Synthesis of Polyfluorinated and Polychlorinated Hydrocarbons

Yong Guan

Feb. 13, 2009

Nicoletti, M.; O'Hagan, D.; Slawin, A.M.Z. *J. Am. Chem. Soc.* **2005**, *127*, 482.
Hunter, L.; O'Hagan, D.; Slawin, A.M.Z. *J. Am. Chem. Soc.* **2006**, *128*, 16422.
Hunter, L.; Slawin, A. M. Z.; Kirsch, P.; O'Hagan, D. *Angew. Chem., Int. Ed.* **2007,** 46, 7887.
Shibuya, G. M., Kanady, J. S., Vanderwal, C. D. *J. Am. Chem. Soc.* **2008**, *130*, 12514.
Yoshimitsu, T., Fukumoto, N., Tanaka, T. *J. Org. Chem.* **2009**, *74*, 696.
Nilewski, C., Geisser, R. W.; Erick M. Carreira. *Nature* **2009**, *457*, 573.

Outline

- Synthesis of Polyfluorinated Hydrocarbons
- Synthesis of Polychlorinated Hydrocarbons

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- Synthesis of Polyfluorinated Hydrocarbons
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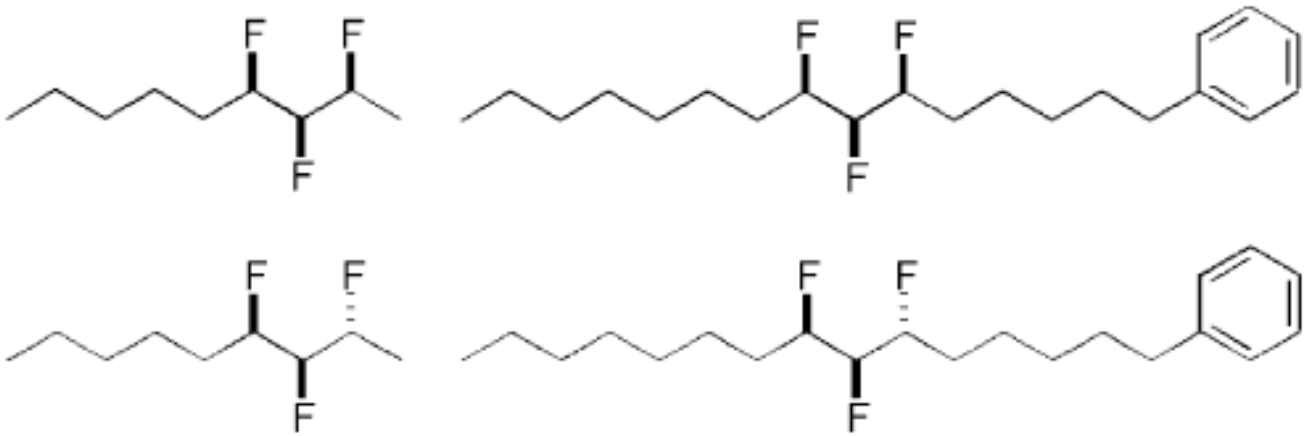
α,β,γ-Trifluoroalkanes



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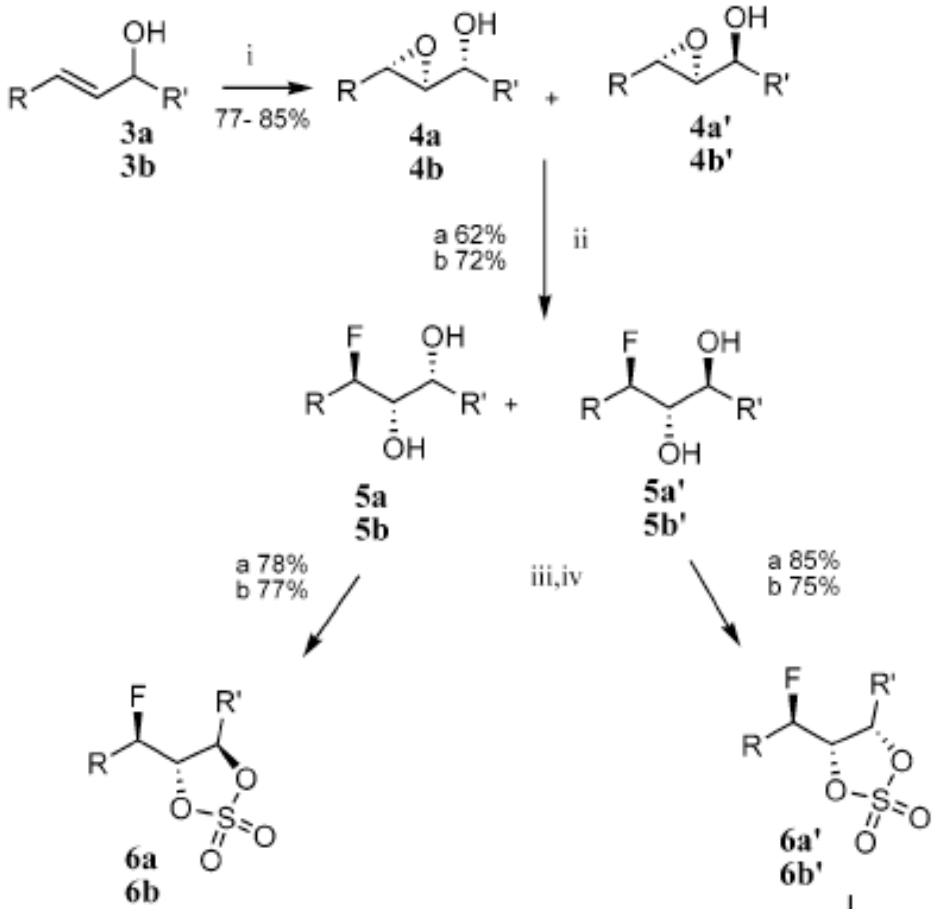
α,β,γ-Trifluoroalkanes



a R = C_5H_{11}, R' = CH_3, **b** R = C_7H_{15}, R' = $C_5H_{10}Ph$. (i) *m*CPBA in DCM, 0 °C, 2 h. (ii) HF•pyridine in DCM, 10 °C, 4 h. (iii,iv) $SOCl_2$, py. in DCM, 0 °C, 45 min then $NaIO_4$/ $RuCl_3$ in CH_3CN/H_2O, 0 °C 1 h. (v) TBAF in acetone, 0 °C 2 h. (vi) Et_2O/H_2SO_4. (vii) Tf_2O, pyr in DCM, -40 °C, 1 h. (viii) TBAF in MeCN, 0 °C, 30 min.

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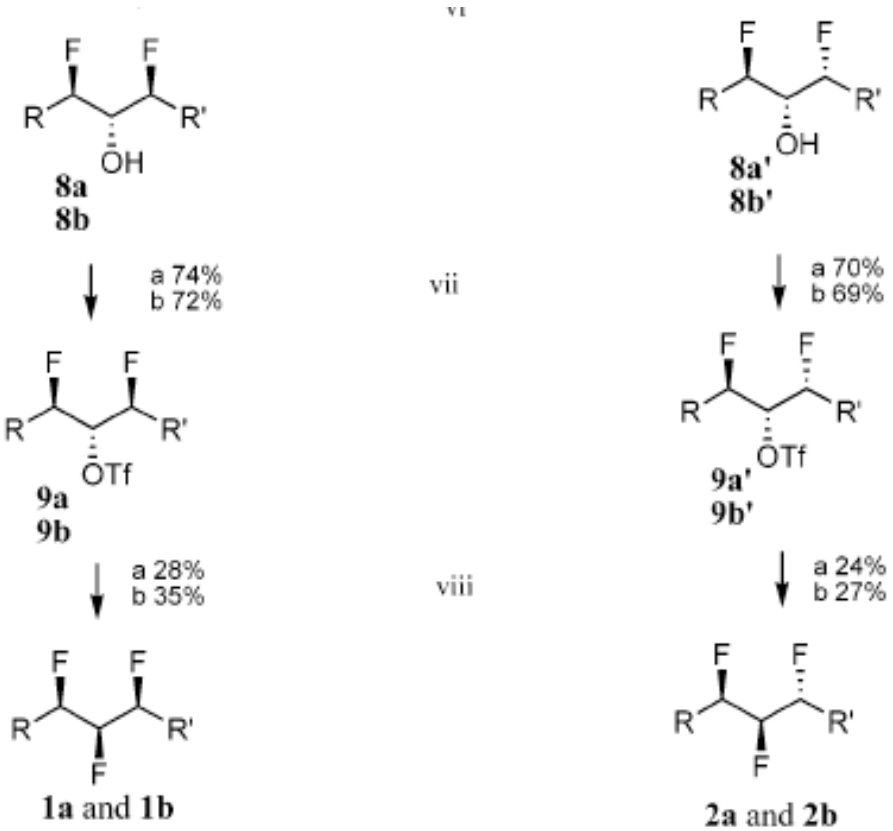
α,β,γ-Trifluoroalkanes



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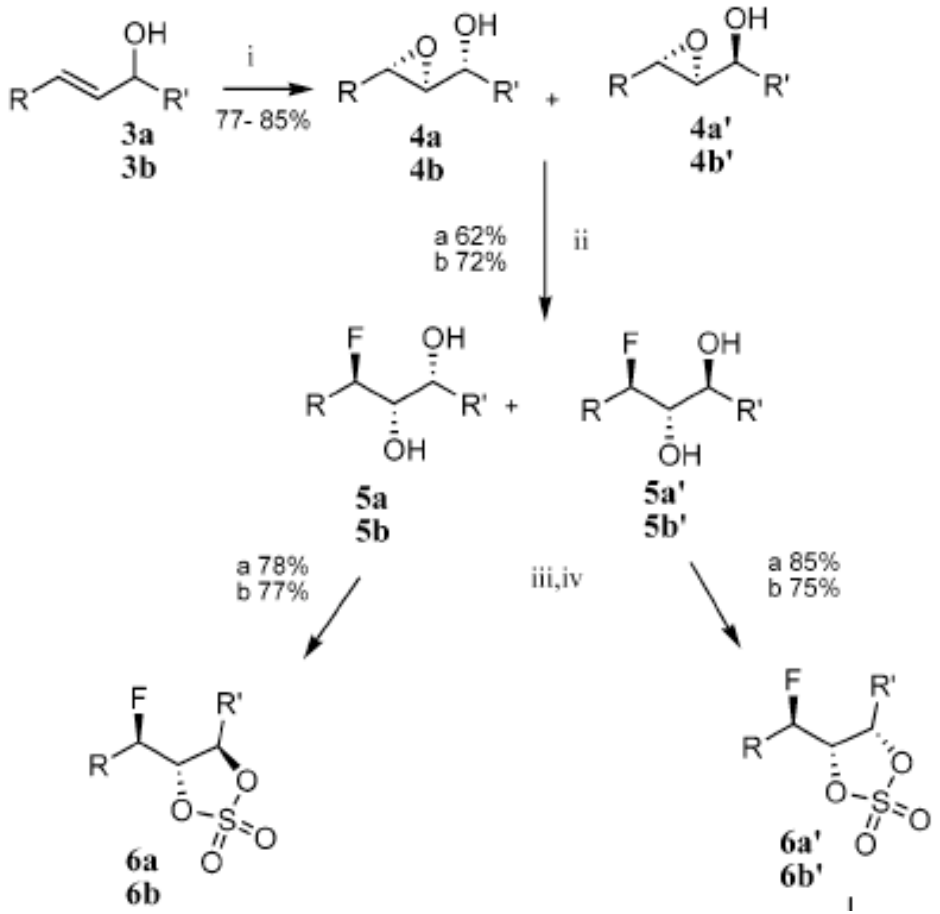
α,β,γ-Trifluoroalkanes



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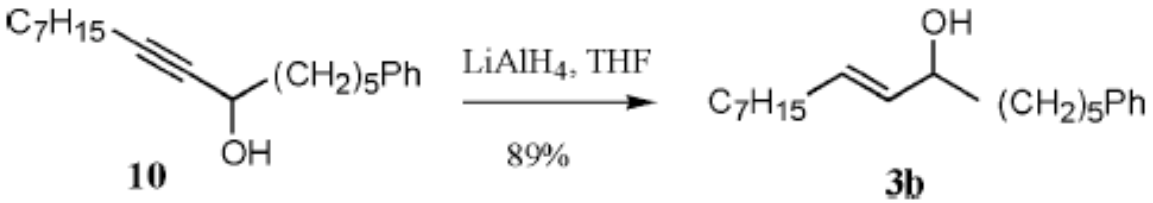
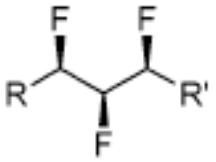
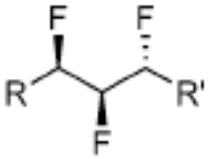


10 **3b**



1a and **1b**



2a and **2b**

Table 1. $^{19}F\{^{1}H\}$ NMR ($CDCl_3$) Data for Compounds **1a**–**2b**

	^{19}F chemical shifts (ppm)			^{19}F–^{19}F coupling constants (Hz)		
	F_α	F_β	F_γ	$J_{\alpha-\beta}$	$J_{\beta-\gamma}$	$J_{\alpha-\gamma}$
1a	−189	−199	−207	12.9	11.2	–
2a	−185	−201	−213	14.4	9.3	3.4
1b	−197	197	−207	12.3	12.3	
2b	−194	−200	−212	14.9	9.2	

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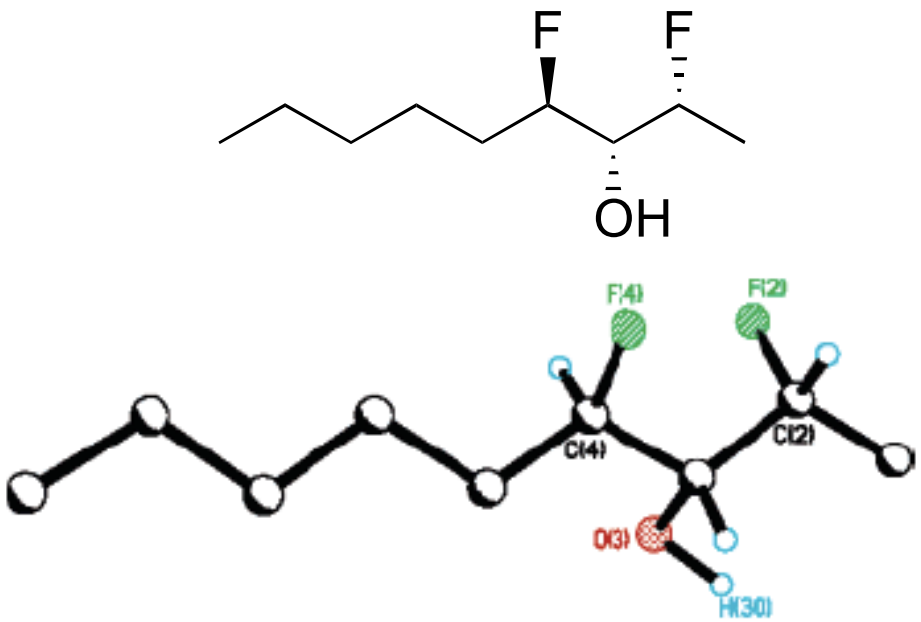
α,β,γ-Trifluoroalkanes



X-ray structure of **8a′** confirming the relative stereochemistry

vicinal C-F bonds preferring to align gauche to each other

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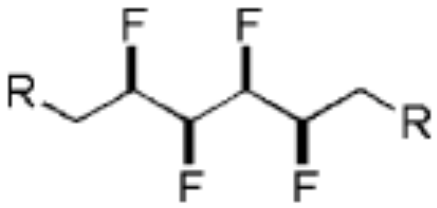
All-*syn* Four Vicinal Fluorine Motif



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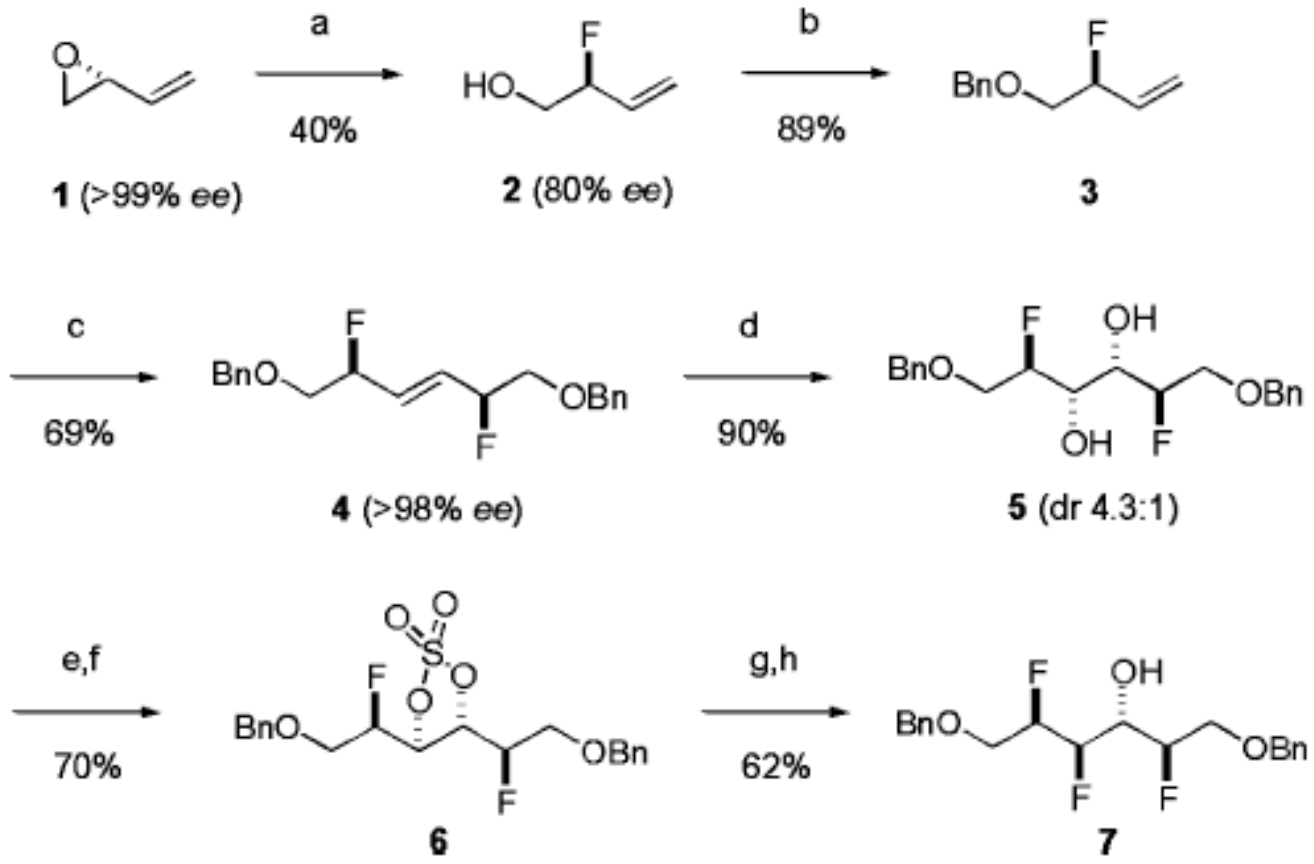
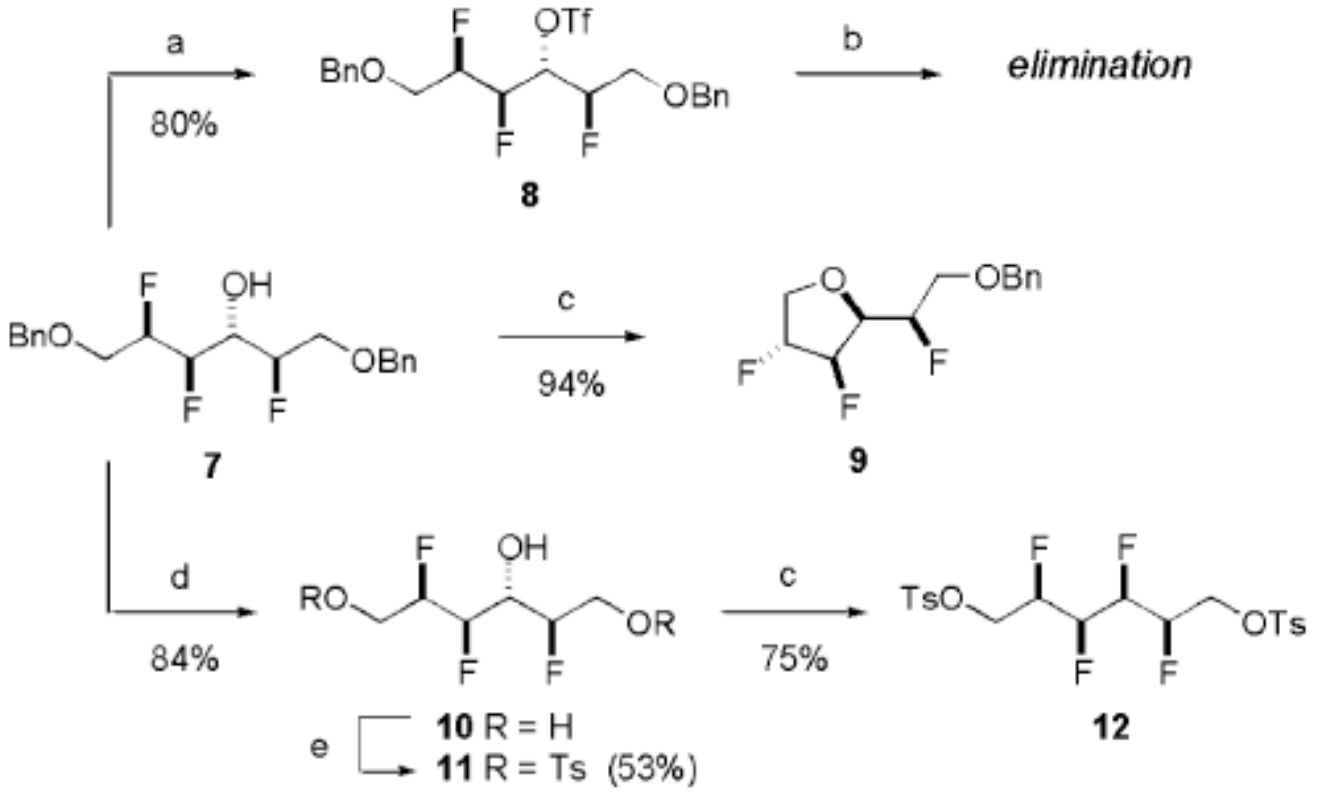
All-*syn* Four Vicinal Fluorine Motif



(a) $Et_3N{\bullet}3HF$, Na_2SO_4, 70 °C; (b) BnBr, NaH, DMF, 40 °C; (c) Grubbs second generation catalyst, DCM, Δ; (d) $KMnO_4$, $MgSO_4$, EtOH, H_2O, -10 °C; (e) $SOCl_2$, pyridine, DCM, 0 °C; (f) $NaIO_4$, $RuCl_3$, MeCN, H_2O, 0 °C; (g) TBAF, MeCN, rt; (h) H_2SO_4, H_2O, THF, rt.

Hunter, L.; O'Hagan, D.; Slawin, A.M.Z. *J. Am. Chem. Soc.* **2006**, *128*, 16422.

All-*syn* Four Vicinal Fluorine Motif



(a) Tf_2O, pyridine, DCM, -40 °C; (b) TBAF, MeCN, 0 °C; (c) Deoxo-Fluor, 70 °C; (d) H_2, Pd/C, MeOH, rt; (e) TsCl, 2,4,6-collidine, 50 °C.

Hunter, L.; O'Hagan, D.; Slawin, A.M.Z. *J. Am. Chem. Soc.* **2006**, *128*, 16422.

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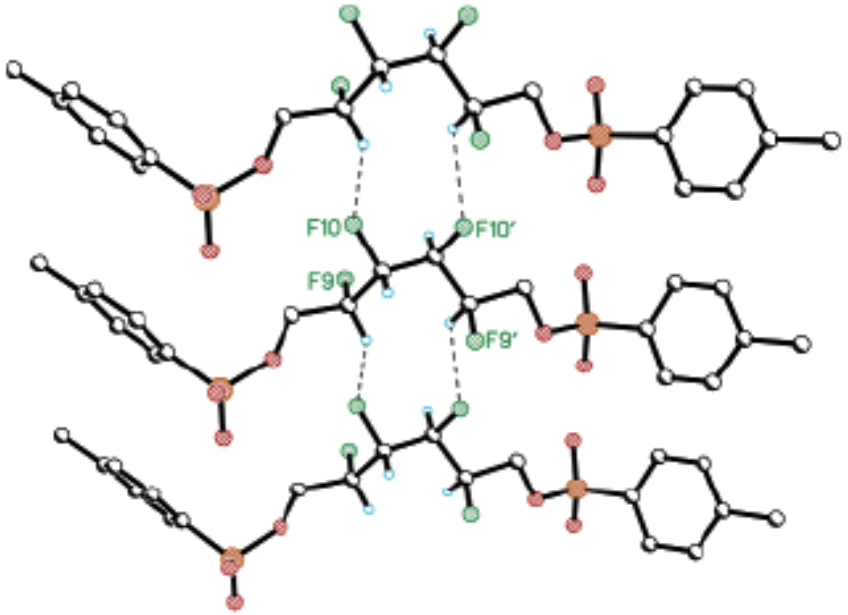
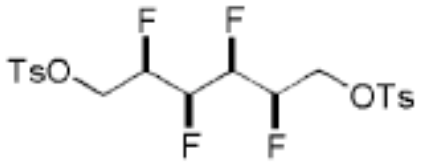


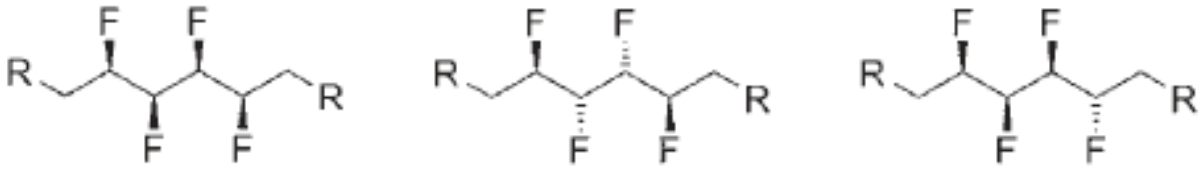


12

C2 symmetry;
Dihedral angles of 66.7° (F9-C-C-F10) and 59.7° (F10-C-C-F10') between vicinal fluorines;
The aryl and fluoroalkyl groups pack in separate domains;
Intermolecular interactions include a hydrogen bond (2.52 Å) from the fluorine atom of C10 (and C10') to the hydrogen atom at C9 (and C9') of an adjacent molecule.

Hunter, L.; O'Hagan, D.; Slawin, A.M.Z. *J. Am. Chem. Soc.* **2006**, *128*, 16422.

$\alpha,\beta,\gamma,\delta$-tetrafluoroalkane



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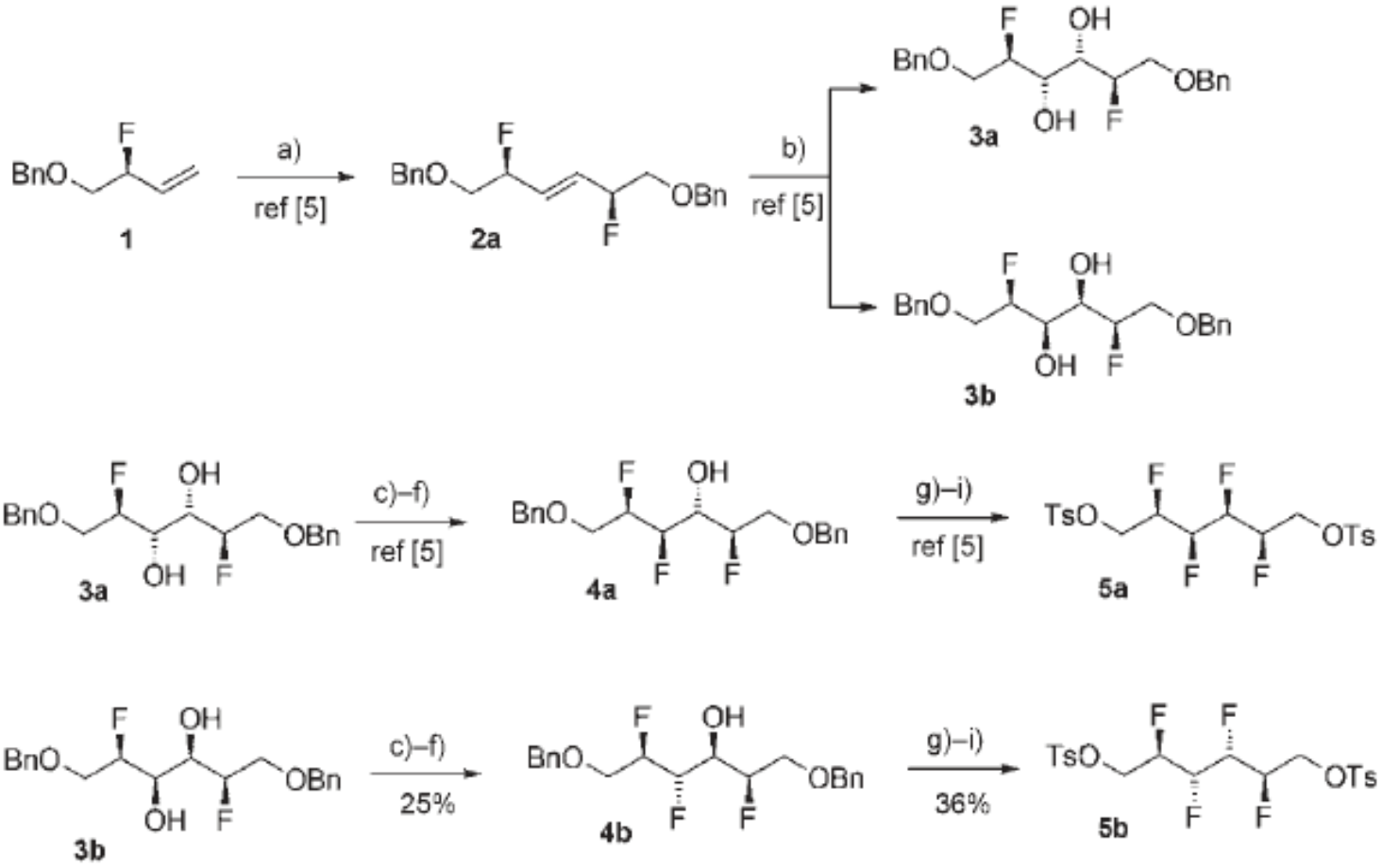

a) Grubbs 2nd-generation catalyst, DCM, Δ; b) $KMnO_4$, $MgSO_4$, EtOH, DCM, H_2O, 0 °C; c) $SOCl_2$, pyridine, DCM, rt; d) $NaIO_4$, $RuCl_3$, MeCN, H_2O, rt; e) Bu_4NF, MeCN, rt; f) H_2SO_4, H_2O, THF, RT; g) H_2, Pd/C, MeOH, rt; h) TsCl, collidine, 50 °C; i) Deoxo-Fluor, DCM, Δ.

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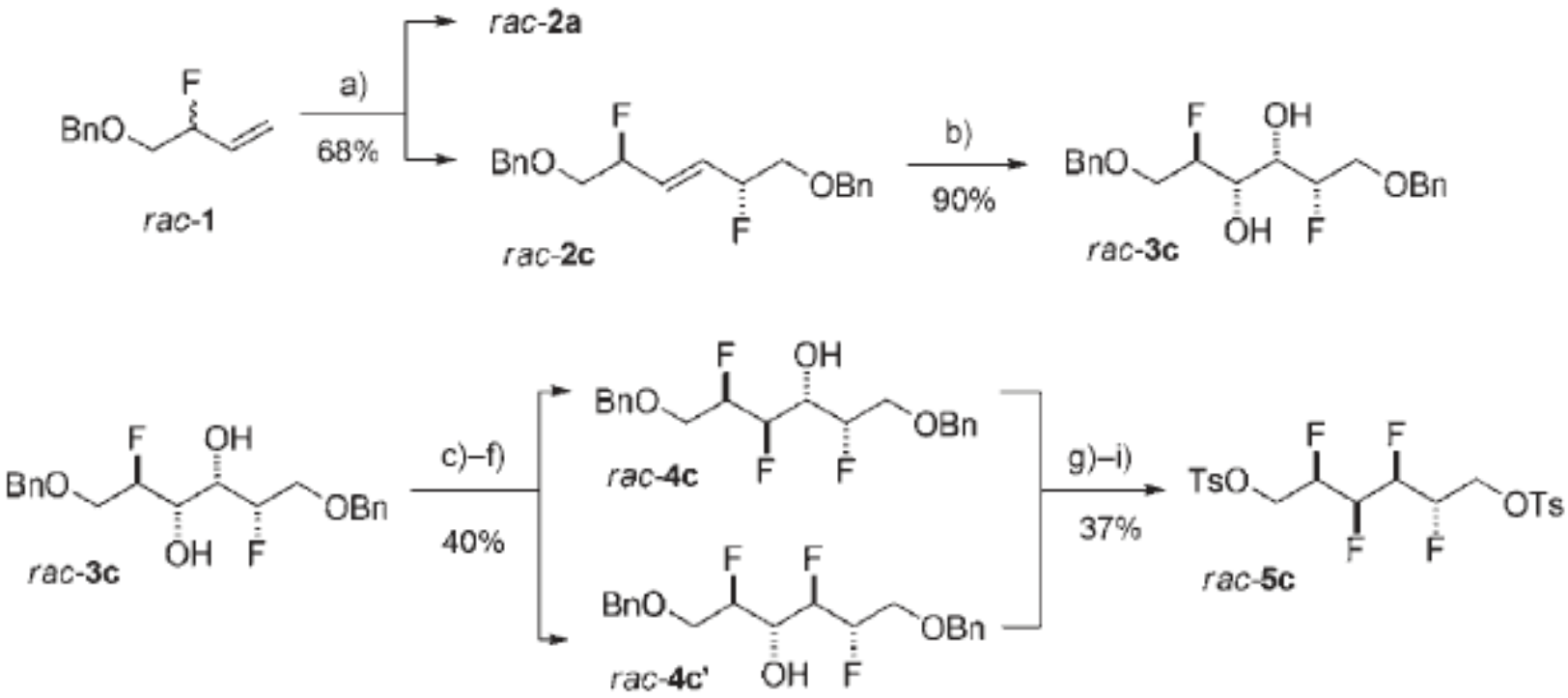

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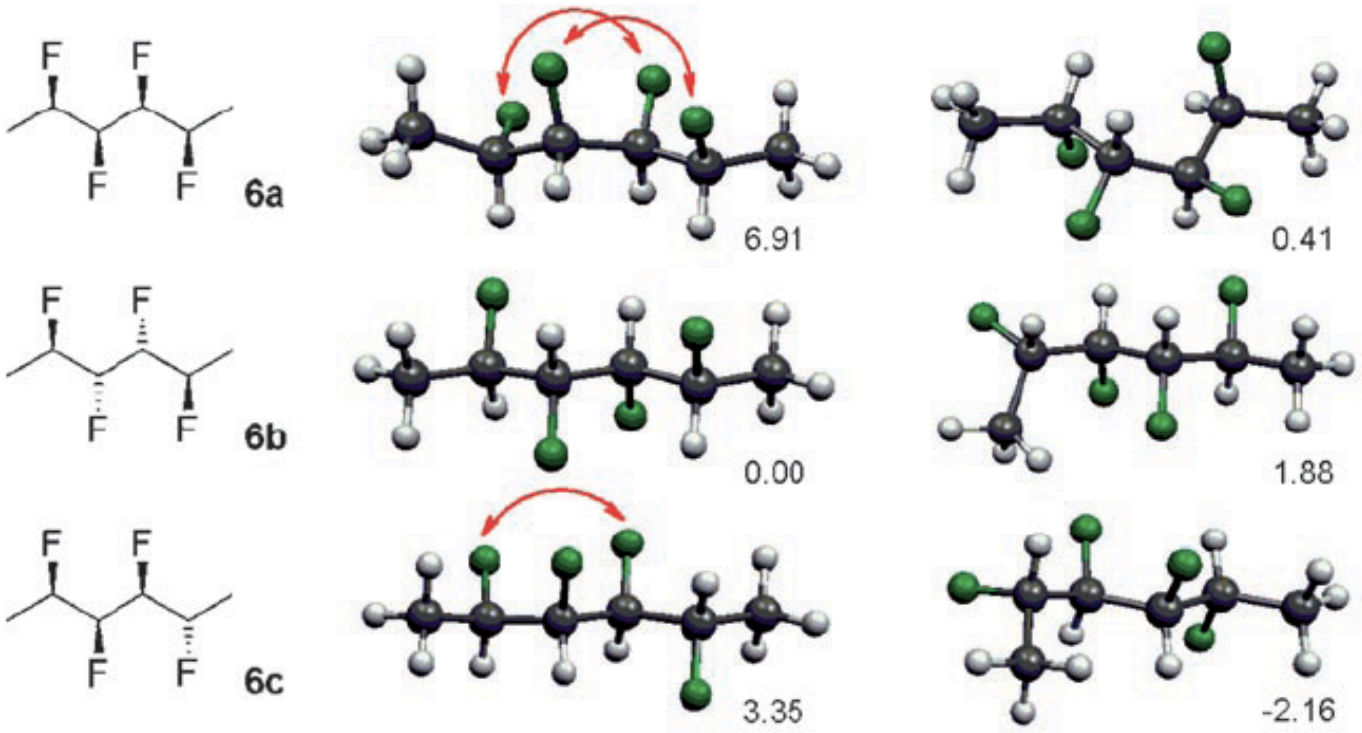

Left: The simplified model system 6. Middle: Calculated linear conformations and right: either minimum (6a, 6c) or next higher energy conformation (6b). C gray, F green, H white; red arrows indicate g^+g^--F–F interactions. Relative energies are in kcal mol^{-1}.

1) g^+g^--F–F interaction costs about 3.4 kcal mol^{-1} in steric strain
2) 1,3-F···CH3 interaction costs 4.04 kcal mol^{-1}
3) vicinal fluorine gauche effect (ca. 0.8 kcal mol^{-1}) has only a secondary influence

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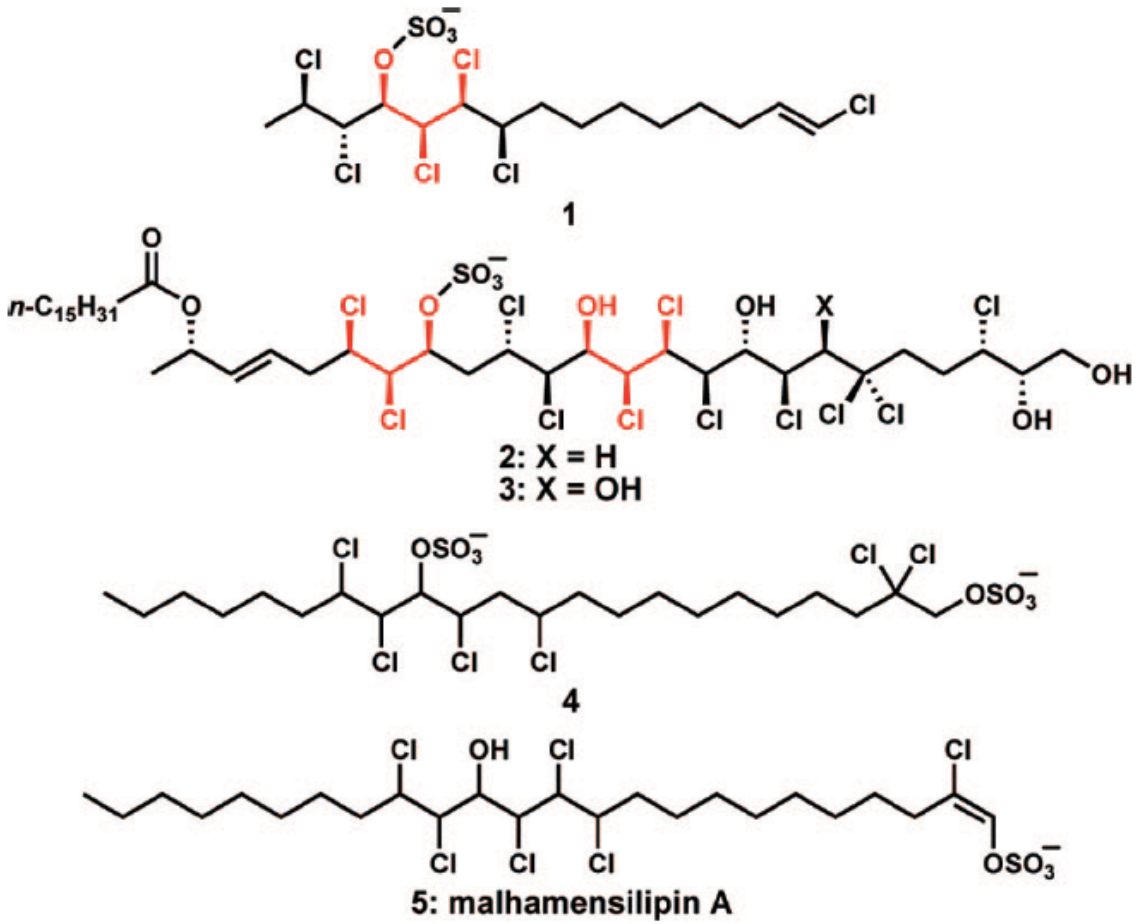
Outline

- Synthesis of Polyfluorinated Hydrocarbons
- Synthesis of Polychlorinated Hydrocarbons

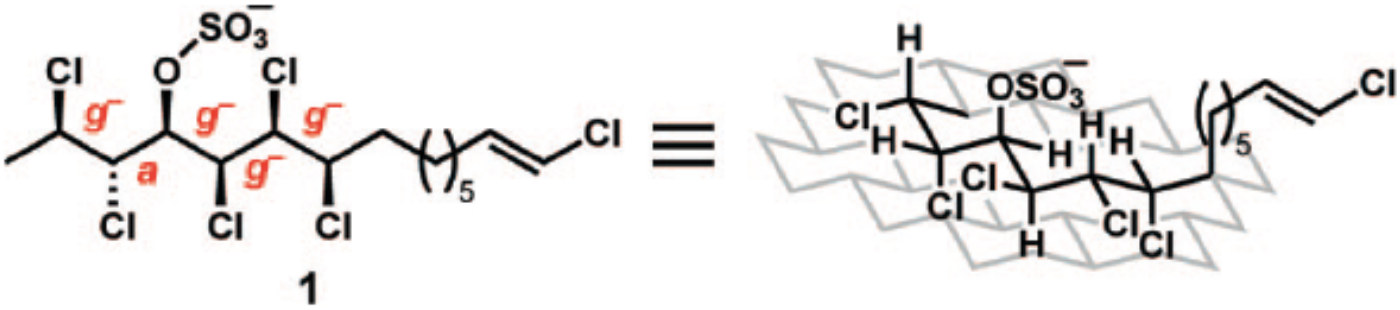
Dichlorination of Allylic Alcohol Derivatives



Unnamed chlorosulfolipids isolated from Adriatic mussels (1-3) and from freshwater algae (4) and algae-derived protein kinase inhibitor malhamensilipin A (5)

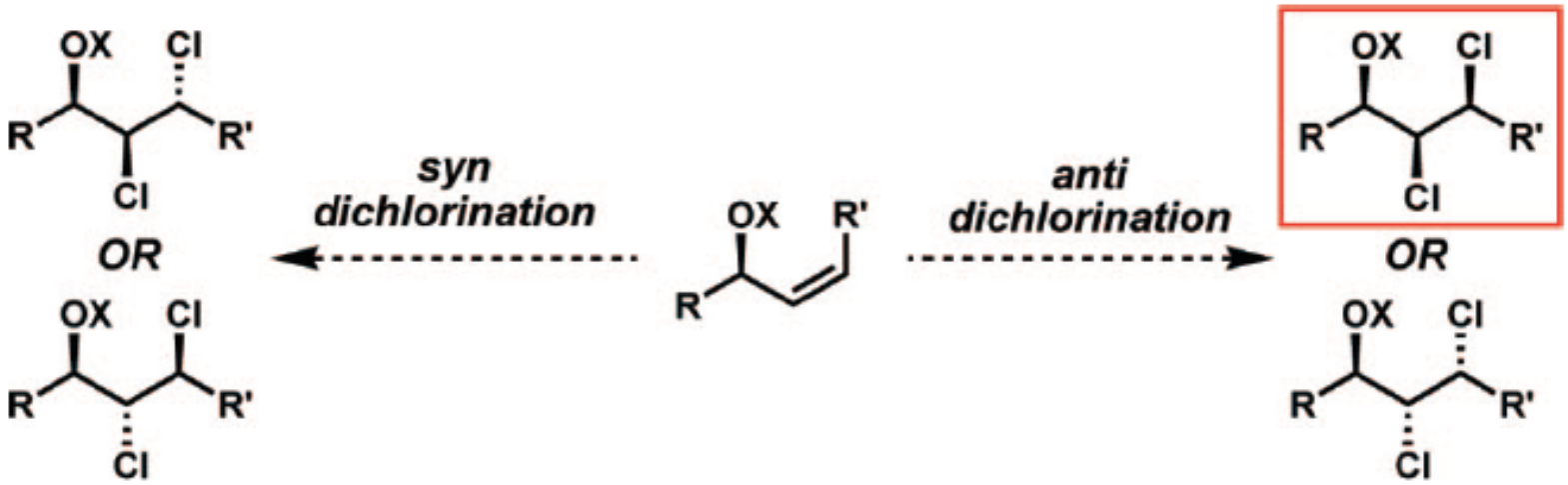
Gerwick, W. H., *et al*. *J. Nat. Prod.* **1994**, *57*, 524
Ciminiello, P., *et al*. *J. Org. Chem.* **2001**, *66*, 578
Ciminiello, P., *et al*. *J. Am. Chem. Soc.* **2002**, *124*, 13114.

Dichlorination of Allylic Alcohol Derivatives



1

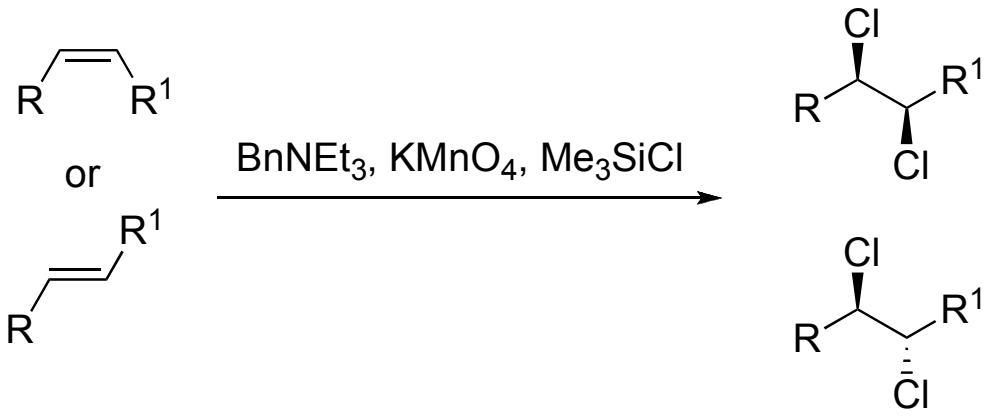
Probable conformational preference of chlorosulfolipid **1.** *g* = gauche, *a* = anti.



Shibuya, G. M., Kanady, J. S., Vanderwal, C. D. *J. Am. Chem. Soc.* **2008**, *130*, 12514.

Dichlorination of Allylic Alcohol Derivatives

Markó-Maguire Reagents



R, R1 = Alkyl, Ary, H
60-95% yield

Markó, I. E.; Richardson, P. R.; Bailey, M.; Maguire, A. R.; Coughlan,N. *Tetrahedron Lett.* **1997,** *38,* 2339.

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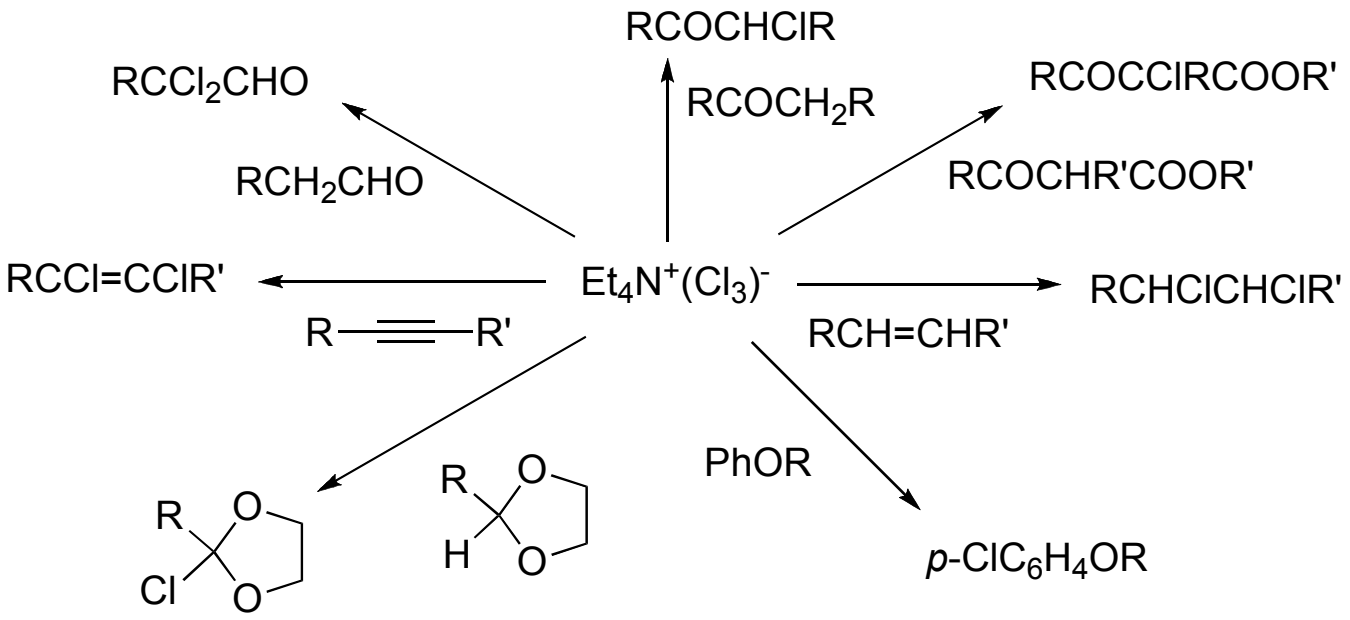
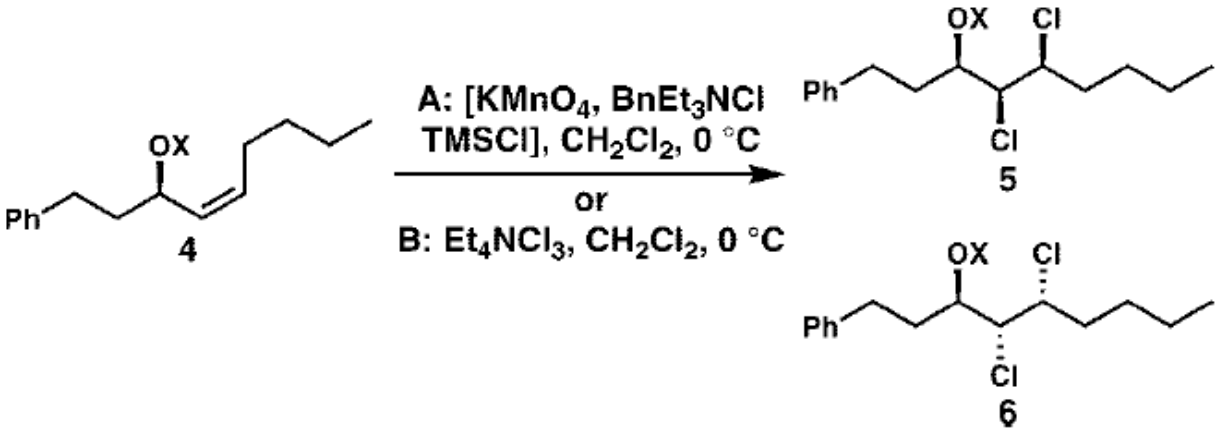
Mioskowski Reagents



Schlama, T.; Gabriel, K.; Gouverneur, V.; Mioskowski, C. *Angew. Chem., Int. Ed.* ***1997,*** *36,* 2341**.**

Dichlorination of Allylic Alcohol Derivatives

Comparison of the Markó-Maguire and Mioskowski Reagents for Diastereoselective Vicinal Dichlorination of Allylic Alcohol Derivatives (TBS = *tert*-Butyldimethylsilyl, Piv = Pivaloate)



X	method	dr (5:6)[a]
H	A	1.2:1
H	B	1.1:1
TBS	A	1.2:1
TBS	B	1.5:1
Piv	A	2.5:1
Piv	B	2.4:1

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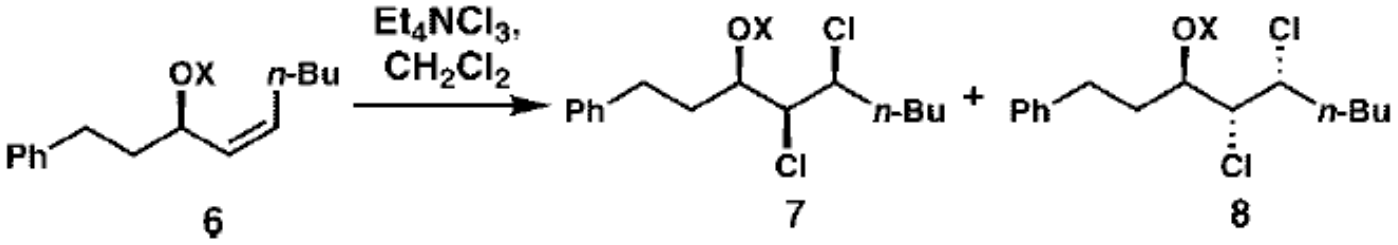

X	temp (°C)	dr (7:8)[a]	X	temp (°C)	dr (7:8)[a]
H	−78	1.0:1	Piv	−78	7.5:1[b]
Me	−78	2.0:1	Piv	−90	7.7:1[b]
TBS	−78	2.0:1	Cl_3CCO	−78	5.0:1
CO_2Me	−78	5.0:1[b]	**Cl_3CCO**	**−90**	**6.5:1**
Boc	−78	5.0:1[b]	F_3CCO	−78	6.0:1
Ac	−78	5.0:1[b]	**F_3CCO**	**−90**	**7.0:1**

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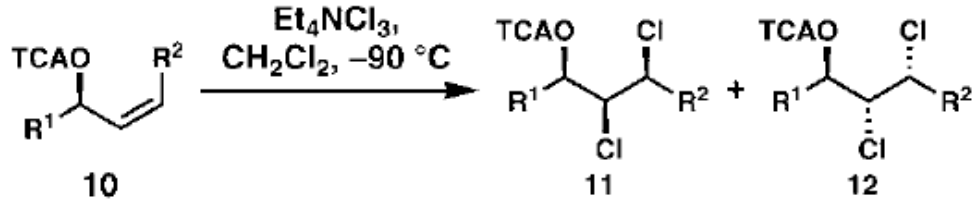
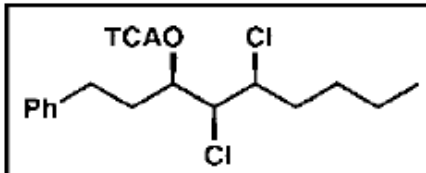
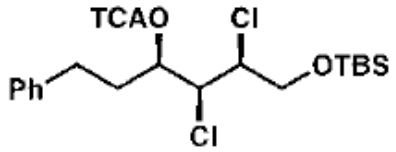


10 11 12

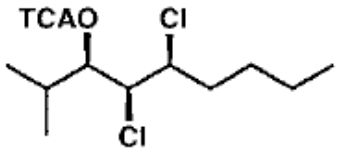
Major Products[a]



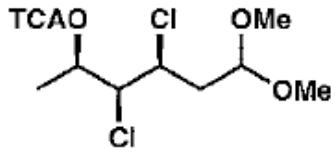
**11a: 82%, 9.2:1*d.r.*
(8.3:1)**



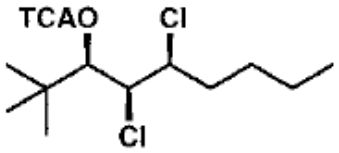
**11d: 70%, 10.9:1*d.r.*
(10.2:1)**



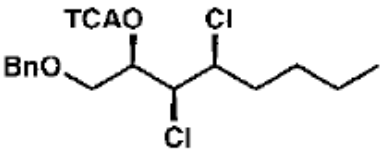
**11b: 77%, 7.7:1*d.r.*
(7.0:1)**



**11e: 78%, >20:1 *d.r.*
(8.3:1)**



11c: 77%, 8.6:1*d.r.*



11f: 67%, 4.6:1*d.r.*

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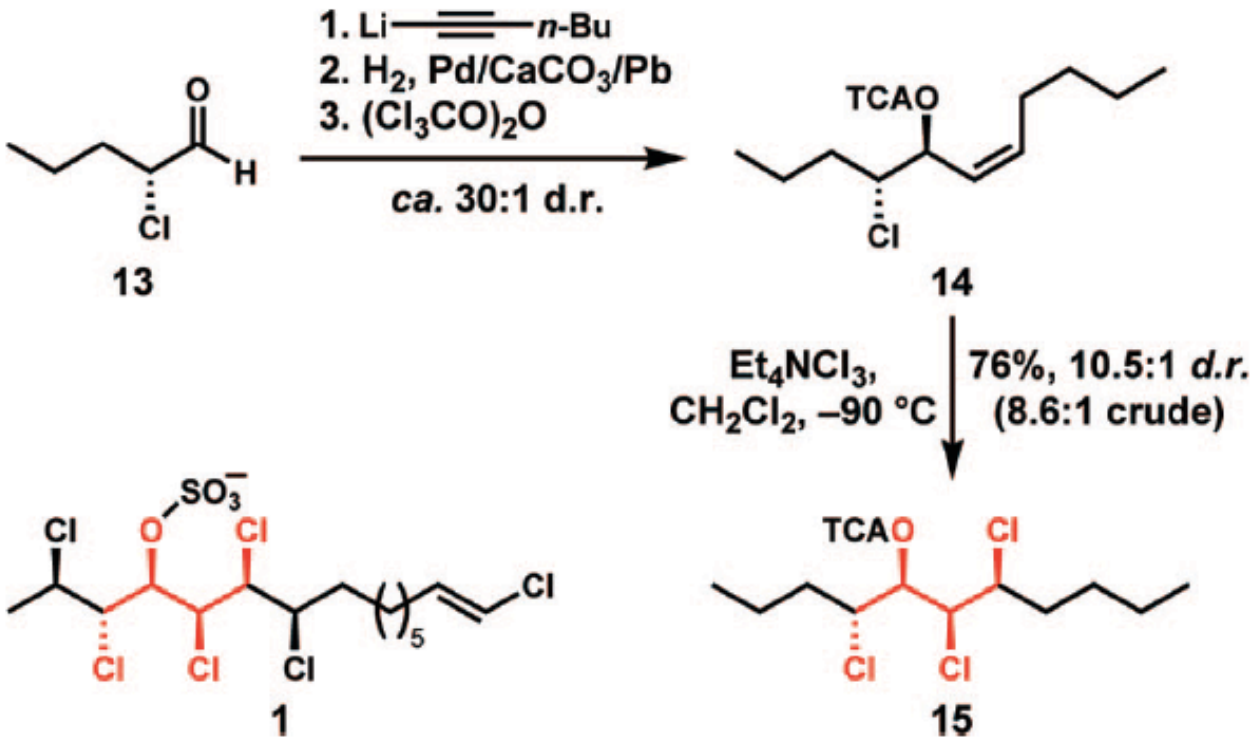
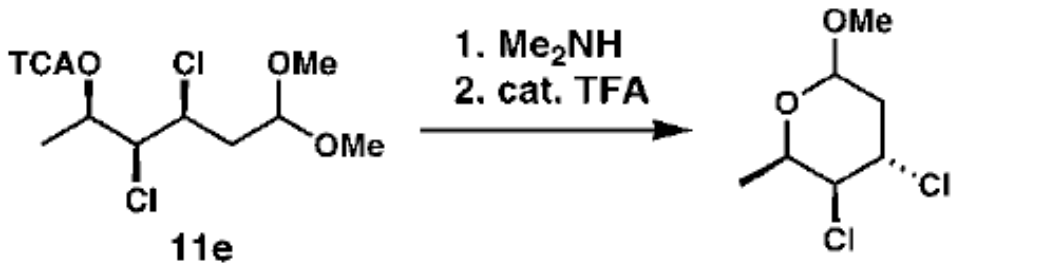
Dichlorination of Allylic Alcohol Derivatives



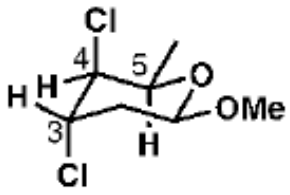
Diastereoselective Synthesis of a Stereotetrad Relevant to Chlorosulfolipid **1**

Shibuya, G. M., Kanady, J. S., Vanderwal, C. D. *J. Am. Chem. Soc.* **2008**, *130*, 12514.

Dichlorination of Allylic Alcohol Derivatives



$^3J_{H3-H4}$ = 2.7 Hz: gauche
$^3J_{H4-H5}$ = 1.2 Hz: gauche
[complete ^{1}H NMR data included in Supporting Information]

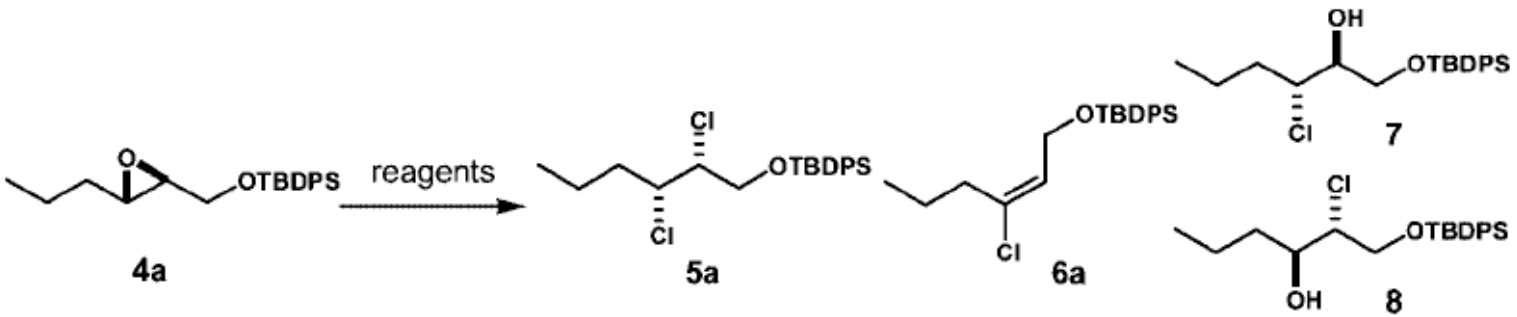


major anomer

Synthesis of Pyran **16** to Confirm the Relative Stereochemistry of Dichlorination

Shibuya, G. M., Kanady, J. S., Vanderwal, C. D. *J. Am. Chem. Soc.* **2008**, *130*, 12514.

Nucleophilic Multiple Chlorination

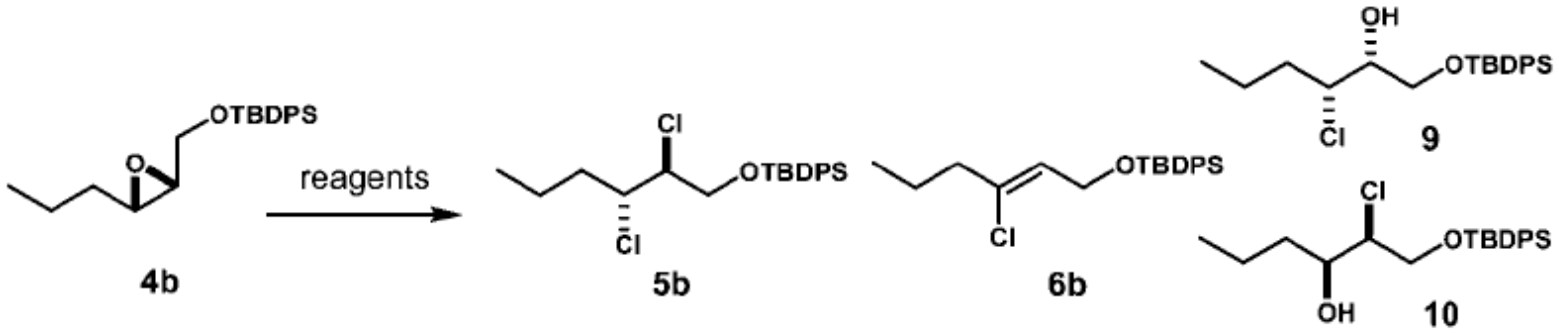


4a 5a 6a 7 8

entry	reagents (equiv)	solvent	T (°C)	time (h)	products[a,b] (%)
1	Cl_2PPh_3 (4)	toluene	80	0.5	**5a** (79), **6a** (18)
2	NCS/Ph_3P (3/3)	toluene[c]	90	0.7	**5a** (76), **6a** (17)
3	NCS/Ph_3P (2.5/2.5)	toluene	90	13	**5a** (69), **6a** (19), **7** (9)
4	NCS/(c-Hex)$_3$P (3/3)	toluene	90	6	**5a** (65), **6a** (11), **7** (4), **8** (2)
5	NCS/*n*-Bu_3P (3/3)	toluene	90	6	**5a** (66), **6a** (11), **7** (19)
6	NCS/*t*-Bu_3P (3/3)	toluene	90	22	**7** (65), **8** (32)
7	Ph_3P (3)	CCl_4	reflux	7	**7** (47), **8** (10) [d]
8	PCl_5 (3), $NaHCO_3$	CH_2Cl_2	rt	1	complex mixture

Yoshimitsu, T., Fukumoto, N., Tanaka, T. *J. Org. Chem.* **2009**, *74*, 696.

Nucleophilic Multiple Chlorination

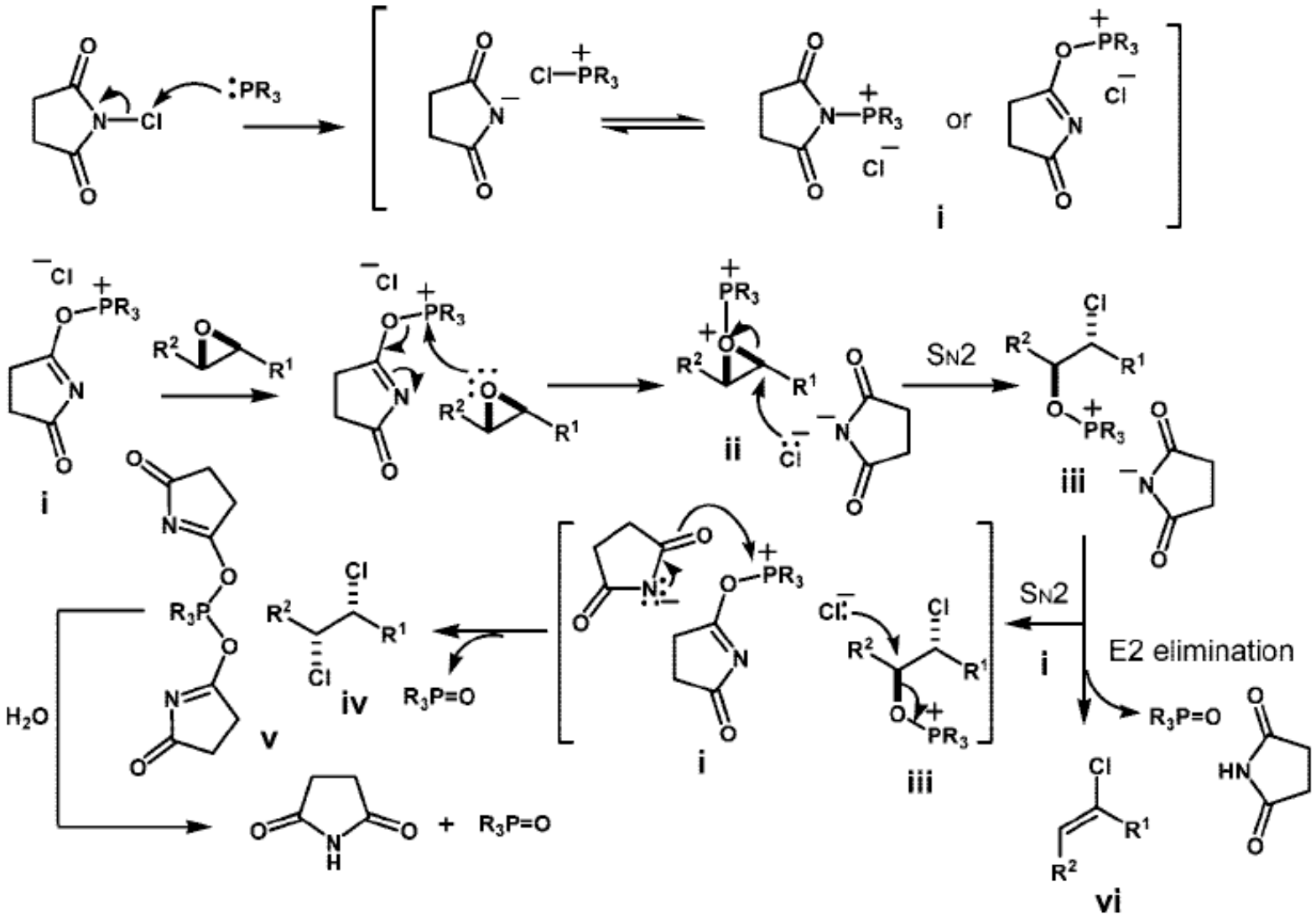


4b 5b 6b 9 10

entry	reagents (equiv)	solvent	*T* (°C)	time (h)	products[a,b] (%)
1	Cl_2PPh_3 (4)	toluene	80	0.5	**5b** (82), **6b** (17)
2	NCS/Ph_3P (3/3)	toluene	90	1	**5b** (88), **6b** (9)
3	NCS/Ph_3P (3/3)	toluene	45	7	**5b** (90), **6b** (6)
4	NCS/(c-Hex)$_3$P (3/3)	toluene	90	4.5	**5b** (86), **6b** (7)
5	NCS/*n*-Bu_3P (3/3)	toluene	90	6	**5b** (82), **6b** (7)
6	NCS/*t*-Bu_3P (3/3)	toluene	90	22	**9** (72), **10** (17)
7	Ph_3P (3)	CCl_4	reflux	7	**5b** (81), **6b** (7)

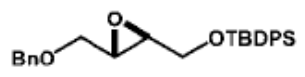
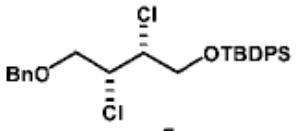
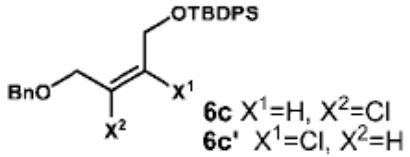
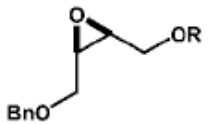
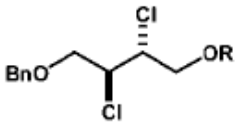
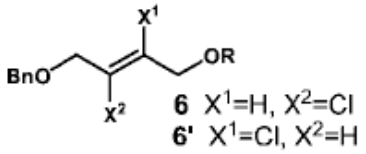
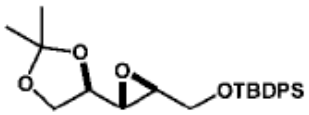
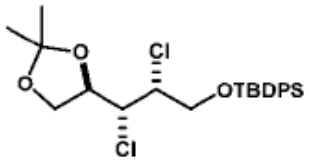
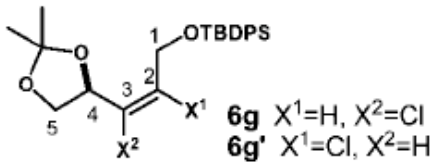
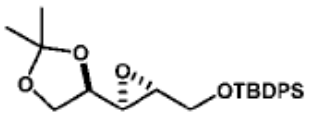
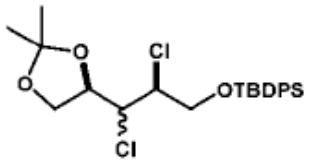
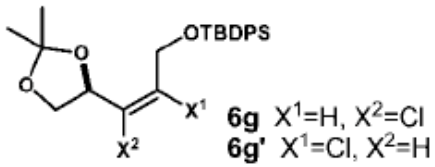
Yoshimitsu, T., Fukumoto, N., Tanaka, T. *J. Org. Chem.* **2009**, *74*, 696.

Nucleophilic Multiple Chlorination



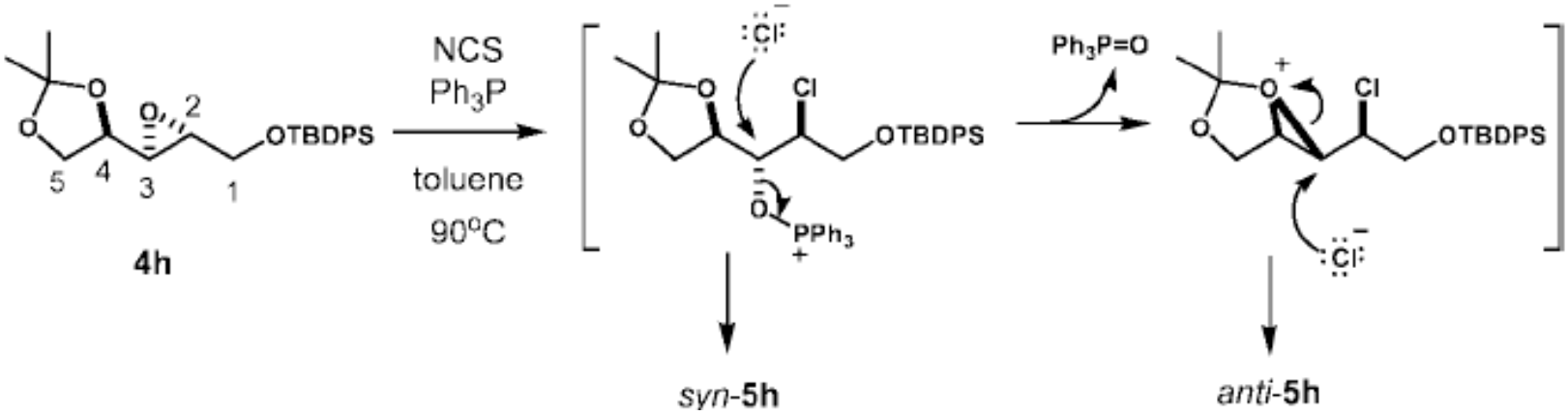
Yoshimitsu, T., Fukumoto, N., Tanaka, T. *J. Org. Chem.* **2009**, *74*, 696.

Nucleophilic Multiple Chlorination

entry	substrate[a]	temp (°C)	products[b,c]	time (h)
1	 **4c**		 **5c**  **6c** X^1=H, X^2=Cl **6c'** X^1=Cl, X^2=H	
		90	82 %	14 % (**6c**:**6c'**=4:1)	3.4
		45	80 %	8 % (**6c**:**6c'**=3:1)	22
			  **6** X^1=H, X^2=Cl **6'** X^1=Cl, X^2=H	
2	**4d** R=TBDPS	90	**5d** 79 %	20 % (**6d**:**6d'**=6:1)	2.7
		45	**5d** 84 %	14 % (**6d**:**6d'**=1:0)	48
3	**4e** R=TBS	90	**5e** 69 %	18 % (**6e**:**6e'**=5:2)	1
4	**4f** R=Piv	90	**5f** 82 %	12 % (**6f**:**6f'**=3:2)	1.5
5	 **4g**	90	 **5g** 56 %	 **6g** X^1=H, X^2=Cl **6g'** X^1=Cl, X^2=H 28 % (**6g**:**6g'**=1:27)[d]	1
6	 **4h**	90	 **5h** 42% (*syn*:*anti* = 3:1)	 **6g** X^1=H, X^2=Cl **6g'** X^1=Cl, X^2=H 33 % (**6g**:**6g'**=3:4)[d]	2.7

All reactions were carried out using NCS (3 equiv) and PPh_3 (3 equiv) in toluene

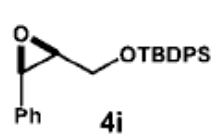
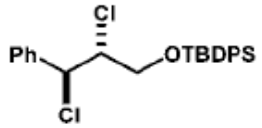
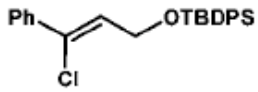
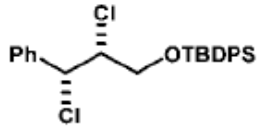
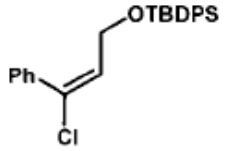
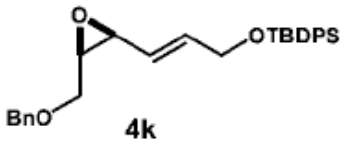
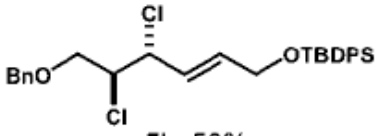
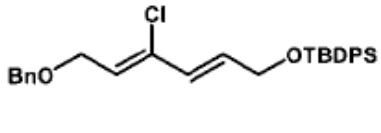
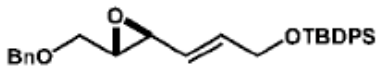
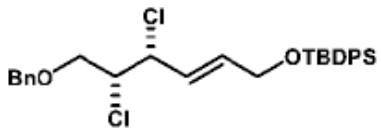
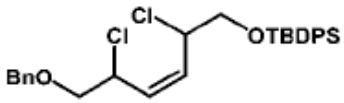
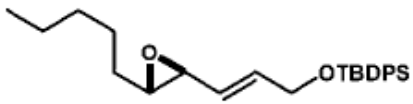
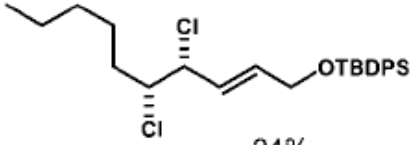
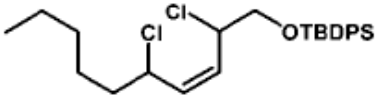
Nucleophilic Multiple Chlorination



Rationale for Configurational Retention at the C3 Position

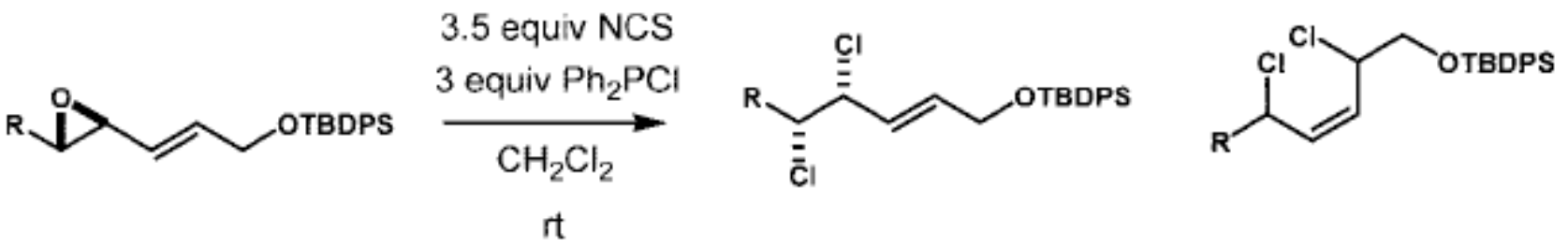
Yoshimitsu, T., Fukumoto, N., Tanaka, T. *J. Org. Chem.* **2009**, *74*, 696.

Nucleophilic Multiple Chlorination

entry	substrate[a]	products[b,c]	time (h)
1	 **4i**	 **5i** 57 % (*syn*:*anti* = 1:50)  **6i** 38 % (*E*:*Z* = 1:13)	1.5
2	 **4j**[d]	 **5j** 19 % (*syn*:*anti* = 14:1)  **6j** 68 % (*E*:*Z* = 19:1)	1.5
3	 **4k**	 **5k** 58%  **6k** 34%	0.7
4	 **4l**	 **5l** 33% 53%[e]  **6l** 52%[f] 7%[e,f]	0.5
5	 **4m**	 **5m** 24% 58%[e]  **6m** 60%[f] 27%[e,f]	1.2

All reactions were carried out using NCS (3 equiv) and PPh_3 (3 equiv) in toluene at 90 °C

Nucleophilic Multiple Chlorination



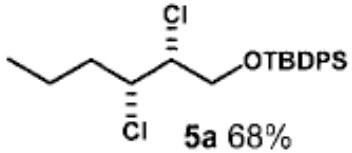
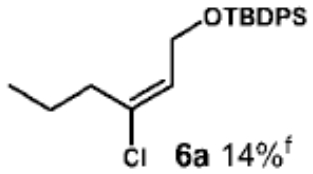
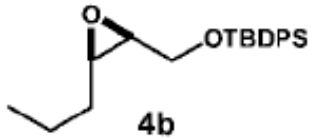
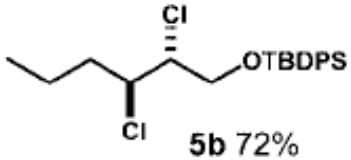
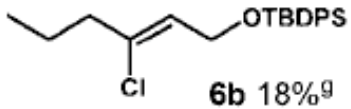
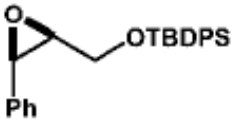
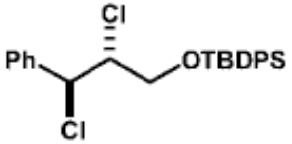
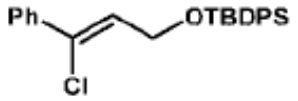
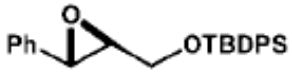
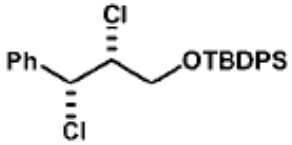
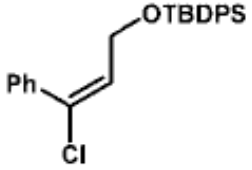
4l R=$BnOCH_2$
4m R=*n*-C_5H_{11}

5l R=$BnOCH_2$ 53%
5m R=*n*-C_5H_{11} 58%

6l R=$BnOCH_2$ 7%
6m R=*n*-C_5H_{11} 27%

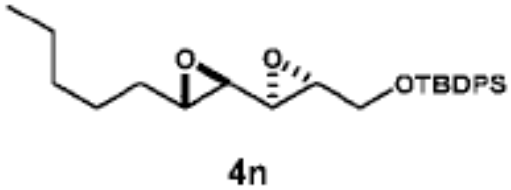
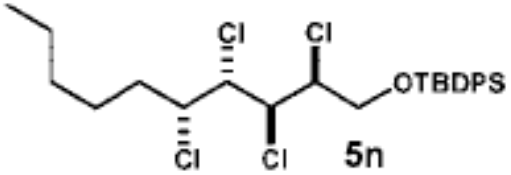
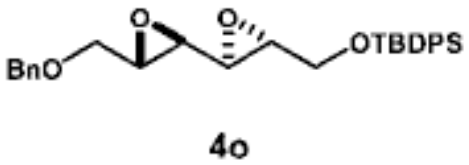
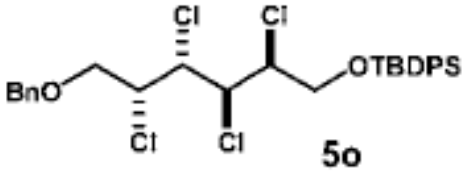
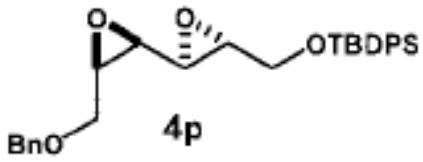
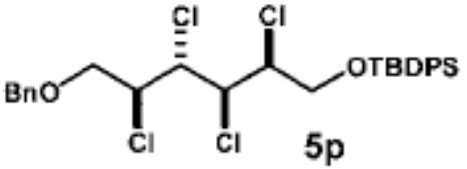
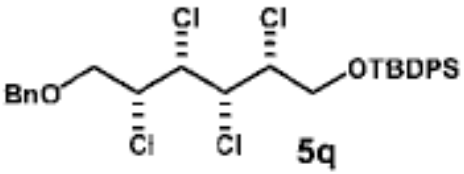
Yoshimitsu, T., Fukumoto, N., Tanaka, T. *J. Org. Chem.* **2009**, *74*, 696.

Nucleophilic Multiple Chlorination

entry	substrate	time (min)	products[d,e]	
1[a,b]	 **4a**	25	 **5a** 68%	 **6a** 14%[f]
2[a,b]	 **4b**	10	 **5b** 72%	 **6b** 18%[g]
3[c]	 **4i**	25	 **5i** 37% (*syn*:*anti* = 1:14)	 **6i** 56% (*E*:*Z* = 1:25)[h]
4[c]	 **4j**	25	 **5j** 36% (*syn*:*anti* = 3.6:1)	 **6j** 52% (*E*:*Z* = 6:1)[i]

[a] The reaction was carried out using NCS (3 equiv) and Ph_2PCl (2 equiv) in CH_2Cl_2 at rt.
[b] Racemic substrate was used.
[c] The reaction was carried out using NCS (3 equiv) and Ph2PCl (3 equiv) in CH_2Cl_2 at rt.

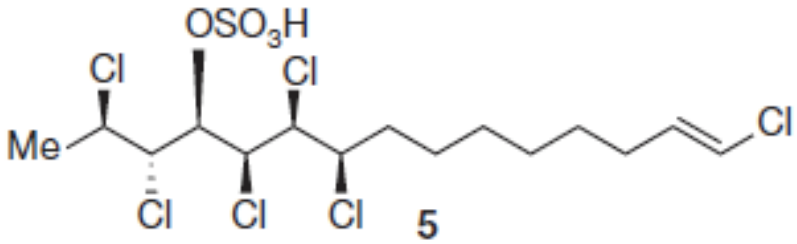
Nucleophilic Multiple Chlorination

entry	substrate	product[d]	yield (%)[e]
1[a]	 **4n**	 **5n**	40[f]
2[b]	 **4o**	 **5o**	42
3[c]	 **4p**	 **5p**	30[f]
4[b]	 **4q**	 **5q**	10

Tetrachlorination of Bisepoxides **4n-q** with NCS/Ph_3P

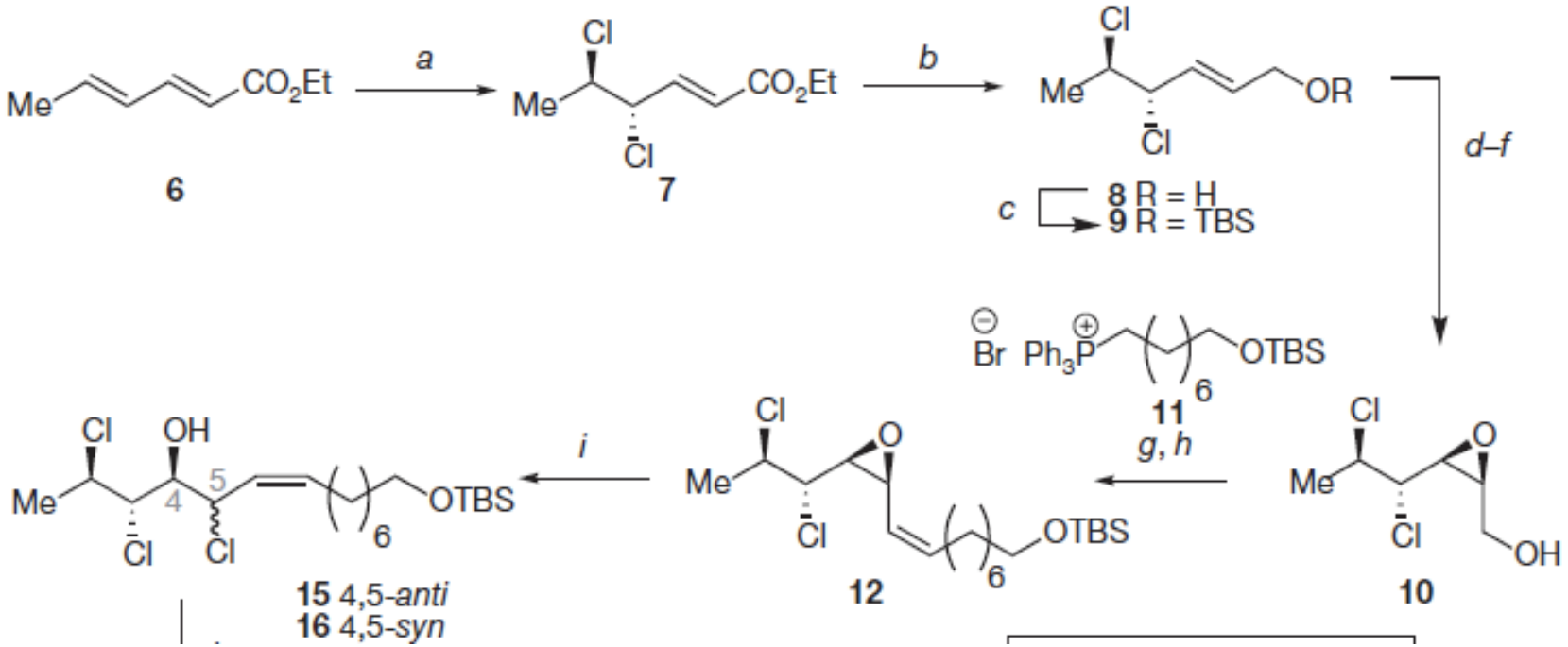
Yoshimitsu, T., Fukumoto, N., Tanaka, T. *J. Org. Chem.* **2009**, *74*, 696.

Total synthesis of a chlorosulpholipid



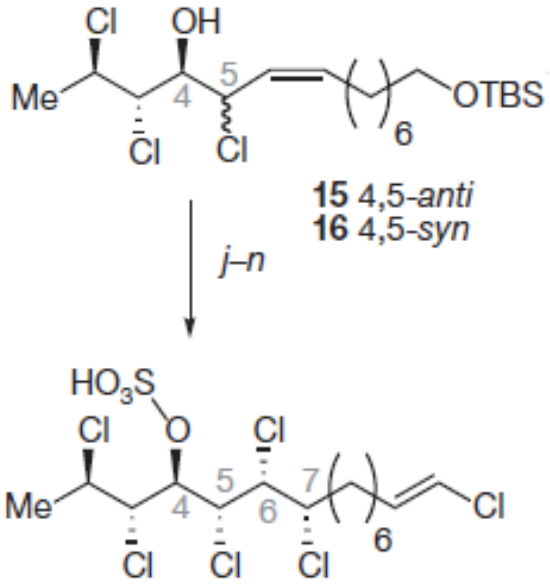
Nilewski, C., Geisser, R. W.; Erick M. Carreira. *Nature* **2009**, *457*, 573.

Total synthesis of a chlorosulpholipid

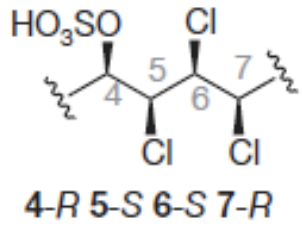


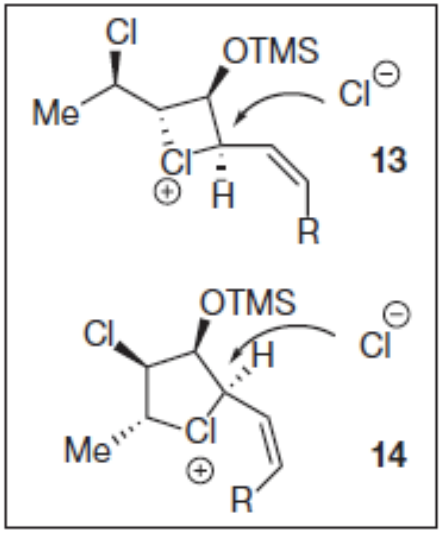
(a) $(H_5C_2)_4NCl_3$, CH_2Cl_2, 0 °C, 45 min, 68%; (b) DIBAL (2.3 equiv.), $H_5C_2H_5C_6$, 0 °C, 10 min, 72%; (c) imidazole (1.5 equiv.), *t*-Bu$(H_3C)_2SiCl$ (1.2 equiv.), CH_2Cl_2, 0 °C to room temperature (RT, 20 °C), 30 min, 87%; (d) OsO_4 (5 mol%),NMO(1.1 equiv.), acetone/H_2O, RT, 19 h, 68%; (e) DABCO (3.0 equiv.), $(F_3CSO_2)_2O$ (1.0 equiv.), -78 °C, 10 min, then diol, -78 °C to RT, 15 h, 75% (96% based on recovered starting material); (f) (1)-CSA (0.1 equiv.), CH_3OH, RT, 3 h, 98%; (g) $(COCl)_2$ (1.3 equiv.), $(H_3C)_2SO$ (2.5 equiv.), CH_2Cl_2, -78 °C, 10 min, then **10** (1.0 equiv.) , -78 °C, 30 min, then $(H_5C_2)_3N$ (5.4 equiv.) , -78 °C to RT, 1h; (h) **11** (1.05 equiv.), n-BuLi (1.05 equiv.), THF, -78 °C, then RT, 10 min, followed by aldehyde (1.0 equiv.) at -78 °C, 5 min, then RT, 30 min, 62% over two steps; (i) $(H_3C)_3SiCl$ (2.0 equiv.), CH_2Cl_2, $H_3CCO_2C_2H_5$, 11.5 h, 39% **15**, 4%**16**, 10% mixture of S_N2' products (31% starting material recovered);

Total synthesis of a chlorosulpholipid



Natural product





anchimeric participation of chlorides

(j) $(H_5C_2)_4NCl_3$ (3.0 equiv.), CH_2Cl_2, 0 °C, 10 min, 51%; (k) (+)-CSA (10 mol%), CH_3OH, 12 h, 80%; (l) DAIB (1.1 equiv.), TEMPO (0.1 equiv.), CH_2Cl_2, RT, 16.5 h; (m) $CrCl_2$ (6.9 equiv.), $CHCl_3$ (2.6 equiv.), THF, 65 °C, 49% over two steps; (n) SO_3-pyridine (6.0 equiv.), THF, 30 min, 27% (66% starting material recovered).

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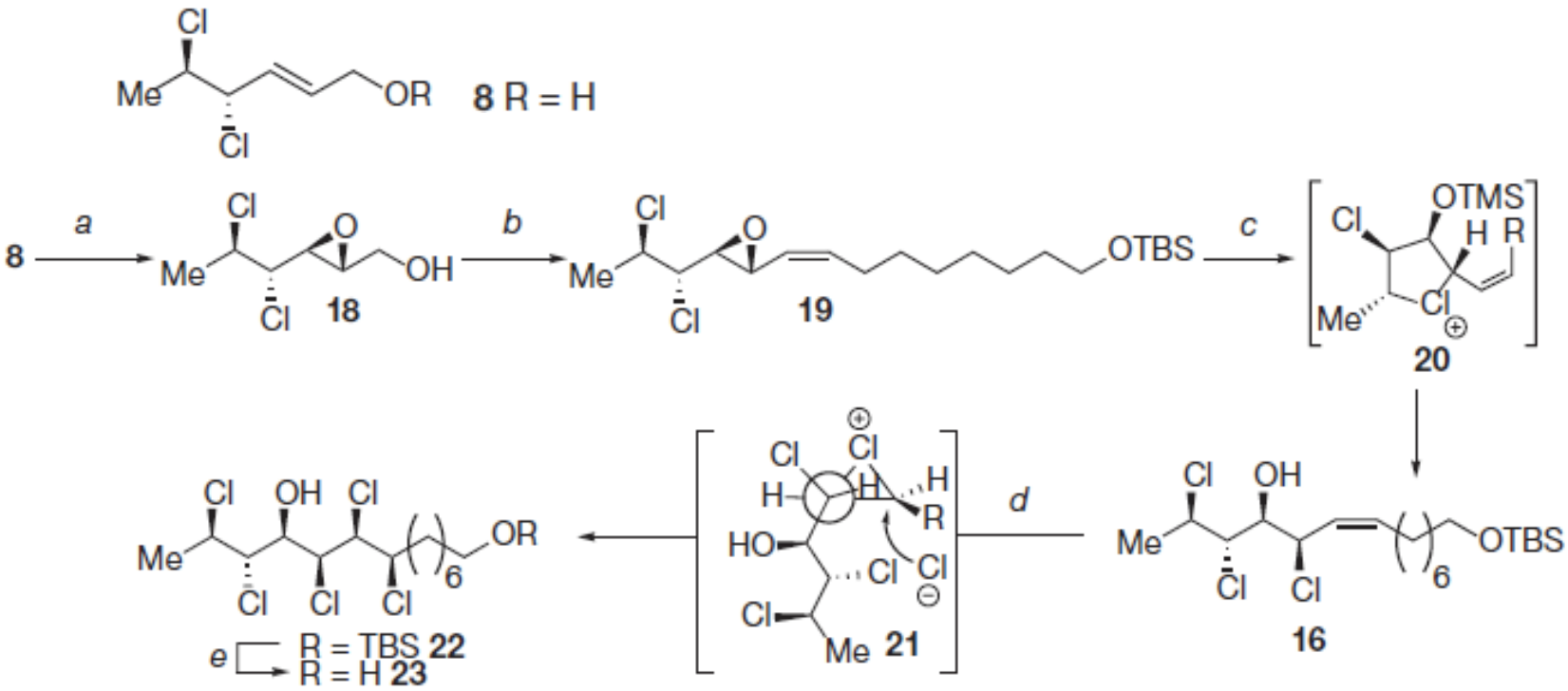
Total synthesis of a chlorosulpholipid



(a) *m*-CPBA, CH_2Cl_2, 0 °C to RT, d.r.=1:1, 95% overall; (b) 4Å molecular sieves, NMO (1.1 equiv.), TPAP (5 mol%), CH_2Cl_2, 6h; **11** (1.6 equiv.), n-BuLi (1.6 equiv.), THF, -78 °C, RT, 10 min; then addition of the aldehyde solution to the phosphonium ylide at -78 °C, 1 h, then RT, 1.5 h, 34% (56% based on recovered starting material); (c) $(H_3C)_3SiCl$ (2.0 equiv.), CH_2Cl_2, $H_3CCO_2C_2H_5$, 9 h, 43% (73% based on recovered starting material); (d) $(H_5C_2)_4NCl_3$ (3.0 equiv.), CH_2Cl_2, -78 °C, 2 h, d.r.=10:1, 93% overall; (e) (+)-CSA (10 mol%), CH_3OH, 12 h, 98%;

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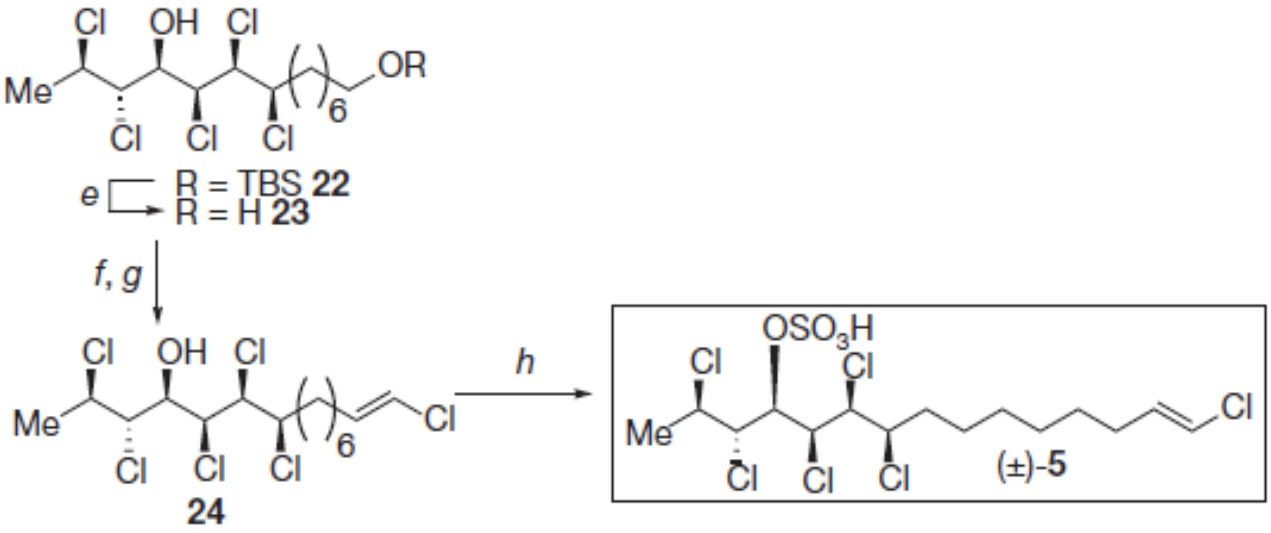
Total synthesis of a chlorosulpholipid



(e) (+)-CSA (10 mol%), CH_3OH, 12 h, 98%; (f) DAIB (1.3 equiv.), TEMPO (0.2 equiv.), CH_2Cl_2, RT, 16.5 h; (g) $CrCl_2$ (6.8 equiv.), $CHCl_3$ (2.5 equiv.), THF, 65 uC, 47% over two steps; (h) SO_3-pyridine (3.0 equiv.), THF, 20 min, 99%.

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Conclusions

- Polyflurinated and polychlorinated compounds have newly gained synthetic interests.

- Enantio- and stereoselective methods are needed.