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Asymmetric synthesis of long chain α-methyl-β-thiotrifluoromethyl ketones employing the SAMP-/RAMP-hydrazone alkylation methodology

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Abstract—The enantioselective synthesis of both enantiomers of (*Z*)-1,1,1-trifluoro-3-methyl-4-thia-13-octadecen-2-one and (*Z*)-1,1,1-trifluoro-3-methyl-4-thia-13-hexadecen-2-one (ee ⩾90%), potential inhibitors of the pheromone action of two major maize pests *Sesamia nonagrioides* and *Ostrinia nubilalis*, is described. The key step is based upon a stereoselective alkylation with methyl iodide using the SAMP-/RAMP-chiral auxiliary methodology, followed by deprotection under non-racemization conditions.

1. Introduction

Enzymatic inhibition is currently an area of crucial importance, particularly in the agrochemical and pharmaceutical fields.[1,2] Illustrative examples of the importance of enzyme inhibitors are the development of inhibitors of human neutrophil elastase for the treatment of pulmonary emphysema,[3] renin inhibitors as therapeutic agents for hypertension related disorders,[4] or inhibitors of neuropathy target esterase, the target enzyme of several neurotoxic organophosphorous compounds.[5]

It is known that the introduction of fluorine atoms into a bioactive molecule significantly alters the physicochemical features of the molecule because of its high electronegativity. At the same time, it causes minimal steric alterations and, hence, can facilitate the interactions of the molecule with enzyme active sites, receptor sites, in transport mechanisms and in other biological processes.[6,4] Furthermore, the presence of fluorine substituents in bioactive molecules enhances their lipophilicities, thereby influencing the 'in vivo' uptake and transport of active ingredients.[7,8] In this context, fluorinated ketones are particularly attractive from a pharmacological point of view as strong inhibitors of a variety of serine hydrolases, including acetylcholinesterase,[9] chymotrypsin,[10] trypsin,[11] juvenile hormone esterase,[12] human liver microsomal carboxylesterases,[13] cytosolic human phospholipase A_2[14] or HIV-1 proteases.[15] The fluorinated ketones function as transition-state analogues of the enzyme, with the inhibition activity arising from the formation of an adduct of tetrahedral geometry between the serine residue, present at the active site of the enzyme, with the highly electrophilic carbonyl moiety.[16,17]

We and others have previously shown that linear saturated or unsaturated trifluoromethyl ketones (TFMKs) are good antagonists of the pheromone activity in insects resulting in potential biorational agents for pest control.[18,1,19,8,20–23] This has been attributed, at least in part, to the inhibition of the esterases present in male's antennae.[24,25,17] In this context, introduction of a sulfur atom at a β-position to the carbonyl group led to a new series of inhibitors of JH esterase derived from the parent compound 3-octylthio-1,1,1-trifluoropropan-2-one (OTFP) with a dramatically enhanced potency.[26] The activity is probably due to the presence of an intramolecular hydrogen bond between the free electron pair of sulfur with an OH group of the hydrate.[27,28] Introduction of a methyl group in alpha position to the carbonyl of OTFP has shown a further increase of the inhibitory potency in comparison to the non-substituted compound.[16]

Following this trend, we herein report the racemic and asymmetric synthesis of α-methyl-β-thiotrifluoromethyl

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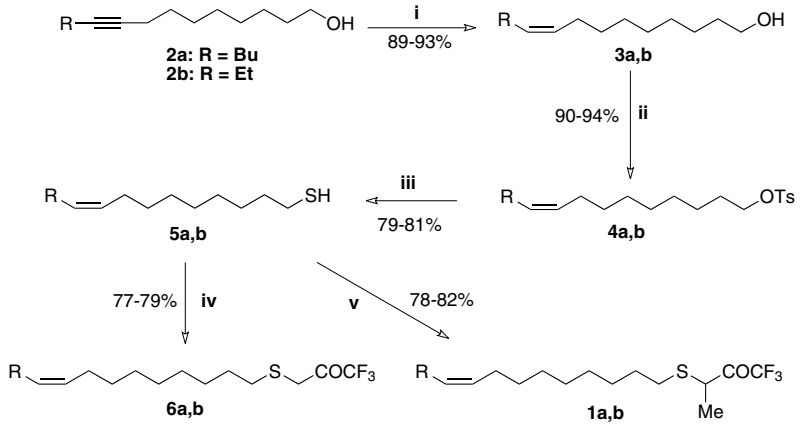
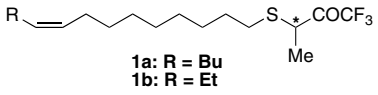


Scheme 1. Synthesis of β-thiotrifluoromethyl ketones **6a** and **6b** and (±)-α-methyl-β-thiotrifluoromethyl ketones **1a** and **1b**. Reagents and conditions: (i) H_2, P-2 Ni, EtOH; (ii) TsCl, Py; (iii) EtOC(S)SK, acetone, reflux, $H_2NCH_2CH_2NH_2$; (iv) DIPEA, $BrCH_2COCF_3$, CH_2Cl_2; (v) Et_3N, $CH_3CH(Br)COCF_3$.

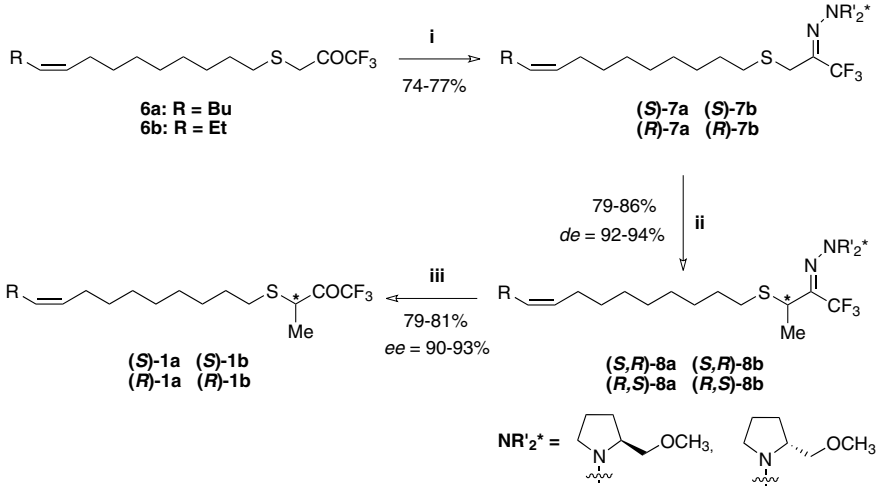
ketones (*R*)-**1a**, (*R*)-**1b**, (*S*)-**1a**, and (*S*)-**1b**, pheromone inhibitors of two major pests of maize, the Mediterranean corn borer *Sesamia nonagrioides*[29,30] and the European corn borer *Ostrinia nubilalis*,[31,32] as new potential biorational pest control agents.



The racemic compounds can be obtained in a straightforward manner by condensation of the corresponding thiol and 3-bromo-1,1,1-trifluoro-2-butanone. For the synthesis of the chiral compounds, induction of chirality can be accomplished using the SAMP-/RAMP-methodology developed by Enders.[33] (*S*)-(−)-1-Amino-2-methoxypyrrolidine (SAMP) and (*R*)-(+)-1-amino-2-methoxypyrrolidine (RAMP) are commercially available chiral auxiliaries and have been successfully applied in the asymmetric synthesis of a number of bioactive natural products,[34,35] in base to their high versatility in diastereotopic and diastereofacial selective reactions.[36–38] In addition, the SAMP-/RAMP-hydrazone methodology allows the establishment of the absolute configuration of the new chiral compounds obtained.[39–41]

2. Results and discussion

The synthesis of compounds **6a** and **6b** and racemics **1a** and **1b** was accomplished by alkylation of the intermediate thiols **5a** and **5b** with 3-bromo-1,1,1-trifluoromethyl-2-propanone or 3-bromo-1,1,1-trifluoromethyl-2-butanone, respectively, in the presence of base[42] in good yields (Scheme 1). The latter bromo-substituted TFMK is not commercially available but can be easily prepared by acid-catalyzed bromination of 1,1,1-trifluoromethyl-2-butanone in 85% yield.[43] Thiols **5a** and **5b** were prepared in a 3-step sequence from acetylenic alcohols **2a** and **2b**. Thus, hydrogenation with P-2 Nickel afforded olefinic alcohols **3a** and **3b** in 89–93% yields with high stereochemical purities (>97% *Z*, no *E*-isomer was detected by ^{13}C NMR). The next step, that is, the transformation of a hydroxyl group into a thiol, required the previous conversion



Scheme 2. Asymmetric synthesis of chiral α-methyl-β-thiotrifluoromethyl ketones (*S*)-**1a**, (*S*)-**1b**, (*R*)-**1a**, (*R*)-**1b**. Reagents and conditions: (i) $H_2NNR'^*_2$, 65 °C; (ii) LDA, CH_3I, Et_2O, −100 °C; (iii) $BF_3{\cdot}OEt_2$, $(CH_2O)_n$, acetone/H_2O.

into a good leaving group, such as a tosylate. This process occurred under standard conditions to obtain tosylates **4a** and **4b** in excellent yields. However, nucleophilic substitution of **4a** under different conditions, that is, reaction with thiourea,[44] or with thioacetic acid, PPh_3 and DIAD under Mitsunobu conditions followed by reaction with LAH,[45] led to the expected thiol mostly with the *E* configuration. Much more convenient was the reaction with potassium ethylxanthate in acetone at reflux for 30 min[46] followed by treatment with ethylenediamine.[47] Under these conditions, compounds **5a** and **5b** were obtained in 79–81% yields with almost no double bond isomerization (*Z*:*E*, 94:6 for **5a** and 93:7 for **5b**).

For the asymmetric synthesis of chiral α-methyl-β-thiotrifluoromethyl ketones **1a** and **1b**, we followed the procedure depicted in Scheme 2. This involved transformation of the starting ketones **6a** and **6b** to the corresponding SAMP- or RAMP-hydrazones (*S*)-**7a**, (*S*)-**7b**, (*R*)-**7a** and (*R*)-**7b**, metallation followed by trapping of the intermediate azaenolates with an electrophile, and then hydrazone cleavage. It is interesting to note that this type of reaction had never been performed on β-thiotrifluoromethyl ketones.

Therefore, SAMP-hydrazones **7a** and **7b** were prepared by heating β-thiotrifluoromethyl ketones **6a** and **6b** with 1.1 equiv of the aminopyrrolidines SAMP (Acros, 97% ee) or RAMP (Aldrich, 99% ee) at 65 °C for 48 h. After chromatographic purification, hydrazones **7a** and **7b** were isolated in 74–77% yields as pale yellow oils, which can be safely stored under Ar in a refrigerator. Metallation of the hydrazones with LDA in ether, followed by alkylation of the resultant azaenolates with methyl iodide at −100 °C, afforded α-methyl-β-thiotrifluoromethyl hydrazones (*S*,*R*)-**8a**, (*S*,*R*)-**8b**, (*R*,*S*)-**8a**, and (*R*,*S*)-**8b** in good yields (79–86%) and high diastereomeric excess (92–94%), as determined by ^{19}F NMR (Table 1). Due to the uniform diastereofacial differentiation common for all asymmetric SAMP-/RAMP-hydrazone alkylations, the absolute configuration which will predominate in the final product can be safely predicted.[48] The absolute configuration was assigned by an analogy with previous results obtained with β-sulfenylated ketones, as well as for the model currently accepted for the relative topicity of electrophilic attack onto lithium azaenolates derived from SAMP-hydrazones.[34,49] Therefore, the newly created stereogenic center has an (*R*)-configuration, whereas the pyrrolidine stereogenic center maintained the original configuration of the starting non-methylated hydrazones. Similarly, the alkylation product with the (*S*) configuration at the new stereogenic center can be obtained from the RAMP-hydrazone. Remarkably, no N-, di- or poly-alkylation side products could be detected.

In order to preserve the enantiomeric excess of the chiral α-substituted trifluoromethyl ketones (*S*)-**1a**, (*S*)-**1b**,

Table 1. Yields and enantiomeric excess of compounds **7a** and **7b**, **8a** and **8b**, and **1a** and **1b**

Entry	Starting product	Hydrazone		Methylated hydrazone			Final product		
		Prod.	Yield (%)	Prod.	Yield (%)	de[a] (%)	Prod.	Yield (%)	ee[b] (%)
1	**6a**	(*S*)-**7a**	74	(*S*,*R*)-**8a**	86	92	(*R*)-**1a**	79	90
2	**6a**	(*R*)-**7a**	77	(*R*,*S*)-**8a**	79	92	(*S*)-**1a**	81	90
3	**6b**	(*S*)-**7b**	75	(*S*,*R*)-**8b**	83	94	(*R*)-**1b**	81	93
4	**6b**	(*R*)-**7b**	74	(*R*,*S*)-**8b**	79	92	(*S*)-**1b**	80	90

[a] Determined by ^{19}F NMR.
[b] Determined by chiral GC on a Cydex-B 0.25 column.

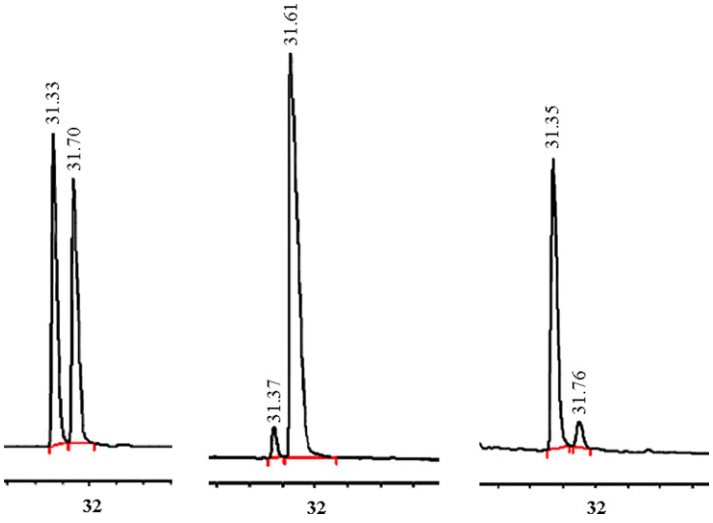


Figure 1. Enantiomeric resolution of (±)-**1b**, (*R*)-**1b**, and (*S*)-**1b** (from left to right) by chiral GC using a Cydex-B 0.25 column (25 m × 0.22 mm).

(*R*)-**1a**, and (*R*)-**1b**, the hydrolysis procedure must take place without any racemization at the newly generated stereogenic center. Classical cleavage procedures, such as heating with acid or base,[50] cannot be used, since the sensitive chiral α-methyl ketones rapidly racemize under these conditions. In the same vein, oxidative cleavage of the C=N double bond of SAMP-hydrazones with ozone[48] was also impractical on our substrates for the presence of a double bond in the molecule. Another common possibility of cleavage is methylation with an excess of methyl iodide followed by hydrolysis with 3 M HCl ('salt method')[51] but, in our case, only mixtures of decomposition products were obtained. Finally, the use of boron trifluoride-ether in acetone:water followed by the addition of paraformaldehyde[52] allowed us to obtain the desired α-methyl ketones **1a** and **1b** in good yields (79–81%). To establish their enantiomeric excesses, several attempts were carried out without success. Thus, neither NMR experiments with tris[3-(trifluoromethylhydroxymethylen)-(+)-camphorato] europium(III) nor resolution by HPLC with a Chiralcel OD (250 mm × 4.6 mm) column resulted in an efficient separation of the enantiomers of the racemic (±)-**1b**. Finally, determination of the enantiomeric excess of the ketones (*S*)-**1a**, (*S*)-**1b**, (*R*)-**1a**, and (*R*)-**1b** was successfully accomplished by chiral GC analysis using a Cydex-B 0.25 column (25 m × 0.22 mm) (Fig. 1). In this way, the ee of all enantiomers could be finally calculated. The results are summarized in Table 1.

3. Conclusion

The enantioselective α-methylation of β-thiotrifluoromethyl ketones, through the SAMP-/RAMP-chiral auxiliary method, presented in this paper opens up a practical entry to this important class of optically active compounds previously unknown in the literature. Following this methodology and as representative examples, both enantiomers of two pheromone antagonists of two major maize insect pests have been synthesized in good overall chemical yields and excellent enantioselectivities. These compounds are now ready for biological activity as new putative biorational pest control agents.

4. Experimental

4.1. General

n-Butyllithium (1.6 M in hexane), $BF_3{\cdot}OEt_2$ and SAMP were purchased from Aldrich. RAMP was obtained from Acros Organics. All reactions employing organometallic compounds were carried out under Ar. All solvents were dried and distilled according to standard procedures. IR spectra were recorded on a Bomen MB-120 or on a Nicolet Avatar 360 FT-IR spectrometer. NMR spectra were recorded at 200, 300, 400 or 500 MHz for ^{1}H, 75 or 100 MHz for ^{13}C and 282 MHz for ^{19}F, on Varian Gemini 200, Varian Unity 300, Varian Mercury 400 or Varian Inova 500 spectrometers. Mass spectra (MS) were obtained on a Fisons MD 800 instrument and high resolution mass spectra (HRMS) on an Autospec-Q Micromass-Ltd UK spectrometer. Optical rotations were measured on a Perkin–Elmer 341 polarimeter. Calculations of the diastereomeric excesses were carried out by ^{19}F NMR, whereas the enantiomeric excesses were determined by chiral GC using a Cydex-B 0.25 column (25 m × 0.22 mm).

4.2. Synthesis of β-thiotrifluoromethyl ketones 6a and 6b

4.2.1. (*Z*)-9-Tetradecen-1-ol 3a.[53] P-2 Nickel was prepared as previously described by Brown and Ahuja.[54] Under a hydrogen atmosphere, 9-tetradecyn-1-ol (3.55 g, 16.90 mmol) was added to the catalyst solution in ethanol (10 ml). After stirring for 2 h at room temperature, the solution was filtered through Celite and the filtrate repeatedly washed with hexane. The solvent was evaporated and the crude again diluted with hexane. The organic layer was washed with brine, dried over $MgSO_4$ and the solvent removed to afford 3.34 g (93%) of **3a** as a colorless oil. The *E*-isomer was not detected by ^{13}C NMR. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.34 (m, 2H); 3.63 (t, $J = 6.0$ Hz, 2H); 2.01 (m, 4H); 1.56 (m, 2H); 1.33 (b, 14H); 0.89 (t, $J = 6.9$ Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 129.9 (CH); 129.8 (CH); 63.1; 32.8; 31.9; 29.7; 29.5; 29.4; 29.2; 27.1; 26.9; 25.7; 22.3; 14.0 (CH_3) ppm. IR (film) *v*: 3464, 3008, 2929, 2860, 1464, 1055, 729 cm^{-1}. MS (EI): *m*/*z* (%) 212 (M^+, 1); 194 (23); 166 (13); 109 (36); 95 (76); 81 (72); 67 (100); 55 (98).

4.2.2. (*Z*)-9-Dodecen-1-ol 3b.[53] Alcohol **3b** was prepared in the same way as **3a**. Starting from 9-dodecyn-1-ol (3.00 g, 16.46 mmol) and $Ni(OAc)_2{\cdot}4H_2O$ (0.52 g, 2.14 mmol), the desired product **3b** (2.70 g, 89%) was obtained as a colorless oil. The *E* isomer was not detected by ^{13}C NMR. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.32 (m, 2H); 3.61 (t, $J = 6.6$ Hz, 2H); 2.02 (m, 4H); 1.73 (s, 1H); 1.55 (m, 2H); 1.26 (b, 10H); 0.94 (t, $J = 7.5$ Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 131.5 (CH); 129.2 (CH); 62.9; 32.7; 29.7; 29.4; 29.4; 29.2; 27.0; 25.7; 20.4; 14.3 (CH_3) ppm. IR (film) *v*: 3403, 3005, 2930, 1461, 1052, 909, 740, 649 cm^{-1}. MS (EI) *m*/*z* (%): 184 (M^+, 0.5); 166 (7); 110 (30); 109 (34); 96 (78); 95 (88); 82 (96); 81 (99); 69 (85); 68 (96); 67 (100); 55 (99); 41 (92).

4.2.3. (*Z*)-1-(*p*-Toluenesulfonyl)-9-tetradecene 4a.[55] A solution of alcohol **3a** (1.00 g, 4.64 mmol), tosyl chloride (2.65 g, 13.90 mmol) and 10 ml of anhydrous pyridine were placed in a round bottomed flask and cooled to 0 °C for 12 h. Then, the solution was acidified with 0.1 M HCl and extracted with hexane. The combined organic layers were washed with brine and dried. Solvent evaporation afforded compound **2** (1.562 g, 90% yield) without the need for further purification. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.77 (d, $J = 8.4$ Hz, 2H); 7.32 (d, $J = 8.4$ Hz, 2H); 5.32 (m, 2H); 3.99 (t, $J = 6.4$ Hz, 2H); 2.42 (s, 3H); 1.97 (m, 4H); 1.59 (m, 2H); 1.27 (b, 14H); 0.94 (t, $J = 7.5$ Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.5 (C); 133.1 (C); 129.8 (CH); 129.7 (2CH); 129.6 (CH); 127.8 (2CH); 70.6; 31.9; 29.6; 29.2; 29.0; 28.8; 28.7; 27.0; 26.8; 25.2; 22.2; 21.5 (CH_3); 13.9 (CH_3) ppm. IR (film) *v*: 3004, 2924, 1362, 1189, 664, 493 cm^{-1}. MS (EI) *m*/*z* (%): 366 (M^+, 1); 195 (11); 194 (73); 173 (35); 155 (29); 138 (36);

124 (55); 110 (88); 96 (95); 95 (93); 91 (93); 82 (98); 81 (100); 67 (93); 55 (92); 41 (82).

4.2.4. (*Z*)-1-(*p*-Toluenesulfonyl)-9-dodecene 4b. A procedure identical to that described above for **4b** was followed. Thus, from alcohol **3b** (2.72 g, 14.74 mmol), tosyl chloride (8.41 g, 44.22 mmol) and pyridine (39 ml), compound **4b** was obtained (4.69 g, 94%) without the need for further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, $J = 8.4$ Hz, 2H); 7.33 (d, $J = 8.4$ Hz, 2H); 5.32 (m, 2H); 4.01 (t, $J = 6.6$ Hz, 2H); 2.44 (s, 3H); 2.02 (m, 4H); 1.62 (m, 2H); 1.25 (b, 10H); 0.94 (t, $J = 7.5$ Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.6 (C); 133.2 (C); 131.5 (CH); 129.7 (2CH); 129.1 (CH); 127.8 (2CH); 70.6; 29.6; 29.2; 29.0; 28.8; 28.7; 27.0; 25.3; 21.6 (CH_3); 20.4; 14.3 (CH_3) ppm. IR (film) *v*: 3002, 2930, 1358, 1181, 909, 739, 651, 554 cm^{-1}. MS (EI) *m*/*z* (%): 338 (M^+, 1); 173 (45); 166 (83); 154 (41); 137 (26); 124 (54); 110 (81); 95 (89); 91 (97); 82 (100); 81 (93); 68 (95); 67 (95); 55 (89); 41 (88).

4.2.5. (*Z*)-9-Tetradecene-1-thiol 5a. Tosylate **4a** (1.52 g, 4.14 mmol) was added to a solution of potassium ethylxanthate (1.03 g, 6.21 mmol) in acetone (15 ml) and the mixture was refluxed for 30 min.[46] Then, the solution was allowed to cool to room temperature, the potassium salt was filtered and the solvent evaporated. Chloroform was added to the residue. The organic layer was washed with brine, dried and evaporated to dryness. The crude xanthogenic ester was decomposed at room temperature to the corresponding thiol by stirring with ethylenediamine (4 ml) for 30 min.[47] The solution was acidified with 0.1 M HCl and extracted with hexane. The combined organic layers were washed with brine and dried. The crude material was purified by column chromatography (silica, hexane) to obtain 0.75 g (79%) of thiol **5a**, partially isomerized (*Z*:*E*, 94:6) as determined by ^{13}C NMR. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.34 (m, 2H); 2.51 (dt, $J_1 = J_2 = 7.6$ Hz, 2H); 1.98 (m, 4H); 1.59 (m, 2H); 1.28 (b, 14H); 0.95 (t, $J = 7.5$ Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 129.9 (CH); 129.8 (CH); 34.0; 31.9; 29.7; 29.4; 29.2; 29.0; 28.3; 27.1; 26.9; 24.6; 22.3; 14.0 (CH_3) ppm. IR (film) *v*: 3004, 2926, 1460, 718 cm^{-1}. MS (EI) *m*/*z* (%): 230 [$(M+2)^+$, 0.6]; 228 (M^+, 10); 227 (15); 199 (7); 185 (25); 171 (27); 157 (16); 143 (32); 129 (45); 115 (73); 101 (99); 87 (100); 81 (79); 69 (82); 67 (83); 55 (90); 41 (79).

4.2.6. (*Z*)-9-Dodecene-1-thiol 5b. Following a similar procedure as for **5a**, tosylate **4b** (0.50 g, 1.48 mmol), potassium ethylxanthate (0.36 g, 2.22 mmol) and ethylenediamine (3.5 ml) afforded thiol **5b** (0.24 g, 81%) after column chromatography purification. This compound was partially isomerized (*Z*:*E*, 93:7) as determined by ^{13}C NMR. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.33 (m, 2H); 2.51 (dt, $J_1 = J_2 = 7.5$ Hz, 2H); 2.01 (m, 4H); 1.58 (m, 2H); 1.33 (b, 10H); 0.95 (t, $J = 7.5$ Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 131.5 (CH); 129.2 (CH); 34.0; 29.7; 29.4; 29.2; 29.0; 28.3; 27.0; 24.6; 20.5; 14.4 (CH_3) ppm. IR (film) *v*: 3005, 2929, 1463, 909, 734, 650 cm^{-1}. MS (EI) *m*/*z* (%): 202 [$(M+2)^+$, 6]; 200 (M^+, 10); 199 (21); 157 (42); 143 (63); 129 (59); 115 (71); 101 (99); 87 (100); 69 (77); 68 (73); 67 (84); 55 (90); 41 (90).

4.2.7. (*Z*)-1,1,1-Trifluoro-4-thia-13-octadecen-2-one 6a. To a solution of thiol **5a** (0.42 g, 1.86 mmol) in 20 ml of anhyd CH_2Cl_2 were added diisopropylethylamine (0.3 ml, 1.86 mmol) and 3-bromo-1,1,1-trifluoro-2-propanone[19] (0.53 g, 2.79 mmol). The mixture was stirred at room temperature for 4 h. The solvent was evaporated at reduced pressure and the crude purified by column chromatography (silica, hexane:ether, 90:10) to afford 0.50 g (79%) of the expected product **6a**, as a mixture of ketone and hydrate in a 45:55 ratio. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.32 (m, 2H); 4.12 (s, 2H, –C(O*H*)$_2$); 3.45 (s, 2H, –SC*H*$_2$CO–); 2.86 (s, 2H, –SC*H*$_2$C(OH)$_2$–); 2.68 (t, $J = 7.5$ Hz, 2H, –C*H*$_2$SCH$_2$C(OH)$_2$–); 2.48 (t, $J = 7.2$ Hz, 2H, –C*H*$_2$SCH$_2$CO–); 1.99 (m, 4H); 1.55 (m, 2H); 1.29 (b, 14H); 0.95 (t, $J = 7.5$ Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.0 (q, $J = 35$ Hz, –*C*OCF$_3$); 129.9 (CH); 129.7 (CH); 122.9 (q, $J = 285$ Hz, –C(OH)$_2$*C*F$_3$); 115.5 (q, $J = 291$ Hz, –CO*C*F$_3$); 92.4 (q, $J = 32$ Hz, –*C*(OH)$_2$CF$_3$); 36.5; 34.7; 33.6; 31.9; 29.7; 29.3; 29.3; 29.2; 29.2; 29.1; 29.0; 28.6; 28.6; 28.5; 27.1; 26.9; 22.3; 14.4 (CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −76.2 (s, 3F, –COC*F*$_3$); −85.8 (s, 3F, –C(OH)$_2$C*F*$_3$) ppm. IR (film) *v*: 3424, 3005, 2927, 2857, 1747, 1188 cm^{-1}. MS (EI) *m*/*z* (%): 338 (M^+, 0.5); 269 (2); 241 (4); 227 (94); 184 (4); 171 (7); 157 (13); 143 (9); 129 (18); 115 (16); 109 (16); 101 (30); 95 (39); 87 (39); 81 (48); 69 (55); 67 (52); 55 (100); 41 (55). HRMS Calcd for $C_{17}H_{29}F_3OS$ (M^+): 338.1891; Found: 338.1890.

4.2.8. (*Z*)-1,1,1-Trifluoro-4-thia-13-hexadecen-2-one 6b.[23] A procedure identical to that described above for **6a** was followed. Starting from thiol **5b** (0.20 g, 1.00 mmol), diisopropylethylamine (0.17 ml, 1.00 mmol), and 3-bromo-1,1,1-trifluoro-2-propanone (0.28 g, 1.50 mmol), the expected product **6b** (0.24 g, 77%) was obtained, after purification, as a mixture of ketone and hydrate in a 45:55 ratio. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.34 (m, 2H); 3.87 (s, 2H, –C(O*H*)$_2$); 3.48 (s, 2H, –SC*H*$_2$CO–); 2.90 (s, 2H, –SC*H*$_2$-C(OH)$_2$–); 2.71 (t, $J = 7.2$ Hz, 2H, –C*H*$_2$SCH$_2$C(OH)$_2$–); 2.51 (t, $J = 7.5$ Hz, 2H, –C*H*$_2$SCH$_2$CO–); 2.03 (m, 4H); 1.59 (m, 2H); 1.34 (b, 10H); 0.95 (t, $J = 7.5$ Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.1 (q, $J = 34$ Hz, –*C*OCF$_3$); 131.6 (CH); 129.2 (CH); 122.9 (q, $J = 284$ Hz, –C(OH)$_2$*C*F$_3$); 115.5 (q, $J = 290$ Hz, –CO*C*F$_3$); 92.4 (q, $J = 32$ Hz, –*C*(OH)$_2$CF$_3$); 36.4; 34.8; 33.6; 31.9; 29.7; 29.3; 29.3; 29.1; 29.1; 29.0; 28.6; 28.6; 28.5; 27.0; 20.5; 14.4 (CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −76.3 (s, 3F, –COC*F*$_3$); −86.0 (s, 3F, –C(OH)$_2$C*F*$_3$) ppm. IR (film) *v*: 3423, 3005, 2928, 2854, 1746, 1182 cm^{-1}. MS (EI) *m*/*z* (%): 310 (M^+, 1); 241 (2); 199 (79); 157 (9); 129 (15); 115 (15); 109 (15); 101 (29); 95 (33); 87 (40); 81 (48); 69 (71); 67 (70); 55 (100); 41 (85), HRMS Calcd for $C_{15}H_{25}F_3OS$ (M^+): 310.1578; Found: 310.1567.

4.3. Synthesis of (±)-1a,b

4.3.1. (±)-(*Z*)-1,1,1-Trifluoro-3-methyl-4-thia-13-octadecen-2-one (±)-1a. To a solution of thiol **5a** (0.32 g, 1.41 mmol) in anhyd CH_2Cl_2 (11 ml) were added Et_3N (0.2 ml, 1.41 mmol) and 3-bromo-1,1,1-trifluoro-2-butanone (0.32, 1.55 mmol).[56] The mixture was stirred at room temperature for 1 h. The solvent was then evaporated off and the residue extracted with hexane, washed with satd soln of $NaHCO_3$,

brine and dried over $MgSO_4$. Purification of the crude by column chromatography (silica, hexane) afforded 0.41 g (82%) of racemic **1a** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.34 (m, 2H); 3.75 (q, $J = 6.9$ Hz, 1H); 2.49 (dt, $J_1 = 11.7$ Hz, $J_2 = 7.5$ Hz, 1H); 2.32 (dt, $J_1 = 12.0$ Hz, $J_2 = 7.2$ Hz, 1H); 2.02 (m, 4H); 1.54 (m, 2H); 1.50 (d, $J = 6.9$ Hz, 3H); 1.32 (b, 14H); 0.89 (t, $J = 6.9$ Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.9 (q, $J = 33$ Hz, $COCF_3$); 129.9 (CH); 129.8 (CH); 115.9 (q, $J = 291$ Hz, $COCF_3$); 40.9 (CH); 31.9; 29.7; 29.3; 29.1; 29.0; 28.8; 28.5; 27.1; 26.9; 22.3; 14.7 (CH_3); 14.0 (CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −74.9 (s, 3F, –$COCF_3$) ppm. IR (film) ν: 3004, 2928, 2856, 1742, 1458, 1276, 1203, 1154, 699 cm^{-1}. MS (EI) m/z (%): 352 (M^+, 1); 255 (35); 227 (100); 141 (13); 129 (18); 115 (27); 109 (46); 101 (50); 97 (36); 95 (82); 87 (73); 81 (87); 75 (78); 69 (87); 55 (96); 43 (43); 41 (78). HRMS Calcd for $C_{18}H_{31}F_3OS$ (M^+): 352.2048; Found: 352.2039.

4.3.2. (±)-(*Z*)-1,1,1-Trifluoro-3-methyl-4-thia-13-hexadecen-2-one (±)-1b. A procedure identical to that described above for **1a** was used. Starting from thiol **5b** (0.20 g, 0.98 mmol), Et_3N (0.10 ml, 0.98 mmol), and 3-bromo-1,1,1-trifluoro-2-butanone (0.22 g, 1.08 mmol), racemic **1b** was obtained as a colorless oil after purification on column chromatography (0.25 g, 78%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.34 (m, 2H); 3.76 (q, $J = 6.9$ Hz, 1H); 2.49 (dt, $J_1 = 12.0$ Hz, $J_2 = 7.2$ Hz, 1H); 2.32 (dt, $J_1 = 12.3$ Hz, $J_2 = 7.2$ Hz, 1H); 2.02 (m, 4H); 1.54 (m, 2H); 1.50 (d, $J = 6.9$ Hz, 3H); 1.32 (b, 10H); 0.95 (t, $J = 7.5$ Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.9 (q, $J = 33$ Hz, $COCF_3$); 131.6 (CH); 129.2 (CH); 115.9 (q, $J = 291$ Hz, $COCF_3$); 40.9 (CH); 29.7; 29.3; 29.1; 29.0; 28.8; 28.5; 27.0; 20.5; 14.7 (CH_3); 14.4 (CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −74.9 (s, 3F, –$COCF_3$) ppm. IR (film) ν: 3004, 2929, 2856, 1742, 1458, 1276, 1205, 1152, 699 cm^{-1}. MS (EI) m/z (%): 324 (M^+, 10); 255 (4); 227 (65); 199 (85); 171 (14); 157 (12); 155 (16); 143 (26); 141 (33); 129 (44); 123 (56); 115 (53); 109 (72); 97 (56); 95 (85); 87 (75); 81 (86); 75 (76); 69 (82); 67 (90); 55 (86); 43 (53); 41 (100). HRMS Calcd for $C_{16}H_{27}F_3OS$ (M^+): 324.1735; Found: 324.17447.

4.4. Asymmetric synthesis of (*R*)-1a, (*S*)-1a, (*R*)-1b, and (*S*)-1b

4.4.1. (*S*)-(+)-[2′-Methoxymethylpyrrolidinyl]hydrazone of (*Z*)-1,1,1-trifluoro-4-thia-13-octadecen-2-one (*S*)-7a. A mixture of **6a** (155 mg, 0.46 mmol) and (*S*)-(−)-1-amino-2-methoxymethylpyrrolidine (68 μl, 0.50 mmol) was stirred at 65 °C for 48 h. When the reaction was complete, the mixture was poured into hexane–H_2O. The aqueous layer was extracted with hexane, the organic layers were combined, washed with brine and dried over $MgSO_4$. After concentration in vacuo, the crude product was purified by column chromatography (silica gel, hexane–Et_2O, 98:2) to afford (*S*)-**7a** (152 mg, 74%) as a light yellow oil, $[\alpha]_D^{20} = +138.5$ (*c* 1.43, $CHCl_3$), ee 97%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.34 (m, 2H); 3.57 (m, 7H); 3.35 (s, 3H); 2.56 (t, $J = 7.6$ Hz, 2H); 2.01 (m, 6H); 1.78 (m, 2H); 1.57 (m, 2H); 1.32 (b, 14H); 0.89 (t, $J = 6.8$ Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 129.9 (CH); 129.8 (CH); 126.5 (q, $J = 32$ Hz, $CNCF_3$); 122.1 (q, $J = 272$ Hz, $CNCF_3$); 74.3; 65.9 (CH); 59.2 (CH_3); 53.3; 33.3; 31.9; 29.7; 29.4; 29.3; 29.2; 29.1; 28.8; 27.2; 27.1; 26.9; 26.1; 23.9; 22.3; 14.0 (CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −66.8 (s, 3F, –$CNCF_3$) ppm. IR (film) ν: 3005, 2927, 2855, 1600, 1460, 1368, 1326, 1226, 1156, 1101, 1041 cm^{-1}. MS (EI) m/z (%): 452 [$(M+2)^+$, 5]; 450 (M^+, 35); 407 (34); 406 (100); 336 (9); 308 (5); 224 (30); 223 (44), 207 (37); 191 (15); 179 (50); 177 (52); 150 (14); 123 (29); 112 (37); 95 (40); 87 (40); 71 (40); 69 (41); 67 (44); 55 (46); 41 (46).

4.4.2. (*R*)-(−)-[2′-Methoxymethylpyrrolidinyl]hydrazone of (*Z*)-1,1,1-trifluoro-4-thia-13-octadecen-2-one (*R*)-7a. A procedure identical to that described above for (*S*)-**7a** was followed, starting from **6a** (50 mg, 0.15 mmol) and (*R*)-(+)-1-amino-2-methoxymethylpyrrolidine (21 μl, 0.16 mmol). After purification, the corresponding hydrazone (*R*)-**7a** was obtained (52 mg, 77%) as a light yellow oil, $[\alpha]_D^{20} = -139.5$ (*c* 0.99, $CHCl_3$), ee 99%. The spectroscopic data are identical to those of the enantiomeric hydrazone (*S*)-**7a**.

4.4.3. (*S*)-(+)-[2′-Methoxymethylpyrrolidinyl]hydrazone of (*Z*)-1,1,1-trifluoro-4-thia-13-hexadecen-2-one (*S*)-7b. A procedure identical to that described above for (*S*)-**7a** was followed, starting from **6b** (200 mg, 0.77 mmol) and (*S*)-(+)-1-amino-2-methoxymethylpyrrolidine (110 μl, 0.84 mmol). After purification, the corresponding hydrazone (*S*)-**7b** was obtained (201 mg, 75%) as a light yellow oil, $[\alpha]_D^{20} = +162.9$ (*c* 1.15, $CHCl_3$), ee 97%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.33 (m, 2H); 3.57 (m, 7H); 3.35 (s, 3H); 2.56 (t, $J = 7.5$ Hz, 2H); 1.99 (m, 6H); 1.78 (m, 2H); 1.57 (m, 2H); 1.31 (b, 10H); 0.95 (t, $J = 7.8$ Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.6 (CH); 129.2 (CH); 126.5 (q, $J = 32$ Hz, $CNCF_3$); 122.1 (q, $J = 272$ Hz, $CNCF_3$); 74.3; 65.9 (CH); 59.2 (CH_3); 53.3; 33.3; 29.7; 29.4; 29.3; 29.2; 29.1; 28.8; 27.2; 27.0; 26.1; 23.9; 20.5; 14.4 (CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −66.8 (s, 3F, –$CNCF_3$) ppm. IR (film) ν: 3004, 2927, 2855, 1599, 1461, 1368, 1326, 1226, 1189, 1154, 1102, 1040 cm^{-1}. MS (EI) m/z (%): 424 [$(M+2)^+$, 1]; 422 (M^+, 15); 379 (7); 378 (22); 377 (100); 223 (16); 179 (57); 177 (62); 150 (5); 123 (10); 112 (13); 95 (20); 87 (23); 81 (19); 69 (41); 55 (66); 45 (31); 41 (60).

4.4.4. (*R*)-(−)-[2′-Methoxymethylpyrrolidinyl]hydrazone of (*Z*)-1,1,1-trifluoro-4-thia-13-hexadecen-2-one [(*R*)-7b]. A procedure identical to that described above for (*S*)-**7a** was followed, starting from **6b** (142 mg, 0.46 mmol) and (*R*)-(+)-1-amino-2-methoxymethylpyrrolidine (68 μl, 0.50 mmol). After purification on column chromatography, the corresponding hydrazone (*R*)-**7b** was obtained (144 mg, 74%) as a light yellow oil, $[\alpha]_D^{20} = -156.4$ (*c* 1.17, $CHCl_3$), ee 99%. The spectroscopic data are identical to those of the enantiomeric hydrazone (*S*)-**7b**.

4.4.5. (2′*S*,3*R*)-(+)-[2′-Methoxymethylpyrrolidinyl]hydrazone of (*Z*)-1,1,1-trifluoro-3-methyl-4-thia-13-octadecen-2-one (*S*,*R*)-8a. A solution of 1.5 M *n*-BuLi in *n*-hexane (0.2 ml, 0.27 mmol) was added dropwise at 0 °C under Ar, via a syringe, to a 0.4 M soln of diisopropylamine in ether (38 μl, 0.27 mmol) and stirred for 15 min. Compound (*S*)-**7a** (115 mg, 0.26 mmol) was added dropwise and the mixture

stirred at 0 °C for 15 min more and cooled to −100 °C. Then MeI (17 μl, 0.27 mmol) was added, stirred further for 1 h at this temperature and allowed to warm up to room temperature for 2 h. The solvent was removed, water was added and the organic material extracted with hexane. After drying over $MgSO_4$, concentration under vacuum left an oil which was purified by column chromatography on silica gel (hexane–ether, 98:2) to afford (*S*,*R*)-**8a** (104 mg, 86%) as a yellow oil, $[\alpha]_D^{20} = +205.1$ (*c* 0.96, $CHCl_3$), de 92%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.34 (m, 2H); 4.22 (q, $J = 7.2$ Hz, 1H); 3.48 (m, 5H); 3.35 (s, 3H); 2.54 (t, $J = 7.2$ Hz, 2H); 1.94 (m, 6H); 1.74 (m, 2H); 1.57 (m, 2H); 1.49 (d, $J = 7.2$ Hz, 3H); 1.30 (b, 14H); 0.89 (t, $J = 6.8$ Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.1 (q, $J = 30$ Hz, *C*NCF$_3$); 129.9 (CH); 129.8 (CH); 121.8 (q, $J = 275$ Hz, CN*C*F$_3$); 74.2; 66.7 (CH); 59.1 (CH_3); 55.2; 36.5 (CH); 32.2; 31.9; 29.7; 29.4; 29.3; 29.2; 28.9; 27.1; 26.9; 26.2; 23.8; 22.3; 18.6 (CH_3); 14.0 (CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −62.5 (s, 3F, –CNC*F*$_3$) ppm. IR (film) *v*: 3003, 2927, 2855, 1591, 1459, 1378, 1328, 1286, 1157, 1112, 1016 cm^{-1}. MS (EI) *m*/*z* (%): 466 [(M+2)$^+$, 6]; 464 (M$^+$, 41); 421 (16); 420 (81); 350 (26); 308 (7); 295 (16); 267 (18); 237 (100); 225 (22); 207 (22); 193 (35); 192 (26); 191 (45); 177 (35); 142 (17); 123 (21); 112 (35); 87 (34); 69 (60); 55 (40); 45 (41); 41 (45).

4.4.6. (2′*R*,3*S*)-(−)-[2′-Methoxymethylpyrrolidinyl]hydrazone of (*Z*)-1,1,1-trifluoro-3-methyl-4-thia-13-octadecen-2-one (*R*,*S*)-8a. A procedure identical to that described above for (*S*,*R*)-**8a** was followed from (*R*)-**7a** (34 mg, 0.08 mmol). After purification, the corresponding product (*R*,*S*)-**8a** was obtained as a light yellow oil (28 mg, 79%), $[\alpha]_D^{20} = -203.2$ (*c* 1.06, $CHCl_3$), de 92%. The spectroscopic data are identical to those of the enantiomeric hydrazone (*S*,*R*)-**8a**.

4.4.7. (2′*S*,3*R*)-(+)-[2′-Methoxymethylpyrrolidinyl]hydrazone of (*Z*)-1,1,1-trifluoro-3-methyl-4-thia-13-hexadecen-2-one (*S*,*R*)-8b. A procedure identical to that described above for (*S*,*R*)-**8a** was followed from (*S*)-**7b** (173 mg, 0.40 mmol). After purification, the corresponding product (*S*,*R*)-**8b** was obtained as a light yellow oil (150 mg, 83%), $[\alpha]_D^{20} = +251.4$ (*c* 1.02, $CHCl_3$), de 94%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.33 (m, 2H); 4.22 (q, $J = 7.2$ Hz, 1H); 3.48 (m, 5H); 3.35 (s, 3H); 2.54 (t, $J = 7.5$ Hz, 2H); 2.00 (m, 6H); 1.73 (m, 2H); 1.57 (m, 2H); 1.49 (d, $J = 7.2$ Hz, 3H); 1.32 (b, 10H); 0.95 (t, $J = 7.5$ Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.2 (q, $J = 30$ Hz, *C*NCF$_3$); 131.6 (CH); 129.2 (CH); 121.9 (q, $J = 275$ Hz, CN*C*F$_3$); 74.3; 66.7 (CH); 59.1 (CH_3); 55.3; 36.5 (CH); 32.2; 29.7; 29.4; 29.3; 29.2; 28.9; 27.0; 26.3; 23.8; 20.5; 18.7 (CH_3); 14.4 (CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ − 62.5 (s, 3F, –CNC*F*$_3$) ppm. IR (film) *v*: 3005, 2929, 2856, 1590, 1461, 1379, 1331, 1285, 1155, 1119, 909, 735 cm^{-1}. MS (EI) *m*/*z* (%): 438 [(M+2)$^+$, 1]; 436 (M$^+$, 19); 391 (36); 322 (11); 237 (49); 193 (29); 191 (39); 177 (26); 112 (30); 87 (28); 70 (100); 55 (36); 45 (37); 41 (42).

4.4.8. (2′*R*,3*S*)-(−)-[2′-Methoxymethylpyrrolidinyl]hydrazone of (*Z*)-1,1,1-trifluoro-3-methyl-4-thia-13-hexadecen-2-one (*R*,*S*)-8b. A procedure identical to that described above for (*S*,*R*)-**8a** was followed from (*R*)-**7b** (125 mg, 0.30 mmol). After purification, the corresponding product (*R*,*S*)-**8b** was obtained as a light yellow oil (103 mg, 79%), $[\alpha]_D^{20} = -248.8$ (*c* 1.29, $CHCl_3$), de 92%. The spectroscopic data are identical to those of the enantiomeric hydrazone (*S*,*R*)-**8b**.

4.4.9. (*R*)-(−)-(*Z*)-1,1,1-Trifluoro-3-methyl-4-thia-13-octadecen-2-one (*R*)-1a. To a soln of hydrazone (*S*,*R*)-**8a** (70 mg, 0.15 mmol) in acetone (7 ml) and water (0.6 ml) was added $BF_3{\cdot}OEt_2$ (57 μl, 0.45 mmol) dropwise at room temperature. Paraformaldehyde (23 mg, 0.75 mmol) was then added, and the reaction mixture stirred for 12 h. The solvent was removed in vacuum, and the residue taken up in ether, washed with NH_4Cl satd soln and brine, and dried over $MgSO_4$. After evaporation of the solvent, the crude was purified by column chromatography (silica, hexane) to afford (*R*)-**1a** (41 mg, 79%) as a colorless oil, $[\alpha]_D^{20} = -132.4$ (*c* 1.36, $CHCl_3$), ee 90%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.34 (m, 2H); 3.75 (q, $J = 6.9$ Hz, 1H); 2.49 (dt, $J_1 = 11.7$ Hz, $J_2 = 7.5$ Hz, 1H); 2.32 (dt, $J_1 = 12.0$ Hz, $J_2 = 7.2$ Hz, 1H); 2.02 (m, 4H); 1.54 (m, 2H); 1.50 (d, $J = 6.9$ Hz, 3H); 1.32 (b, 14H); 0.89 (t, $J = 6.9$ Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.9 (q, $J = 33$ Hz, *C*OCF$_3$); 129.9 (CH); 129.8 (CH); 115.9 (q, $J = 291$ Hz, CO*C*F$_3$); 40.9 (CH); 31.9; 29.7; 29.3; 29.1; 29.0; 28.8; 28.5; 27.1; 26.9; 22.3; 14.7 (CH_3); 14.0 (CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −74.9 (s, 3F, –COC*F*$_3$) ppm. IR (film) *v*: 3004, 2928, 2856, 1742, 1458, 1276, 1203, 1154 cm^{-1}. MS (EI) *m*/*z* (%): 352 (M$^+$, 1); 283 (1); 255 (36); 227 (100); 213 (16); 199 (10); 185 (15); 171 (25); 157 (26); 143 (31); 142 (10); 141 (32); 129 (33); 123 (38); 115 (35); 109 (47); 101 (40); 97 (36); 95 (55); 81 (61); 69 (75); 55 (98); 43 (38); 41 (61). HRMS Calcd for $C_{18}H_{31}F_3OS$ (M$^+$): 352.2048; Found: 352.2036.

4.4.10. (*S*)-(+)-(*Z*)-1,1,1-Trifluoro-3-methyl-4-thia-13-octadecen-2-one (*S*)-1a. A procedure identical to that described above for (*R*)-**1a** was followed from (*R*,*S*)-**8a** (15 mg, 0.03 mmol). After purification, ketone (*S*)-**1a** (9 mg, 81%) was obtained as a colorless oil, $[\alpha]_D^{20} = +126.5$ (*c* 0.88, $CHCl_3$), ee 90%. The spectroscopic data are identical to those of the enantiomeric ketone (*R*)-**1a**.

4.4.11. (*R*)-(−)-(*Z*)-1,1,1-Trifluoro-3-methyl-4-thia-13-hexadecen-2-one (*R*)-1b. A procedure identical to that described above for (*R*)-**1a** was followed from (*S*,*R*)-**8b** (35 mg, 0.08 mmol). After purification, the corresponding trifluoromethyl ketone (*R*)-**1b** (21 mg, 81%) was obtained as a colorless oil, $[\alpha]_D^{20} = -182.5$ (*c* 0.95, $CHCl_3$), ee 93%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.34 (m, 2H); 3.76 (q, $J = 6.9$ Hz, 1H); 2.49 (dt, $J_1 = 12.0$ Hz, $J_2 = 7.2$ Hz, 1H); 2.32 (dt, $J_1 = 12.3$ Hz, $J_2 = 7.2$ Hz, 1H); 2.02 (m, 4H); 1.54 (m, 2H); 1.50 (d, $J = 6.9$ Hz, 3H); 1.32 (b, 10H); 0.95 (t, $J = 7.5$ Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.9 (q, $J = 33$ Hz, *C*OCF$_3$); 131.6 (CH); 129.2 (CH); 115.9 (q, $J = 291$ Hz, CO*C*F$_3$); 40.9 (CH); 29.7; 29.3; 29.1; 29.0; 28.8; 28.5; 27.0; 20.5; 14.7 (CH_3); 14.4 (CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −74.9 (s, 3F, –COC*F*$_3$) ppm. IR (film) *v*: 3004, 2929, 2856, 1742, 1458, 1276, 1205, 1152 cm^{-1}. MS (EI) *m*/*z* (%): 326 [(M+2)$^+$,

1]; 324 (M^+, 2); 255 (6); 229 (74); 228 (30); 227 (83); 199 (100); 155 (23); 143 (41); 141 (51); 129 (62); 123 (68); 115 (68); 109 (86); 101 (75); 95 (93); 87 (86); 81 (84); 75 (86); 69 (82); 67 (83); 55 (87); 41 (90). HRMS Calcd for $C_{16}H_{27}F_3OS$ (M^+): 324.1735; Found: 324.1731.

4.4.12. (*S*)-(+)-(*Z*)-1,1,1-Trifluoro-3-methyl-4-thia-13-hexadecen-2-one (*S*)-1b. A procedure identical to that described above for (*R*)-**1a** was followed from (*R*,*S*)-**8b** (79 mg, 0.18 mmol). After purification by column chromatography, the corresponding trifluoromethyl ketone (*S*)-**1b** (46 mg, 80%) was obtained as a colorless oil, $[\alpha]_D^{20} = +173.7$ ($c = 0.93$, $CHCl_3$), ee 90%. The spectroscopic data are identical to those of the enantiomer (*R*)-**1b**.

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