 

# Stereoselective Formation of *trans*-2,5-Disubstituted Tetrahydropyrans by Intramolecular Nucleophilic Substitution and a Computational Study at the AM1 Level

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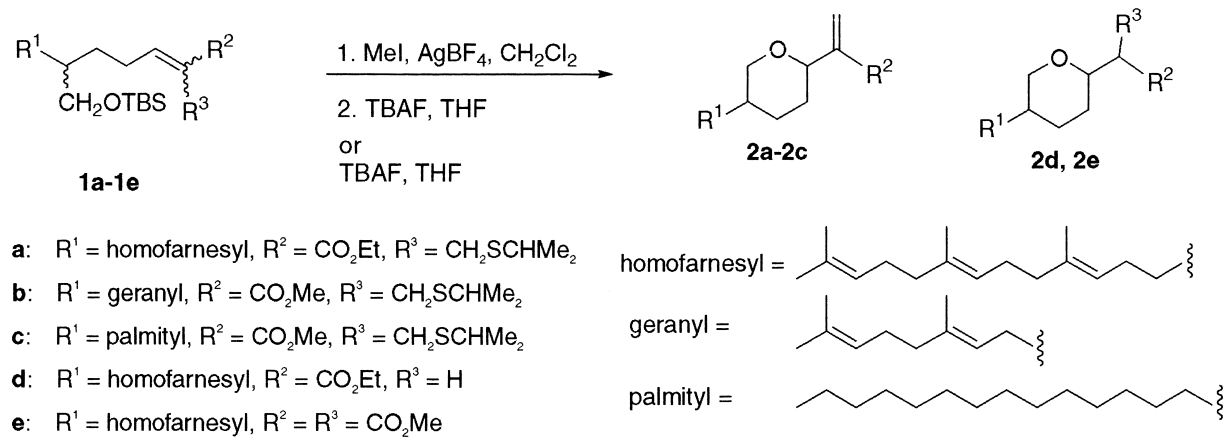
The synthesis of 2,5-disubstituted tetrahydropyrans bearing a hydrophobic moiety at the C5 position from (*E*)- and (*Z*)-7-hydroxy-6-substituted 2,3-unsaturated esters by way of intramolecular nucleophilic substitution proceeded with high stereoselectivity. A theoretical study at the AM1 level of the cyclization reaction suggested that the reaction is kinetically controlled and that the preferred path for the cyclization reaction proceeds via a transition state in which 1,3-diaxial-like repulsions are minimized to give the *trans* product in accordance with experimental results.

Although the stereocontrolled synthesis of 2,3- or 2,6-disubstituted tetrahydropyran derivatives, which often constitute the structure of marine toxins, has been investigated to a large extent,[1,2] less attention has been paid to the stereoselective construction of 2,5-disubstituted pyran rings. During the course of our studies towards the total synthesis of rhopaloic acid A,[3] a highly stereoselective method for the formation of 2,5-disubstituted tetrahydropyrans was developed (Scheme 1). Herein we present a full account of our findings along with AM1 calculations to provide support for our preliminary rationalization that the products are consequences of transition states in which 1,3-diaxial-like repulsions are minimized.[3,4]

## Results and Discussion

Cyclization precursors **1b**-**e** were prepared by a method previously described for **1a**.[3] The treatment of (*E*)-**1a** with a methylating reagent, MeI/$AgBF_4$, followed by desilylation with TBAF, afforded pyran **2a** (*cis*/*trans* 6/94, Table 1, entry 1) in a one-pot reaction.[3] The reaction of (*Z*)-**1a** with MeI/$AgBF_4$ under the same reaction conditions also gave *trans*-**2a** as the major product (*cis*/*trans* 5/95, Table 1, entry 2). The intramolecular nucleophilic substitution of cyclization precursors **1b** and **1c** also afforded *trans* pyrans **2b** and **2c** as the major product, respectively (Table 1, entries 5 and 6). Thus, the *trans* selectivities in the cyclization reaction were apparently not affected by the size of the hydrophobic chain ($R^1$) (Table 1, entries 1–6) and the double-bond geometry of the cyclization precursor (Table 1, entries 1 and 2). This stands in contrast to previously reported systems in which the geometry affected the stereochemical course of cyclization.[2] However, it has been known that differences in the geometric restraints due to a 1,3-diaxial-like repulsion in the supposed chair-like transition state are

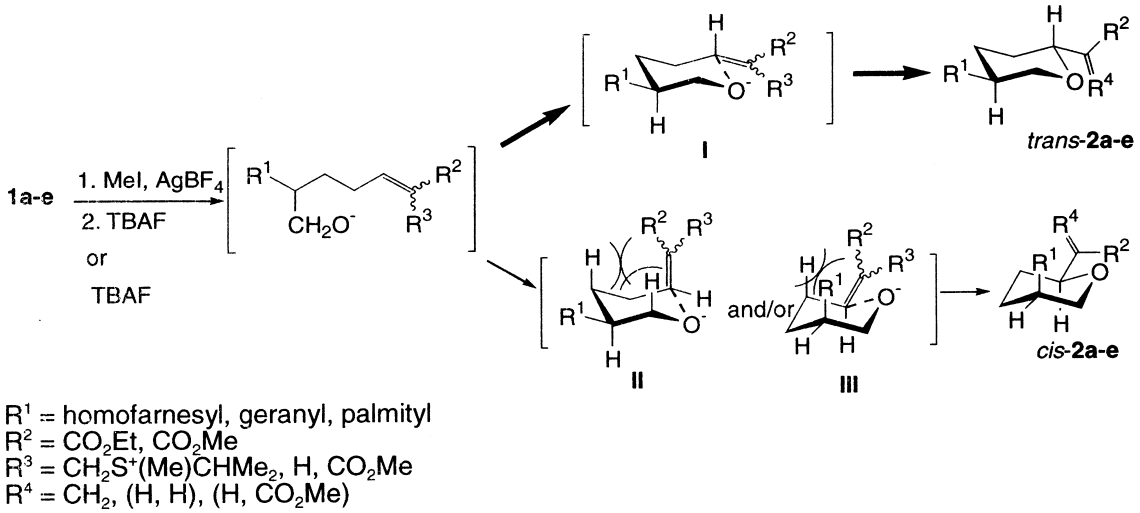



Scheme 1. Formation of 2,5-disubstituted tetrahydropyrans.

Table 1. Formation of 2,5-Disubstituted Tetrahydropyrans **2a**–**e** by Intramolecular Nucleophilic Substitution

| Entry | Substrate | $R^1$ | Reagents and conditions | Product | *cis*: *trans* | yield/%[a] |
|---|---|---|---|---|---|---|
| 1[b] | (*E*)-**1a** | homofarnesyl | 1. MeI (3 eq), $AgBF_4$(1.3 eq), 25 °C, 5 h<br>2. TBAF (4.4 eq), 25 °C, 5 h | **2a** | 6: 94 | 31 |
| 2[b] | (*Z*)-**1a** | homofarnesyl | 1. MeI (4 eq), $AgBF_4$(1.2 eq), 25 °C, 2 h<br>2. TBAF (3 eq), 25 °C, 11 h | **2a** | 5: 95 | 37 |
| 3[b] | (*Z*)-(*S*)-**1a** | homofarnesyl | 1. MeI (excess), $AgBF_4$(3.8 eq), 25 °C, 5 h<br>2. TBAF (3 eq), 0 °C, than 25 °C, 15 h | **2a** | 2: 98 | 33 |
| 4[b] | (*Z*)-(*R*)-**1a** | homofarnesyl | 1. MeI (2 eq), $AgBF_4$(1.1 eq), 25 °C, 5 h<br>2. TBAF (5.6 eq), 25 °C, 13 h | **2a** | 4: 96 | 35 |
| 5 | (*Z*)-(*R*)-**1b**[c] | geranyl | 1. MeI (12 eq), $AgBF_4$(3.2 eq), 25 °C, 1 h<br>2. TBAF (1.6 eq), 25 °C, 30 h | **2b** | 6: 94 | 28 |
| 6 | (*Z*)-**1c**[d] | palmityl | 1. MeI (4.3 eq), $AgBF_4$(2.2 eq), 25 °C, 4.5 h<br>2. TBAF (3.8 eq), 25 °C, 13.5 h | **2c** | 1: 99 | 25 |
| 7 | (*E*)-**1d** | homofarnesyl | TBAF (6 eq), 25 °C, 5 h | **2d** | 30: 70 | 77 |
| 8 | **1e** | homofarnesyl | TBAF (3 eq), 25 °C, 24 h | **2e** | 20: 80 | 13 |

a) The product ratios were determined by $^1$H NMR spectra.
b) Ref. 2
c) *Z*/*E* = 94/6.
d) *Z*/*E* = 90/10.



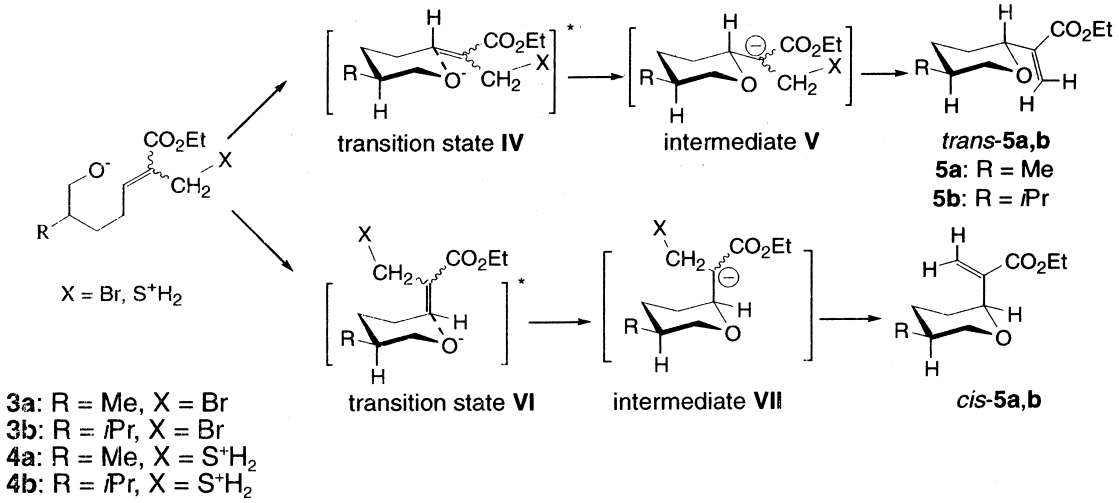

Scheme 2. The possible reaction path in the intramolecular nucleophilic substitution.

sufficient for the stereoselective construction of 5–6 membered ring heterocyclic systems.[5]

In order to evaluate the effect of the alkene moiety at the $\alpha,\beta$-position of the carboxylate group upon the stereochemistry, related substrates (*E*)-**1d** and **1e** were prepared. The reactions of (*E*)-**1d** and **1e** also gave *trans* tetrahydropyran derivatives **2d** and **2e** as the major products (*cis*/*trans* 30/70 for **2d** and 20/80 for **2e**), respectively (Table 1, entries 7 and 8). Judging from the lower selectivity for **1d**,**e** relative to **1a**-**c** in the intramolecular nucleophilic substitution, the sulfonium moiety and the reaction pattern in **1a**-**c** are very effective for high stereoselectivity.

The stereochemistry of the cyclization reaction can be rationalized to preferentially proceed via transition state I in which both the acrylate moiety and the long hydrophobic side chain occupy quasi-equatorial positions to avoid 1,3-diaxial-like repulsion, regardless of the geometry of the conjugated alkene moiety (Scheme 2).

In order to rationalize the observed high stereoselectivities in the cyclization, semi-empirical calculation studies on model systems (**3a**,**b** and **4a**,**b**) of the intramolecular nucleophilic substitution were carried out by AM1[6] using the Hamiltonian




Scheme 3. The model system of the intramolecular nucleophilic substitution.

Table 2. AM1 Energies of the Reaction Products **5a,b**

| Entry | Pyran | R | Geometry | Energy/kcal mol$^{-1}$ | $\Delta\Delta H^{*a)}$ |
|---|---|---|---|---|---|
| 1 | **5a** | Me | *trans* | −138.092917 | |
| 2 | | | *cis* | −136.955532 | 1.137385 |
| 3 | **5b** | *i*Pr | *trans* | −147.702097 | |
| 4 | | | *cis* | −146.566805 | 1.135292 |

a) Energy difference between the AM1 energies of the reaction products **5a,b**, in kcal/mol.

Table 3. AM1 Energies of the Intermediates **3a,b-V,VII** and **4a,b-V,VII** in the Intramolecular Nucleophilic Substitution

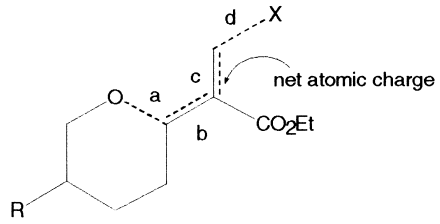
| Entry | Ester | X | R | Geometry | Energy/kcal mol$^{-1}$ | $\Delta\Delta H^{*a)}$ |
|---|---|---|---|---|---|---|
| 1 | **3a** | Br | Me | *trans* | −182.182038 | |
| 2 | | | | *cis* | −181.810646 | 0.371392 |
| 3 | **3b** | Br | *i*Pr | *trans* | −189.728634 | |
| 4 | | | | *cis* | −189.081613 | 0.647021 |
| 5 | **4a** | $S^+H_2$ | Me | *trans* | −132.037431 | |
| 6 | | | | *cis* | −131.214283 | 0.823148 |
| 7 | **4b** | $S^+H_2$ | *i*Pr | *trans* | −141.822442 | |
| 8 | | | | *cis* | −140.538646 | 1.283796 |

a) Energy difference between the intermediates leading to *cis* and *trans* pyrans, in kcal/mol.

implemented in MOPAC 6.0[7] (Scheme 3). First of all, the reaction products, *cis*- and *trans*-**5a**,**b**, were calculated with AM1. The results are shown in Table 2. The conformation of the *cis* compounds was fixed to have the R group disposed equatorial. The AM1 calculations showed that *trans*-**5a**,**b** are more stable than the corresponding *cis*-**5a**,**b** in the ground state, as shown in Table 2. However, the differences are too small to account for the observed high *trans* stereoselectivity shown in Table 1. Since an explanation upon thermodynamic grounds seemed to be unsuitable, we decided to inspect the kinetic processes. A stepwise mechanism of the cyclization was considered as the model system; in the first step, model compounds **3a**,**b** and **4a**,**b** in which the leaving groups are bromide ion and sulfide, respectively, afford reaction intermediates V, VII by intramolecular nucleophilic substitution; in the following step the elimination of X affords pyran **5a**,**b**. Another possible mechanism for the stereoselective formation of 2,5-disubstituted tetrahydropyrans is a $S_N2'$ reaction.[8] Whichever is the mechanism, the major factor governing the differences in the activation energies at the stereo-determination step was envisioned to result from steric strain in the transition state.

Intermediates V leading to *trans* pyrans *trans*-**5a**,**b** and the other intermediates VII leading to *cis* pyrans *cis*-**5a**,**b** were optimized, respectively. The results are given in Table 3. As with

Table 4. Bond Lengths and Net Atomic Charge of the Reaction Intermediates **3**,**4**




| | Bond length[a)] | | | | |
|---|---|---|---|---|---|
| Intermediate | *a* | *b* | *c* | *d* | Net atomic charge[b)] |
| **3a-V** | 1.453 | 1.479 | 1.429 | 2.034 | −0.4864 |
| **3a-VII** | 1.449 | 1.482 | 1.439 | 2.024 | −0.5182 |
| **3b-V** | 1.449 | 1.475 | 1.436 | 2.029 | −0.4890 |
| **3b-VII** | 1.452 | 1.479 | 1.444 | 2.022 | −0.5209 |
| **4a-V** | 1.437 | 1.499 | 1.343 | 2.539 | −0.1662 |
| **4a-VII** | 1.427 | 1.504 | 1.342 | 2.550 | −0.1783 |
| **4b-V** | 1.438 | 1.502 | 1.342 | 2.585 | −0.1734 |
| **4b-VII** | 1.427 | 1.504 | 1.341 | 2.551 | −0.1780 |

a) bond length: Å

b) net atomic charge of the $\alpha$ carbon of the ester group.

Table 5. AM1 Energies of the Transition States in the Intramolecular Nucleophilic Substitution of the (*Z*)-Ester of **3a,b** and **4a,b**

| Entry | Ester | X | R | Geometry | Energy/kcal mol$^{-1}$ | $\Delta\Delta H^{*a)}$ |
|---|---|---|---|---|---|---|
| 1 | **3a** | Br | Me | *trans* | −144.958190 | |
| 2 | | | | *cis* | −143.178910 | 1.779280 |
| 3 | **3b** | Br | *i*Pr | *trans* | −154.688854 | |
| 4 | | | | *cis* | −152.928250 | 1.760604 |
| 5 | **4a** | $S^+H_2$ | Me | *trans* | −39.293806 | |
| 6 | | | | *cis* | −37.801168 | 1.492638 |
| 7 | **4b** | $S^+H_2$ | *i*Pr | *trans* | −48.729992 | |
| 8 | | | | *cis* | −47.181169 | 1.548823 |

a) Energy difference between the transition states leading to the *cis* and *trans* product, in kcal/mol.

the final products, here again differences in energy between intermediates were found to be too small to account for the high stereoselectivities. This further supports the notion that the reaction is kinetically controlled. Selected bond lengths near the reaction sites and the net atomic charge of the carbon α to the newly formed C–O bond are given in Table 4. Significantly large structural differences were observed between the group of compounds bearing a Br leaving group and a sulfide leaving group. The values for the former group were reasonable for ordinary enolates. However, for the latter, while the bond lengths of the newly formed C–O bond are comparable with those of the Br series, the values of 1.50 Å for b and 1.34 Å for c are essentially those of a C–C single bond and a C–C double bond, respectively. Furthermore, the C–S bond to be cleaved is exceptionally long (2.54 to 2.59 Å) and the charge on the α carbon is more appropriate for a neutral charge unseparated species (−0.166 to −0.178); judging from these structural parameters and considering the level of approximation of semi-empirical calculations, it may well be that for the sulfonium series, no intermediate actually exists and the reaction proceeds via the $S_N2'$ mechanism (concerted mechanism).

Since the above calculations of the intermediates implied that the transition states leading to these intermediates were the stereo-determining states, these were next examined. Transition states IV and VI were located by calculating the bond-breaking process of the C$\beta$–O bond starting from the optimized intermediates, V and VII, by systematically increasing the C–O bond length in successive increments and optimizing all of the remaining geometrical parameters. The results of AM1 calculations with respect to the pyran ring geometry and energy for the ring-closure of the (*Z*)- and (*E*)-esters are summarized in Tables 5 and 6. An assessment of Table 5 reveals that the transition states leading to the *trans*-pyrans are of lower energy than those for *cis*-pyrans and that the energy difference ($\Delta\Delta H^*$) and the expected selectivity is much larger for the sulfide-elimination reaction. The results for (*E*)-esters of **3a**,**b** and **4a**,**b** were likewise, as given in Table 6. These results are consistent with the experimental results, and suggest that the

Table 6. AM1 Energies of the Transition States in the Intramolecular Nucleophilic Substitution of the (*E*)-Ester of **3a,b** and **4a,b**

| Entry | Ester | X | R | Geometry | Energy/kcal mol$^{-1}$ | $\Delta\Delta H^{*a)}$ |
|---|---|---|---|---|---|---|
| 1 | **3a** | Br | Me | *trans* | −145.227447 | |
| 2 | | | | *cis* | −143.544540 | 1.682907 |
| 3 | **3b** | Br | *i*Pr | *trans* | −154.924364 | |
| 4 | | | | *cis* | −153.208130 | 1.716234 |
| 5 | **4a** | $S^+H_2$ | Me | *trans* | −39.937533 | |
| 6 | | | | *cis* | −38.807654 | 1.129879 |
| 7 | **4b** | $S^+H_2$ | *i*Pr | *trans* | −51.188499 | |
| 8 | | | | *cis* | −48.588716 | 2.599783 |

a) Energy difference between the transition states leading to the *cis* and *trans* product, in kcal/mol.

formation of *trans*-**2** is a kinetically controlled process. A similar cyclization reaction of (*E*)- and (*Z*)-7-hydroxy-4-substituted 2,3-unsaturated esters leading to 2,3-disubstituted tetrahydropyrans has been found to be kinetically controlled.[8] The second step involving the elimination should thus be a fast process relative to the nucleophilic attack process, if an intermediate exists at all.

The *trans* selectivity of the cyclization reaction at 0 °C rose slightly (Table 1, entry 3). This may also be an indication that the formation of the *trans* pyran **2a** is kinetically controlled and irreversible.[9] Furthermore, substrates **1d**,**e** in which the retro-Michael process is not restricted due to the lack of an ensuing irreversible process, gave rise to lower selectivity, which is consistent with thermodynamic calculations of **4a**,**b**.

## Conclusion

In conclusion, we have developed a highly *trans* selective method for preparing 2,5-disubstituted pyran derivatives via a reaction involving a intramolecular nucleophilic reaction. AM1 calculations indicate the stereoselectivity to be of kinetic control origin, and that the use of the sulfide leaving group was essential for the high selectivity.

## Experimental

**General Methods.** NMR spectra were recorded on a JEOL GSX-270 or a JMN-LA500 instrument and calibrated using TMS as an internal reference ($\delta$ = 0.0). High-resolution mass spectra (HRMS) were recorded on a JEOL SX-102A mass spectrometer under electron ionization (EI) conditions. Optical rotations, recorded on a JASCO DIP-370 polarimeter, are given as $10^{-1}$ deg cm$^2$ g$^{-1}$. The calculations were made using the MOPAC 6.0 program package.

The syntheses of **1a** and **2a** have been described in a preceding paper.[3]

**Methyl (2*Z*,6*R*,8*E*)-6-(*t*-butyldimethylsilyloxymethyl)-2-(isopropylthiomethyl)-9,13-dimethyl-2,8,12-tetradecatrienoate ((*Z*)-1b).** To a suspension of NaH (60% in mineral oil, 80 mg, 2.0 mmol, washed with hexane) in THF (3.0 mL) was added propane-2-thiol (0.15 mL, 1.6 mmol) and $(EtO)_2P(O)C(=CH_2)CO_2Me$ (353 mg, 1.59 mmol) in THF (5.0 mL) at 0 °C. After the mixture was stirred for 10 min at 0 °C, (4*S*,6*E*)-4-(*t*-butyldimethylsilyloxymethyl)-7,11-dimethyl-6,10-dodecadiene-1-al (353 mg, 1.00 mmol) in THF (3.0 mL) was added to it and stirring was continued for 12 h at 0 °C to room temperature. The reaction mixture was then poured into aqueous $NH_4Cl$ and extracted with $CH_2Cl_2$. The combined extracts were washed with brine, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography of the crude product gave **1b** (296 mg, 59%, *E*/*Z* = 94/6) as a colorless oil; $R_f$ (silica gel, EtOAc/hexane = 1:5) 0.5; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.03 (s, 6H, $(CH_3)_2Si$), 0.89 (s, 9H, $(CH_3)_3CSi$)), 1.28 (d, *J* = 6.7 Hz, 6H, $CH(CH_3)_2$), 1.45–1.74 (m, 3H, 5-H, 6-H), 1.60 (s, 6H, (vinyl-$CH_3$) × 2), 1.68 (s, 3H, vinyl-$CH_3$), 1.88–2.12 (m, 6H, 7-H, 10-H, 11-H), 2.28 (td, *J* = 7.8, 7.8 Hz, 2H, 4-H), 2.92 (sept, *J* = 6.7 Hz, 1H, $CH(CH_3)_2$), 3.47 (dd, *J* = 5.5, 10.7 Hz, 1H, $CH_2OSi$), 3.51 (dd, *J* = 5.5, 10.7 Hz, 1H, $CH_2OSi$), 3.46 (s, 2H, $CH_2S$), 3.76 (s, 3H, $OCH_3$), 5.06–5.17 (m, 2H, 8-H, 12-H), 6.81 (t, *J* = 7.3 Hz, 1H, 3-H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ −5.5 (×2), 16.1, 17.6, 18.2, 23.4, 25.6, 25.9 (×3), 26.2, 26.5, 26.6, 28.6, 29.1, 29.9, 35.5, 39.8, 41.0, 51.8, 64.8, 122.4, 124.3, 129.2, 131.2, 136.2, 145.1, 167.4; EI-HRMS Found: *m*/*z* 481.3171. Calcd for $C_{27}H_{49}O_3SiS$ M-$CH_3$: 481.3172.

**Methyl 6-(*t*-butyldimethylsilyloxymethyl)-2-(isopropylthiomethyl)-2-eicosenoate ((*Z*)-1c).** To a suspension of NaH (60% in mineral oil, 70 mg, 1.75 mmol, washed with hexane) in THF (3.0 mL) was added propane-2-thiol (0.15 mL, 1.6 mmol) and $(EtO)_2P(O)C(=CH_2)CO_2Me$ (321 mg, 1.44 mmol) in THF (5.0 mL) at 0 °C. After the mixture was stirred for 10 min at 0 °C, 4-(*t*-butyldimethylsilyloxymethyl)-2-(isopropylthiomethyl)-octadecan-1-al (513 mg, 1.24 mmol) in THF (2.0 mL) was added to it and stirring was continued for 12 h at 0 °C to room temperature. The reaction mixture was then poured into aqueous $NH_4Cl$ and extracted with $CH_2Cl_2$. The combined extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography of the crude product gave the sulfide (423 mg, 61%, *E*/*Z* = 90/10) as a colorless oil; $R_f$ (silica gel, EtOAc/hexane = 1:9) 0.34; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.02 (s, 6H, $(CH_3)_2Si$), 0.87 (s, 9H, $(CH_3)_3CSi$), 0.93–0.83 (m, 3H, 20-H), 1.55-1.15 (m, 35H, 5-H, 6-H, 7-H, 8-H, 9-H, 10-H, 11-H, 12-H, 13-H, 14-H, 15-H, 16-H, 17-H, 18-H, 19-H, $SCH(CH_3)_2$), 2.25 (dt, *J* = 7.9 Hz, 2H, 4-H), 2.90 (sept, *J* = 6.7 Hz, 1H, $SCH(CH_3)_2$), 3.44 (dd, *J* = 5.5, 9.8 Hz, 1H, $CH_2O$), 3.45 (s, 2H, $CH_2S$), 3.51 (dd, *J* = 4.9, 9.8 Hz, 1H, $CH_2O$), 3.74 (s, 3H, $CO_2CH_3$), 6.80 (t, *J* = 7.6 Hz, 1H, 3-H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ −5.5 (×2), 14.1, 18.2, 22.6, 23.4 (×2), 25.9

(×2), 26.2, 26.4, 26.8, 29.3, 29.6 (×5), 29.7 (×3), 30.0, 30.2, 30.8, 31.9, 35.5, 40.2, 51.8, 65.1, 129.2, 145.2, 167.4; EI-HRMS Found: *m/z* 499.3641. Calcd for $C_{28}H_{55}O_3SSi$ M-*t*Bu: 499.3641.

**Ethyl (2*E*,9*E*,13*E*)-6-(*t*-butyldimethylsilyloxylmethyl)-10,14,18-trimethyl-2,9,13,17-nonadecatetraenoate (1d).** To a suspension of NaH (10.2 mg, 0.26 mmol) in THF (0.5 mL) at 0 °C was slowly added a solution of $(EtO)_2P(O)CH_2CO_2Et$ (79.9 mg, 0.36 mmol) in THF (0.5 mL). After the reaction mixture was stirred at 0 °C for 30 min, a solution of (7*E*,11*E*)-4-(*t*-butyldimethylsilyloxylmethyl)-8,12,16-trimethyl-7,11,15-heptadecatrien-1-al (32.9 mg, 0.076 mmol) in THF (0.5 mL) was added to the solution. The mixture was stirred at 25 °C for 4 h and quenched with aqueous $NH_4Cl$. The aqueous layer was extracted with ether. The combined organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and evaporated. The crude product was purified with preparative TLC (silica gel, EtOAc/hexane = 1:5 ) to give *trans* **1d** as a colorless oil (35.5 mg, 93%); $R_f$ (silica gel, EtOAc/hexane = 1:5) 0.73; IR (thin film) 2900, 2870, 1710, 1650, 1430, 1360, 1250, 1170, 1090, 830, 770 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 0.03 (s, 6H, $(CH_3)_2Si$), 0.89 (s, 9H, $(CH_3)_3CSi$), 1.29 (t, $J$ = 7.1 Hz, 3H, $OCH_2CH_3$), 1.30–1.54 (m, 5H, 5-H, 6-H, 7-H), 1.60 (s, 6H, vinyl-$CH_3$), 1.68 (s, 6H, vinyl-$CH_3$), 1.91-2.13 (m, 10H, 8-H, 11-H, 12-H, 15-H, 16-H), 2.16–2.27 (m, 2H, 4-H), 3.43–3.57 (m, 2H, $CH_2OSi$), 4.18 (q, $J$ = 7.1 Hz, 2H, $OCH_2CH_3$), 5.04–5.18 (m, 3H, 9-H, 13-H, 17-H), 5.81 (d, $J$ = 16.1 Hz, 1H, 2-H), 6.92–7.06 (m, 1H, 3-H): EI-HRMS Found: *m/z* 504.4019. Calcd for $C_{31}H_{56}O_3Si$ M: 504.3999.

**Methyl (9*E*,13*E*)-6-(*t*-butyldimethylsilyloxymethyl)-2-methoxycarbonyl-10,14,18-trimethyl-2,9,13,17-nonadecatetraenoate (1e).** To a solution of dimethyl malonate (0.1 mL, 0.85 mmol) in MeOH (1.0 mL) were added $H_3N^+CH_2CH_2NH_3^+$ $2Ac^-$ (catalytic amount) and (7*E*,11*E*)-4-(*t*-butyldimethylsilyloxylmethyl)-8,12,16-trimethylheptadeca-7,11,15-trien-1-al[3] (104 mg, 0.24 mmol). The mixture was stirred at 25 °C for 23 h and quenched with aqueous $NH_4Cl$. MeOH was removed under reduced pressure and the remaining aqueous layer was extracted with ether. The combined organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The crude product was purified with preparative TLC to give **1e** as a colorless oil (53.7 mg, 41%); $R_f$ (silica gel, EtOAc/hexane = 1:5) 0.55; $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 0.03 (s, 6H, $(CH_3)_2Si$), 0.89 (s, 9H, $(CH_3)_3CSi$), 1.10–1.71 (m, 5H, 5-H, 6-H, 7-H), 1.60 (s, 6H, vinyl-$CH_3$), 1.68 (s, 6H, vinyl-$CH_3$), 1.93–2.15 (m, 10H, 8-H, 11-H, 12-H, 15-H, 16-H), 2.30 (td, $J$ = 8.3 Hz, 2H, 4-H), 3.43–3.47 (m, 2H, $CH_2OSi$), 3.78 (s, 3H, $OCH_3$), 3.82 (s, 3H, $OCH_3$), 5.06–5.17 (m, 3H, 9-H, 13-H, 17-H), 7.03 (t, $J$ = 8.3 Hz, 1H, 3-H); EI-HRMS Found: *m/z* 548.3886. Calcd for $C_{32}H_{56}O_5Si$ M: 548.3897.

**Methyl (2*R*,5*R*)-$\alpha$-Methylene-5-[(2*E*)-3,7-dimethyl-2,6-octadienyl]-tetrahydro-2*H*-pyran-2-acetate (2b).** To a mixture of **1b** (30.7 mg, 0.062 mmol) and $AgBF_4$ (39.1 mg, 0.20 mmol) in $CH_2Cl_2$ (1.0 mL) was added MeI (0.05 mL, 0.803 mmol). The reaction mixture was stirred for 1 h at room temperature and then filtered. After the filtrate was concentrated, the residue was diluted with THF (1.0 mL) and treated with a 1.0 M solution of TBAF in THF (0.10 mL, 0.10 mmol). After stirring for 30 h at room temperature, the reaction was quenched with aqueous $NH_4Cl$ and the aqueous layer was separated and extracted with $CH_2Cl_2$. The combined extracts were washed with brine, dried with anhydrous $MgSO_4$, and evaporated. Purification of the crude product by preparative TLC (silica gel, EtOAc/hexane = 1:10) of the crude product gave **2b** (5.22 mg, 28%, *cis*/*trans* = 6/94) as a colorless oil.

**Methyl *trans*-(2*R*,5*R*)-$\alpha$-Methylene-5-[(2*E*)-3,7-dimethyl-2,6-octadienyl]-tetrahydro-2*H*-pyran-2-acetate (*trans*-2b).** Colorless oil; $R_f$ (silica-gel, EtOAc/hexane = 1:5) 0.6; $[\alpha]^D_{25}$ +41.3 ($c$ = 0.50, $CHCl_3$); $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 1.34–1.22 (m, 2H, 3-ax-H, 4-ax-H), 1.53–1.70 (m, 1H, 5-H), 1.58 (s, 3H, vinyl-$CH_3$), 1.60 (s, 3H, vinyl-$CH_3$), 1.68 (s, 3H, vinyl-$CH_3$), 2.08–1.74 (m, 8H, 1-H, 4-H, 5-H of octadientyl, 3-eq-H, 4-eq-H), 3.17 (t, $J$ = 11.2 Hz, 1H, 6-ax-H), 3.76 (s, 3H, $OCH_3$), 4.02 (ddd, $J$ = 2.0, 3.9, 11.2 Hz, 1H, 6-eq-H), 4.13 (d, $J$ = 9.3 Hz, 1H, 2-H), 5.14–5.05 (m, 2H, 2-H, 6-H of octadienyl), 5.89 (s, 1H, $\alpha$-methylene), 6.24 (s, 1H, $\alpha$-methylene); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 16.1, 17.7, 25.7, 26.6, 30.4, 30.8, 32.4, 36.7, 39.8, 51.7, 73.8, 75.5, 121.7, 124.2, 124.3, 131.4, 136.4, 142.0, 166.5; EI-HRMS Found: *m/z* 306.2235. Calcd for $C_{19}H_{30}O_3$ M: 306.2195.

**Methyl *cis*-(2*S*,5*R*)-$\alpha$-methylene-5-[(2*E*)-3,7-dimethyl-2,6-octadienyl]-tetrahydro-2*H*-pyran-2-acetate (*cis*-2b).** Colorless oil; $R_f$ (EtOAc/hexane = 1:5) 0.6; $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 1.34–1.22 (m, 2H, 3-ax-H, 4-ax-H), 1.53–1.70 (m, 1H, 5-H), 1.58 (s, 3H, vinyl-$CH_3$), 1.60 (s, 3H, vinyl-$CH_3$), 1.68 (s, 3H, vinyl-$CH_3$), 2.08–1.74 (m, 8H, 1-H, 4-H, 5-H of octadienyl, 3-eq-H, 4-eq-H), 3.65 (dd, $J$ = 2.4, 11.2 Hz, 1H, 6-ax-H), 3.76 (s, 3H, $OCH_3$), 3.82–3.88 (m, 1H, 6-eq-H), 4.10–4.11 (m, 1H, 2-H), 5.14–5.05 (m, 2H, 2-H, 6-H of octadienyl), 5.89 (s, 1H, $\alpha$-methylene), 6.24 (s, 1H, $\alpha$-methylene).

**Methyl *trans*-$\alpha$-methylene-5-tetradecanyl-tetrahydro-2*H*-pyran -2-acetate (2c).** Colorless oil; $R_f$ (silica gel, EtOAc/hexane = 1:5) 0.58; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.88 (t, $J$ = 7.0 Hz, 3H, 14-H of tetradecanyl), 1.36–1.03 (m, 28H, 1-H, 2-H, 3-H, 4-H, 5-H, 6-H, 7-H, 8-H, 9-H, 10-H, 11-H, 12-H, 13-H of tetradecanyl, 3-ax-H, 4-ax-H), 1.63–1.51 (m, 1H, 5-H), 1.99–1.87 (m, 2H, 3-eq-H, 4-eq-H), 3.14 (t, $J$ = 11.1 Hz, 1H, 6-ax-H), 3.76 (s, 3H, $CO_2CH_3$), 4.02 (ddd, $J$ = 1.2, 4.0, 11.0 Hz, 1H, 6-eq-H), 4.13 (d, $J$ = 10.7 Hz, 1H, 2-H), 5.89 (s, 1H, $\alpha$-methylene), 6.24 (s, 1H, $\alpha$-methylene); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 14.1, 22.7, 26.6, 29.4, 29.6, 29.7 (×6), 29.8, 30.6, 31.9, 32.3, 32.4, 35.7, 51.8, 74.1, 75.5, 124.2, 142.0, 166.5; EI-HRMS Found: *m/z* 366.3143. Calcd for $C_{23}H_{42}O_3$ M: 366.3134.

**Ethyl 5-[(3*E*,7*E*)-4,8,12-trimethyl-3,7,11-tridecatrienyl]-tetrahydro-2*H*-pyran-2-acetate (2d).** To a solution of **1d** (22.4 mg, 0.045 mmol) in THF (0.5 mL) was added a 1.0 M solution of TBAF in THF (0.3 mL, 0.3 mmol). The reaction mixture was stirred at 25 °C for 5 h and quenched with aqueous $NH_4Cl$. The aqueous layer was extracted with ether and the organic layer was combined. The combined organic extracts were washed with water and brine, dried over $MgSO_4$, filtered, and evaporated. The crude product was purified with preparative TLC to give a mixture of *cis*- and *trans*-**2d** as a colorless oil (13.4 mg, 77%, *cis*/*trans* = 3:7); $R_f$ (silica gel, AcOEt/hexane = 1:5) 0.79; IR (thin film) 2900, 2850, 1730, 1440, 1370, 1280, 1180, 1090 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 1.25 (t, $J$ = 7.3 Hz, 3H, $OCH_2CH_3$), 0.82–1.56 (m, 7H, 3-H, 4-H, 5-H, 1-H of tridecatrienyl), 1.57 (s, 6H, vinyl-$CH_3$), 1.59 (s, 3H, vinyl-$CH_3$), 1.67 (s, 3H, vinyl-$CH_3$), 1.84–2.10 (m, 10H, 2-H, 5-H, 6-H, 9-H, 10-H of tridecatrienyl), 2.31–2.61 (m, 2H, $CH_2CO_2Et$), 3.05 (t, $J$ = 11.2 Hz, *trans*-6-ax-H), 3.56–3.96 (m, 2-ax-H, 6-eq-H, *cis*-6-ax-H), 4.14 (q, $J$ = 7.3 Hz, 2H, $OCH_2CH_3$), 5.05–5.18 (m, 3H, 3-H, 7-H, 11-H of tridecatrienyl); EI-HRMS Found: *m/z* 390.3134. Calcd for $C_{25}H_{42}O_3$ M: 390.3134.

**Methyl $\alpha$-methoxycarbonyl-5-[(3*E*,7*E*)-4,8,12-trimethyl-3,7,11-tridecatrienyl]-tetrahydro-2*H*-pyran-2-acetate (2e).** To a solution of **1e** (53.7 mg, 0.1 mmol) in THF (0.5 mL) at 25 °C, was added a 1.0 M solution of TBAF in THF (0.5 mL, 0.5 mmol),

and the reaction mixture was stirred at 25 °C. After 24 h, aqueous $NH_4Cl$ was added to the reaction mixture and the aqueous layer was extracted with ether. The combined organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The crude product was purified with preparative TLC to give a mixture of *cis*- and *trans*-**2e** as a colorless oil (5.77 mg, 13%, *cis*/*trans* = 20: 80); $R_f$ (silica gel, EtOAc/hexane = 1: 5) 0.51; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.84–1.81 (m, 7H, 1-H of tridecatrienyl, 3-H, 4-H, 5-H), 1.57 (s, 6H, vinyl-$CH_3$), 1.60 (s, 3H, vinyl-$CH_3$), 1.68 (s, 3H, vinyl-$CH_3$), 1.86–2.20 (m, 10H, 2-H, 5-H, 6-H, 9-H, 10-H of tridecatrienyl), 3.06 (t, $J$ = 11.2 Hz, *trans*-6-ax-H), 3.48 (d, $J$ = 8.8 Hz, 1H, $CH(CO_2CH_3)$), 3.73 (s, 3H, $OCH_3$), 3.76 (s, 3H, $OCH_3$), 3.80–3.98 (m, 2-H, 6-eq-H, *cis*-6-ax-H), 5.06–5.18 (m, 3H, 3-H, 7-H, 11-H of tridecatrienyl); EI-HRMS Found: *m*/*z* 434.3018. Calcd for $C_{26}H_{42}O_5$ M: 434.3032.

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