-Silyloxy Allylic Stannane

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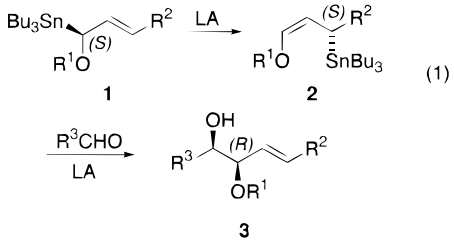
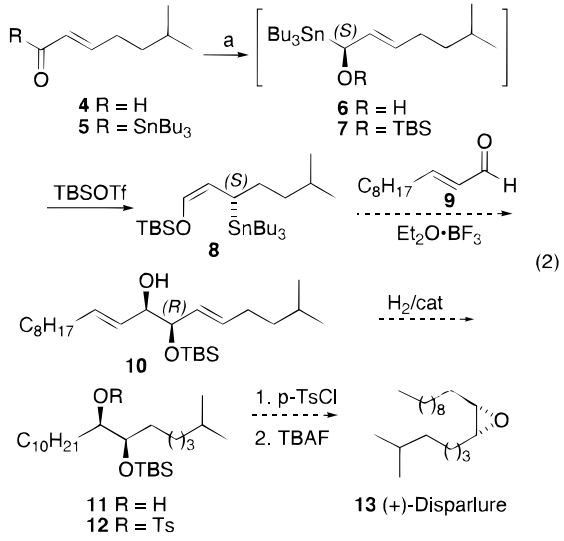
In 1991, we described studies on the stereospecific 1,3-isomerization of enantioenriched α-alkoxy allylic stannanes **1** to their γ-isomers **2** and the subsequent Lewis acid-promoted addition of these γ-isomers to various aldehydes to afford monoprotected syn 1,2-diols **3** (eq 1).[1]



Since that time, we have employed this reaction as a key step in the synthesis of various prototypes of carbohydrates, amino sugars, and acetogenins.[2] Initially, these applications utilized crotyl OMOM or OTBS stannanes (**2**, R^1 = MOM or TBS; $R^2 = CH_3$) as the chiral reagents.[3] More recently, we have directed our attention to longer chain and more highly functionalized stannane reagents for the synthesis of natural products bearing chiral vicinal diol units or derivatives thereof.[4] Although applications of this nature may appear to be routine extensions of our crotyl stannane work, we observed a significant loss of diastereoselectivity with a longer chain stannane (**2**, R^1 = TBS; $R^2 = n\text{-}C_{10}H_{21}$) vs crotyl (**2**, R^1 = TBS; $R^2 = CH_3$) in our synthesis of (+)- and (−)-muricatacin.[3b] Moreover, recent findings by Quintard and co-workers on BF_3-promoted additions of γ-ethoxy allylic stannanes (**2** R^1 = Et) with branched α-substituents (R^2) to benzaldehyde showed significant erosion of syn diastereoselectivity.[5] In fact, the *i*-Pr and *t*-Bu reagents (**2**, R^1 = Et; R^2 = *i*-Pr, *t*-Bu) yielded mainly the anti adducts. Additional investigations of additions involving long-chain γ-oxygenated allylic stannanes therefore seemed desirable.

For these studies, we targeted the sex attractant of the female gypsy moth, (+)-disparlure (**13**). This relatively simple substance has been the object of numerous synthetic investigations.[6] The earliest approaches employed chiral pool starting materials with extant diol functionality of appropriate chirality. More recently, the Sharpless asymmetric epoxidation[6b] and dihydroxylation[6c] have been employed to introduce the requisite epoxide chirality.

Our approach differs from the others by combining chain elongation and introduction of the chiral diol centers in a single step. The stannane reagent provides the desired stereogenicity. Initially, we planned to pursue the route outlined in eq 2 in which the *(S)*-stannane **8** would undergo BF_3-promoted addition to 2-undecenal (**9**) to afford the syn adduct **10**. Our choice of a conjugated



aldehyde for this step was based on the higher syn/anti ratios of adducts observed with such aldehydes as opposed to their saturated counterparts.[2,3b] Hydrogenation of the dienic adduct **10** followed by tosylation would lead to the precursor **12**, which upon silyl ether cleavage with TBAF, would expectedly cyclize to (+)-disparlure (**13**).

However, this plan was stymied by our inability to separate stannane **8** from tin byproducts. Accordingly, we reversed the aldehyde and stannane partners hoping for an easier purification of the long-chain OTBS stannane **16** (eq 3). This, in fact, turned out to be the case. Thus, addition of Bu_3SnLi to (*E*)-2-undecenal (**9**)[7] followed by in situ oxidation afforded the acylstannane **14**. Reduction with (*S*)-BINAL-H[8] and in situ treatment with TBSOTf yielded the (*R*)-γ-silyloxy stannane **16** via the α-isomer **15** in 42% overall yield (eq 3).[2]

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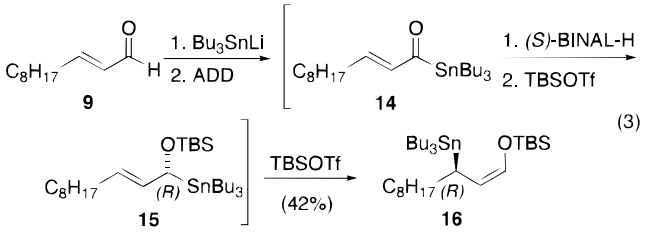
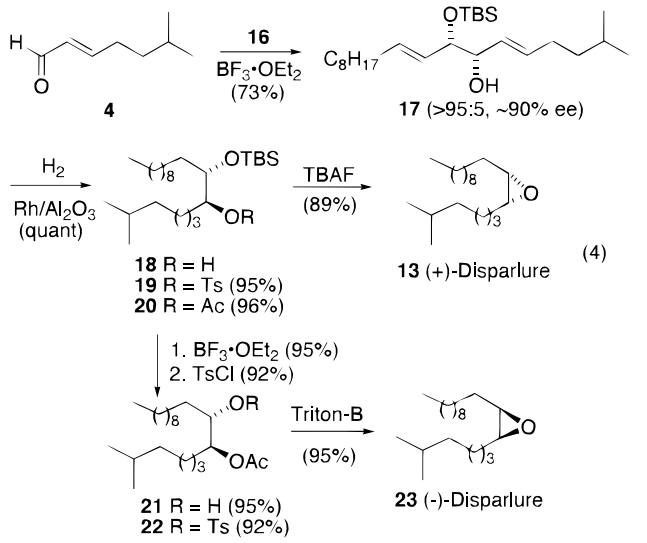


Stannane **16** was readily purified by column chromatography on silica gel. Addition of **16** to enal **4**[9] in the presence of BF_3·OEt_2 afforded the syn adduct **17** in 73% yield. Analysis of the (*S*)-Mosher ester derivative[10] indicated an ee of >95% for this adduct. Less than 5% of the anti diastereomer was formed in the addition.

Hydrogenation of **17** over Rh/Al_2O_3 afforded the tetrahydro adduct **18** quantitatively. The tosylate derivative **19**, upon treatment with TBAF in THF, smoothly cyclized to (+)-disparlure (**13**) in high yield. The spectral data and optical rotation of this material compared favorably with the reported values (eq 4).[6]



The enantiomer (−)-disparlure (**23**) was also prepared from alcohol **18**. This was achieved through acetylation followed by silyl ether cleavage with BF_3·OEt_2 in CH_2Cl_2 and tosylation. The more conventional desilylation with TBAF led to a mixture of acetate regioisomers. Treatment of the tosylate **22** with Triton-B in methanol effected saponification and cyclization to **23**. As expected, this material was identical to the (+)-enatiomer **13** except for the sign of its optical rotation.

Returning to the issue of diastereoselectivity, our present findings indicate that high levels of syn stereocontrol are possible with long-chain γ-oxygenated allylic stannanes. Our previous observations to the contrary were based on additions to aliphatic aldehydes with polar β-substituents,[3b] and Quintard's studies did not involve aliphatic aldehydes.[5] Thus, it would appear that aldehyde structure and stannane substituents both play a role in controlling the diastereoselectivity of such additions. Current mechanistic thinking on these reactions fails to account for subtleties such as the strong preference of conjugated aldehydes to yield syn adducts with γ-oxygenated allylic stannanes.[11] Nonetheless, quite useful levels of syn selectivity can be realized with this combination as illustrated in the present synthesis of disparlure.

Experimental Section

(+)-(7*R*,8*S*)-*cis*-7,8-Epoxy-2-methyloctadecane [(+)-Disparlure] (13). Tosylate **19** (59 mg, 0.10 mmol) and TBAF (1.0 M in THF, 400 μL, 0.40 mmol) in 1 mL of THF was stirred overnight, at which point TLC analysis indicted that all the starting material had been consumed. The reaction was quenched with saturated NH_4Cl solution, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic extracts were dried over sodium sulfate, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel with 2.5% ethyl acetate in hexane as eluent affording 24 mg (89%) of epoxide **13**: $[\alpha]^{26}_D$ 0.9 (*c* 1.1, CCl_4) [lit.[6] $[\alpha]^{23}_D$ 0.8 (*c* 10, CCl_4)]; ^{1}H NMR (300 MHz) δ 2.91 (dm, J = 3.8 Hz, 1H), 2.89 (dm, J = 4.6 Hz, 1H), 1.69−1.10 (m, 29H), 1.04−0.72 (m, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 57.2, 38.9, 31.9, 29.5, 29.3, 27.9, 27.3, 26.6, 22.7, 22.6, 14.1 ppm. Anal. Calcd for $C_{19}H_{38}O$ C, 80.78; H, 13.56. Found: C, 80.85; H, 13.63.

(*Z*)-(*R*)-1-(*tert*-Butyldimethylsilyloxy)-3-(tri-*n*-butylstannyl)-1-undecene (16). Diisopropylamine (1.67 mL, 11.9 mmol) in 75 mL of anhydrous THF was cooled to 0 °C, *n*-BuLi was added (2.5 M solution in hexane, 4.72 mL, 11.8 mmol) followed after 15 min by tributyltin hydride (3.17 mL, 11.8 mmol), and the resulting yellow solution was stirred for 20 min. The solution was cooled to −78 °C, and aldehyde **9**[7] (1.81 g, 10.8 mmol) was added, followed after 30 min by 1,1′-(azodicarbonyl)dipiperidine (4.15 g, 16.5 mmol), and the resulting dark red reaction mixture was warmed to 0 °C and stirred for 1 h. The reaction was then quenched with dilute aqueous ammonium chloride solution and extracted with ether. The organic extracts were combined and dried over magnesium sulfate, and the solvent was removed under reduced pressure. Hexane was added to the orange residue, and the solution was concentrated under reduced pressure to remove any traces of THF. The acyl stannane was purified by adding hexane to precipitate residual ADD. The solid was removed by vacuum filtration and the filtrate concentrated to provide the acyl stannane. Because of the lability of the acyl stannane it is important to have a freshly prepared solution of BINAL-H at −78 °C ready for the subsequent reduction. This is best achieved by starting the following procedure for BINAL-H just prior to the acyl stannane sequence.

$LiAlH_4$ powder (1.02 g, 27.0 mmol) was suspended in 50 mL of THF. Over a period of 15 min, a solution of EtOH (1.24 g, 27.0 mmol) in 5 mL of THF was added with vigorous evolution of hydrogen gas, after which (*S*)-1,1′-bi-2-naphthol (7.73 g, 27.0 mmol) in 50 mL of THF was added by cannula over 1 h. The resulting cloudy, milky solution was refluxed for 1 h and allowed to cool to room temperature. The solution was cooled to −78 °C, and a solution of the acyl stannane in 45 mL of THF was added by cannula over 1.0 h. After being stirred for 16 h at −78 °C, the solution was quenched at −78 °C with dilute aqueous ammonium chloride (100 mL) over 0.5 h. The solution was allowed to warm to room temperature and then diluted with water and ether. The layers were separated, and the aqueous phase was diluted with 1 M HCl and extracted with ether. The organic extracts were combined, dried over magnesium sulfate, and filtered, and the solvent was removed under reduced pressure. The residual hydroxy stannane (yellow oil) and binaphthol (white powder) were triturated twice with hexane. The binaphthol was recovered by filtration, and the hexane extracts were concentrated under reduced pressure to afford crude hydroxy stannane.

The hydroxy stannane was dissolved in CH_2Cl_2 and cooled to 0 °C. Diisopropylethylamine (2.5 mL, 27.0 mmol) was added followed by TBSOTf (4.96 mL, 21.6 mmol). The reaction mixture was stirred overnight to ensure complete isomerization. The

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reaction was then quenched with saturated $NaHCO_3$, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic extracts were dried over sodium sulfate, and the solvent was removed under reduced pressure. The material was purified by column chromatography on silica gel with hexane as eluent, affording 2.6 g (42%) of stannane **16**: $[\alpha]^{26}_D$ 117 (*c* 1.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99 (dd, J = 4.8, 1.0 Hz, 1H), 4.24 (ddd, J = 11.1, 5.7, 1.0 Hz, 1H), 2.55 (dq, J = 11.0, 6.4 Hz, 1H), 1.64−1.39 (m, 6H), 1.40−1.12 (m, 18H), 1.02−0.69 (m, 20H), 0.92 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 134.0, 115.1, 33.4, 32.0, 30.6, 29.7, 29.5, 29.4, 27.7, 25.8, 23.0, 22.8, 18.4, 14.2, 13.8, −2.8, −5.0, −5.3 ppm; IR (film) ν 3563, 3450 cm^{-1}.

(*E*,*E*)-(7*S*,8*S*)-8-(*tert*-Butyldimethylsilyloxy)-2-methyloctadeca-5,9-dien-7-ol (17). A solution of stannane **16** (552 mg, 0.97 mmol) and aldehyde **4**[9] (67 mg, 0.54 mmol) in CH_2Cl_2 was cooled to −78 °C, BF_3·OEt_2 (96 μL, 0.94 mmol) was added, and the mixture was stirred for 1.5 h. TLC analysis indicated that the aldehyde had not been consumed, so additional BF_3·OEt_2 (100 μL, 0.98 mmol) was added. After 1 h, the reaction was quenched with saturated $NaHCO_3$ solution, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic extracts were dried over sodium sulfate, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel with 2.5% ethyl acetate in hexane as eluent to afford 213 mg (73%) of adduct **17**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.64 (m, 2H), 5.35 (m, 2H), 3.84 (m, 2H), 2.04 (m, 4H), 1.56 (m, 1H), 1.46−1.08 (m, 16H), 1.03−0.73 (m, 9H), 0.90 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 133.8, 133.7, 129.6, 128.4, 77.9, 76.0, 38.3, 32.2, 31.9, 30.3, 29.5, 29.3, 29.2, 29.1, 27.4, 25.9, 22.7, 22.6, 22.5, 18.2, 14.1, −3.8, −4.7 ppm; IR (film) ν 3563, 3450 cm^{-1}. Anal. Calcd for $C_{25}H_{50}O_2Si$ C, 73.10; H, 12.27. Found: C, 73.00; H, 12.24.

^{1}H NMR analysis of the (*S*)-Mosher ester[10] indicated an ee of >95%.

(7*S*,8*S*)-8-(*tert*-Butyldimethylsilyloxy)-2-methyloctadecan-7-ol (18). A mixture of 0.10 g (0.24 mmol) of dienol **17** and a catalytic amount of Rh/Al_2O_3 (5%) in 2.0 mL of EtOAc was placed under a H_2 atmosphere. The reaction mixture was stirred for 8 h and filtered through Celite. Solvent was removed under reduced pressure to afford 0.10 g (100%) of alcohol **18**: $[\alpha]_D$ +4.9 (*c* 0.60, $CHCl_3$); IR (film) 3465 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.49 (m, 1 H), 3.42 (m, 1 H), 1.65−1.07 (m, 27 H), 0.90 (m, 12 H), 0.86 (d, J = 6.5 Hz, 6 H), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 76.2, 75.2, 39.0, 34.2, 34.0, 32.0, 30.0, 29.6, 29.4, 28.0, 27.5, 26.2, 26.0, 25.1, 22.7, 18.2, 14.2, −4.0, −4.5. Anal. Calcd for $C_{25}H_{54}O_2Si$: C, 72.39; H, 13.12. Found: C, 72.40; H, 13.18.

(7*S*,8*S*)-8-(*tert*-Butyldimethylsilyloxy)-2-methyl-7-(*p*-toluenesulfonyloxy)octadecan-7-ol (19). Alcohol **18** (45 mg, 0.11 mmol) and *p*-toluenesulfonyl chloride (25 mg, 0.13 mmol) in 1.5 mL of pyridine was stirred for 48 h, quenched with saturated aqueous $CuSO_4$, and diluted with CH_2Cl_2. The organic extract was washed first with saturated aqueous $CuSO_4$ three times and then with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with 2.5% ethyl acetate in hexane as eluent, affording 59 mg (95%) of tosylate **19**: $[\alpha]^{26}_D$ −28.3 (*c* 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 4.32 (ddd, J = 9.6, 6.6, 3.5 Hz, 1H), 3.74 (ddd, J = 8.9, 6.9, 3.8 Hz, 1H), 2.44 (s, 3H), 1.75−1.03 (m, 18H), 0.98−0.60 (m, 12H), 0.86 (s, 9H), 0.81 (d, J = 6.9 Hz, 6H), 0.06 (s, 3H), 0.01 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.6, 127.8, 84.8, 72.1, 38.7, 32.0, 30.4, 29.7, 29.6, 29.4, 27.8, 27.5, 27.0, 26.0, 25.8, 25.7, 22.8, 22.6, 21.7, 18.0, 14.2, −4.3, −4.7 ppm; IR (film) ν 2950, 2900, 1550, 1450, 1350 cm^{-1}. Anal. Calcd for $C_{32}H_{60}O_4SiS$ C, 67.55; H, 10.63. Found: C, 67.65; H, 10.68.

(7*S*,8*S*)-7-Acetoxy-8-(*tert*-butyldimethylsilyloxy)-2-methyloctadecane (20). To a solution of 0.10 g (0.24 mmol) of alcohol **18** in 0.50 mL of pyridine was added 0.15 mL (1.6 mmol) of acetic anhydride. The reaction mixture was stirred for 12 h, quenched with water, and extracted with ether. The ether extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (elution with 5% EtOAc in hexane) to afford 0.11 g (96%) of acetate **20**: $[\alpha]_D$ −13.4 (*c* 1.0, $CHCl_3$); IR (film) 1737 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.80 (ddd, J = 7.9, 2.7, 1.6 Hz, 1 H), 3.66 (m, 1 H), 2.05 (s, 3 H), 1.70−1.01 (m, 27 H), 0.92−0.80 (m, 18 H), 0,09 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 76.3, 72.3, 38.9, 32.2, 31.9, 29.9, 29.7, 29.6, 29.4, 28.6, 28.0, 27.3, 26.2, 25.9, 25.5, 22.8, 22.7, 22.6, 21.3, 14.1, −4.3, −4.4.

(7*S*,8*S*)-7-Acetoxy-2-methyloctadecan-8-ol (21). To a stirred solution of 0.022 g (0.05 mmol) of silyl ether **20** in 1.5 mL of CH_2Cl_2 was added 0.014 mL (0.11 mmol) of BF_3·OEt_2. The reaction mixture was stirred for 1 h, quenched with saturated $NaHCO_3$, and extracted with ether. The ether extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (elution with 15% EtOAc in hexane) to afford 0.016 g (95%) of alcohol **21**: $[\alpha]_D$ −11.2 (c 0.22, $CHCl_3$); IR (film) 3458, 1728 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.83 (m, 1 H), 3.58 (m, 1 H), 2.09 (s, 3 H), 1.67−1.13 (m, 27 H), 0.96−0.74 (m, 9 H).

(7*S*,8*S*)-7-Acetoxy-8-(*p*-toluenesulfonyloxy)-2-methyloctadecane (22). To a solution of 0.044 g (0.13 mmol) of alcohol **21** in 0.50 mL of pyridine was added 0.12 g (0.63 mmol) of *p*-TsCl. The reaction mixture was stirred for 12 h, quenched with water and extracted with ether. The ether extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (elution with 8% EtOAc in hexane) to afford 0.060 g (92%) of tosylate **22**: $[\alpha]_D$ −7.4 (c 0.39, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 7.7 Hz, 2 H), 7.33 (d, J = 7.7 Hz, 2 H), 4.95 (m, 1 H), 4.62 (m, 1 H), 2.44 (s, 3 H), 2.01 (s, 3 H), 1.62−1.01 (m, 27 H), 0.92−0.80 (m, 9 H).

(−)-Disparlure (23). To 0.017 g (0.03 mmol) of tosylate **22** was added 0.50 mL (1.1 mmol) of benzyltrimethylammonium hydroxide (Triton B). The reaction mixture was stirred for 1 h, quenched with water, and extracted with ether. The ether extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (elution with 5% EtOAc in hexane) to afford 0.009 g (95%) of (−)-disparlure (**23**): $[\alpha]_D$ −0.9 (c 0.21, CCl_4). Anal. Calcd for $C_{19}H_{38}O$: C, 80.78; H, 13.56. Found: C, 80.93; H, 13.58.

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Supporting Information Available: ^{1}H NMR spectra for **16**, the (*S*)-Mosher ester of **17**, **20**, **21**, and **22**. This material is available free of charge from the Internet at http://pubs.acs.org.

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