Threo Aryl Trifluoromethyl Chlorohydrins: Synthesis, Reactivity, and Structure

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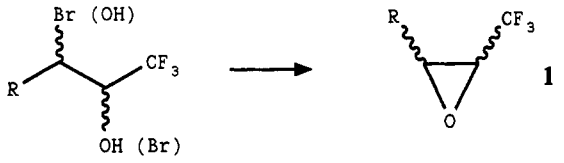
Threo trifluoromethyl chlorohydrins (1-aryl-2-chloro-3,3,3-trifluoropropan-1-ols) have been synthesized from the corresponding dichloro alcohols via an 85/15 threo diastereoselective monodechlorination using Ph_3SnH. The threo structures have been determined by X-ray and NMR. These chlorohydrins have been easily transformed into the epoxides which have then been opened with NaN_3.

Type 1 (trifluoromethyl)oxiranes have been obtained from trifluoromethyl bromohydrins. Although they could constitute useful intermediates in the synthesis of bioactive compounds,[1] most of the interest has stemmed from the possibility of using them as monomers to prepare fluorinated epoxy resins.[2-4] Until now, the starting trifluoromethyl bromohydrins have been synthesized as 2/1 or undetermined erythro/threo mixtures and in their racemic state.[1,5-7] We report here the synthesis and reactivity of threo trifluoromethyl chlorohydrins **5a,b** together with the NMR and X-ray structural assignments.



(1) Synthesis. As we recently described the synthesis of optically pure 1-aryl-2,2-dichloro-3,3,3-trifluoropropan-1-ol **2a,b** in 60% and 76% yield,[8] we decided to use these alcohols to synthesize the corresponding chlorohydrins through reductive monodehalogenation. However, the method was first developed using the less expensive racemic alcohols.

Reductive dehalogenation of the free alcohols **2a,b** using tin hydrides in diethyl ether with simultaneous irradiation led to the chlorohydrins as the only product but with poor diastereoselectivity, Table I, and it is noteworthy that, in accord with known results,[9] less reactive Bu_3SnH led to 0% diastereoselectivity while more reactive Ph_3SnH gave 20% to 30% diastereoselectivity.

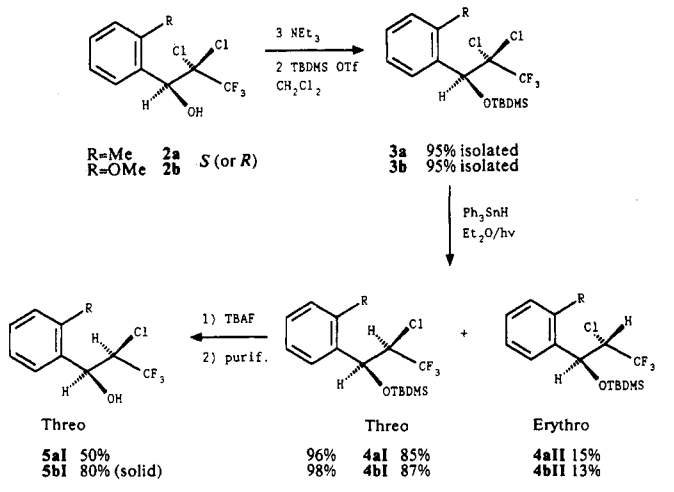
Fortunately, reductive dehalogenation (using Ph_3SnH) of the protected alcohols **3a,b**, obtained from **2a,b** in 95% yield, Scheme I, led to the protected chlorohydrins **4a,b** as the only product and with satisfying diastereoselectivity, 85-87/15-13 (Table I).

Table I. Reductive Dehalogenation of 2a,b and 3a,b using R_3SnH/Et_2O

	R_3SnH		4		5		2	3
	R	equiv	yield (%)	I/II	yield (%)	I/II	(%)	(%)
2a	Bu	1			74	50/50	26	
2a	Ph	1			73	35/65	27	
2b	Bu	1			75	48/52	25	
2b	Ph	1.5			87	40/60	13	
3a	Ph	1.1	96	85/15				4
			76[a]	92/8	50[b]	100/0		
3b	Ph	1	98	87/13				2
			90[a]	90/10	80[b]	100/0		

[a] Yield obtained after purification by flash chromatography. [b] Yield after purification by flash chromatography or crystallization.

Scheme I



Deprotection of compounds **4a,b** (using TBAF in THF) then provided the desired trifluoromethyl chlorohydrins **5a,b** which have been isolated as pure diastereomers after purification: **5aI** (50% yield after flash chromatography) and **5bI** (in 80% yield after crystallization).

Ring closure of thus obtained threo chlorohydrins **5aI** and **5bI** (using powdered KOH and catalytic amounts of 18-crown-6 in Et_2O) worked well and led to only one isomer of the corresponding trifluoromethyl oxirane **1a,b** as seen

(1) Walborsky, H. M.; Baum, M. E. *J. Am. Chem. Soc.* **1958**, *80*, 187.
(2) Tarrant, P.; Allison, C. G.; Barthold, K. P. *Fluor. Chem. Rev.* **1971**, *77*, 77.
(3) Trischler, F. D. Whitaker Corp. US Patent US 3.452.103 June 24, 1969.
(4) Sulzback, R. A. Gen. Offen. *55 7655*, 1977, 2.
(5) Mc Bee, E. T.; Burton, T. M. *J. Am. Chem. Soc.* **1952**, *74*, 3022 and 3902; *Ibid.* **1953**, *75*, 1609.
(6) Rausch, D. A.; Lovelace, A. M.; Coleman, I. E. *J. Org. Chem.* **1956**, *21*, 1328.
(7) Coudures, C.; Pastor, R.; Cambon, A. *J. Fluor. Chem.* **1984**, *24*, 93.
(8) Solladié-Cavallo, A.; Quazzotti, S. *Synthesis* **1991**, 177.
(9) Kuivila, H. G. *Synthesis* **1970**, 499.

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Table II. Positional Parameters and Their ESD[a]

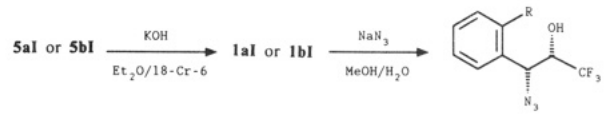
atom	x	y	z	B (Å²)
Cl1	0.619 35 (9)	0.108 48 (4)	0.791 88 (6)	4.78 (2)
F1	0.8625 (2)	−0.0623 (1)	0.8199 (2)	9.39 (7)
F2	0.9176 (2)	0.0496 (1)	0.8639 (2)	8.21 (7)
F3	0.8094 (2)	0.0206 (2)	0.7017 (2)	10.37 (8)
O1	0.5068 (2)	−0.0191 (1)	0.6377 (1)	3.92 (5)
O2	0.5900 (2)	−0.1043 (1)	0.9334 (1)	3.80 (5)
C1	0.8161 (4)	0.0059 (2)	0.7990 (3)	6.6 (1)
C2	0.6743 (3)	0.0150 (2)	0.8137 (2)	3.89 (7)
C3	0.5567 (3)	−0.0377 (2)	0.7474 (2)	3.31 (6)
C4	0.4364 (3)	−0.0387 (2)	0.7887 (2)	2.89 (6)
C5	0.3047 (3)	−0.0061 (2)	0.7349 (2)	3.49 (7)
C6	0.1961 (3)	−0.0072 (2)	0.7764 (2)	4.21 (8)
C7	0.2192 (3)	−0.0413 (2)	0.8711 (2)	4.15 (7)
C8	0.3495 (3)	−0.0752 (2)	0.9267 (2)	3.71 (7)
C9	0.4571 (3)	−0.0733 (2)	0.8851 (2)	2.93 (6)
C10	0.6180 (3)	−0.1408 (2)	1.0326 (2)	4.59 (8)
Cl2	1.252 90 (9)	0.204 95 (5)	0.327 02 (6)	5.07 (2)
F4	1.5726 (2)	0.1853 (1)	0.4159 (2)	7.09 (5)
F5	1.5171 (2)	0.2992 (1)	0.3955 (2)	7.47 (6)
F6	1.6117 (2)	0.2544 (2)	0.5512 (2)	8.04 (7)
O3	1.4029 (2)	0.0949 (1)	0.4997 (2)	4.83 (5)
O4	1.3294 (2)	0.2544 (1)	0.6804 (2)	4.88 (5)
C11	1.5186 (4)	0.2403 (2)	0.4549 (3)	5.48 (9)
C12	1.3714 (3)	0.2242 (2)	0.4579 (2)	4.24 (7)
C13	1.3712 (3)	0.1640 (2)	0.5357 (2)	3.95 (7)
C14	1.2329 (3)	0.1624 (2)	0.5558 (2)	3.75 (7)
C15	1.1203 (4)	0.1143 (2)	0.5014 (2)	4.82 (8)
C16	0.9959 (4)	0.1139 (2)	0.5245 (3)	6.3 (1)
C17	0.9829 (4)	0.1599 (2)	0.5994 (3)	6.3 (1)
C18	1.0911 (3)	0.2077 (2)	0.6545 (3)	5.47 (9)
C19	1.2156 (3)	0.2091 (2)	0.6317 (2)	4.07 (7)
C20	1.3323 (4)	0.2939 (2)	0.7726 (3)	5.61 (9)

[a] Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as: $(^4/_3)[a^2\beta(1,1) + b^2\beta(2,2) + c^2\beta(3,3) + ab(\cos\gamma)\beta(1,2) + ac(\cos\beta)\beta(1,3) + bc(\cos\alpha)\beta(2,3)]$.

Table III. Dihedral Angles and Distances between Nonbonded Atoms

angle	deg	distance	Å
F3–C1–C2–C11	59	O1–Cl1	3.03
C1–C2–C3–O1	70	O1–F3	2.90
O1–C3–C4–C5	28	O1–F2	4.30
C4–C9–O2–C10	168	O1–F1	3.55

from the 200-MHz proton NMR of the crude compound. Further opening of these epoxides using sodium azide in $MeOH/H_2O$ provides azides **6aI** and **6bI** in high yields, both as a single diastereoisomer and as a single regioisomer in accord with literature results.[10]



Threo **6aI** 75%
6bI 95%

(2) X-ray Crystallography of Compound 5bI. The racemic chlorohydrin **5bI** being solid was crystallized in THF and studied by X-ray crystallography. Table II lists the coordinates of all non-hydrogen atoms.

All bond distances and bond angles are in the normal range. Important dihedral angles and interatomic distances are given in Table III. The structure, Figure 1, shows that **5bI** is the threo diastereomer: C3*R*, C2*S* (using the numbering used in the crystallographic work) and that the methoxy group of the phenyl ring has an anti relationship with the hydroxyl group of the chain.

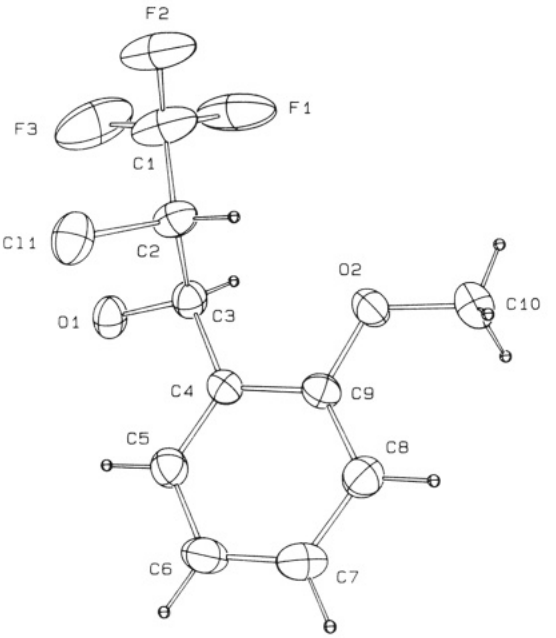


Figure 1. ORTEP plot of one molecule of **5bI** showing the labeling scheme used. Ellipsoids are scaled to enclose 50% of the electronic density. Selected mean bond lengths (Å): C–F, 1.325 (3); C–Cl, 1.771 (3); C1–C2, 1.514 (4); C2–C3, 1.522 (4); C3–C4, 1.502 (3); C3–O1, 1.422 (3); C9–O2, 1.367 (3); C10–O3, 1.427 (3); Cphen–Cphen, 1.384 (6). Selected mean bond angles (deg): C1–C2–C3, 114.1 (2); C2–C3–C4, 110.8 (3); C1–C2–C1, 108.8 (2); C2–C3–O1, 111.8 (2); C9–O2–C10, 117.8 (2).

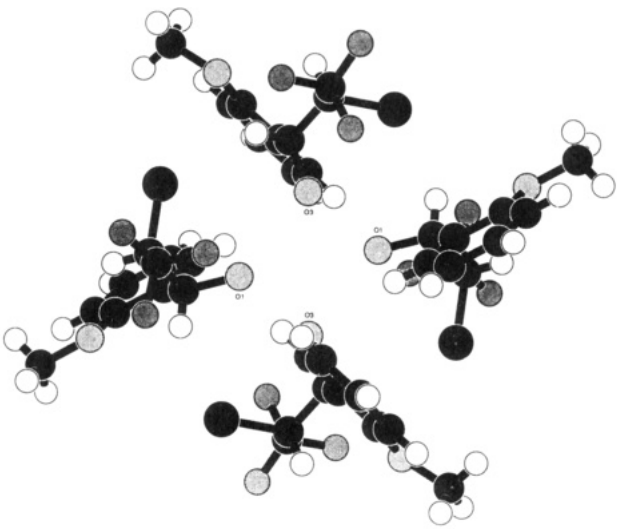


Figure 2. Drawing showing how four molecules are associated via H bonds between hydroxyl groups and are related by pair of enantiomers through a crystallographic inversion center.

Eight molecules are present in the unit cell. Molecules are linked by four H bonds between the hydroxyl groups and are related by pair of enantiomers (C3*R*,C2*S*/C3*S*,-C2*R*) through an inversion center, Figure 2.

(3) NMR Spectroscopy. In Table IV are gathered the ^1H NMR (200-MHz) data of compounds **2a,b** to **6a,b**.

The assignment of the signals to protons H3 and H2 (using the numbering used in the crystallographic work) was made from analysis of the pattern (presence of J_{HF} and J_{HOH} or not).

One must notice that in the four compounds, **4a**, **4b**, **5a**, and **5b**, diastereomer I exhibits for the proton H2 a similar pattern (a quadruplet of doublets) with a small J_{32} coupling constant (2–3 Hz), different from the pattern of diaste-

(10) (a) Mc Bee, E. T.; Hathaway, C. E.; Roberts, C. W. *J. Am. Chem. Soc.* **1956**, *78*, 3851. (b) Takahashi, O.; Furuhashi, K.; Fukumasa, M.; Hirai, T. *Tetrahedron Lett.* **1990**, *31*, 7031.

Scheme II

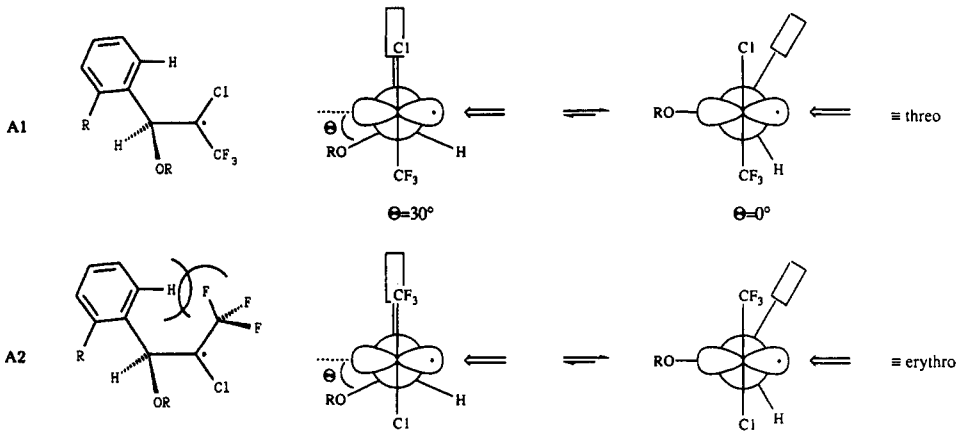


Table IV. ^{1}H NMR Data in $CDCl_3$

	δ H3	δ H2	$^3J_{32}$	$^3J_{F2}$	δ OH	^3J OH
2a	5.64 (d)				2.7 (d)	5.6
2b	5.62 (d)				4.0 (d)	7.6
3a	5.69 (s)					
3b	5.93 (s)					
4aI	5.43 (d)	4.13 (qd)[a]	2.5	7		
4aII	5.23 (d)	4.29 (qu)[a]	7	7		
4bI	5.65 (d)	4.35 (qd)	2	7		
4bII	5.41 (d)	4.5 (qd)	6	7		
5aI	5.5 (dd)	4.31 (qd)	3	7	2.56 (d)	5
5aII	5.35 (dd)	4.41 (qd)	8	6.5	2.45 (d)	3
5bI	5.58 (dd)	4.63 (qd)	2.5	7	2.90 (d)	7.5
5bII	5.07 (t)	4.67 (qd)	7.5	7	3.32 (d)	7.5
1aII[b]	4.28 (d)	3.38 (qd)	2	5		
1bI[c]	4.29 (d)	3.68 (qd)	4	6		
6aI	5.14 (d)	4.10 (m)	3.7		3.01 (d)	8.5
6bI	5.35 (d)	4.21 (m)	2.6		2.88 (d)	9.5

[a] q = quadruplet, qu = quintruplet. [b] Determined on crude product. [c] Determined on pure **1bI** isolated by distillation.

reomer II (a quadruplet of doublets or a quintuplet) with a larger J_{32} coupling constant (5–8 Hz).

Therefore, as the structure of diastereomer I in compound **5b** has been determined by X-ray crystallography to be threo, diastereomers I in the three other compounds **4a**, **4b**, and **5a** have also been assigned the threo configuration.

The 4-Hz value of the J_{32} coupling constant measured on trifluoromethyloxirane **1bI** obtained from pure threo chlorohydrin **5bI** is consistent with the expected cis structure[11] for these compounds.

Trifluoromethyl oxirane **1aII** has been obtained from a 65 erythro/35 threo mixture of **2a** (Table, line 2) as a mixture of **1aII** trans and untransformed threo **2a**. The 2-Hz value of the J_{32} coupling constant is also cinsistent with the expected trans structure.

The multiplicity of the signals of H2 in compounds **6aI** and **6bI** with a J_{HOH} coupling constant of 8.5 and 9.5 Hz shows that the hydroxyl group is at C2 (and only there) as expected from the known direction of opening of trifluoromelthyl oxiranes.[10]

Discussion and Conclusion

It is noteworthy that the 2.5-Hz value found for the J_{32} coupling constant in compound **5bI** is identical to the value (<≈3 Hz) predicted from the dihedral angle (70°) found in the solid state and the Karplus–Conroy curve suggesting that the conformations around the C2–C3 bond are similar in the solid state and in solution.

However, the strong intermolecular H bonds which link four molecules together in the solid state disappear in solution allowing an intramolecular H bond (O–H–OCH_3) to be formed, and one can think that the dihedral angle O1–C3–C4–C5, which is +28° in the solid state, could well be about −180° in solution, which would be consistent with the observed internal H bond (ν_{OH} = 3450–3500 cm^{-1}).

It must be noticed that the diastereoselectivities, 70% and 74%, are the highest obtained with reactions involving acyclic free radicals.[12]

As already invoked by Giese et al.[13,14] in the case of glycosyl radicals, this diastereoselectivity can be interpreted in terms of a preferred conformation in the radical together with a sterically directed approach of Ph_3SnH during the H$^\bullet$ transfer step.

As a matter of fact, an interaction between the p-half-occupied orbital (SOMO) at the radical center and the σ^* orbital of the β-C–O bond (–CH–$OSiMe_2tBu$) may also be envisaged in our case,[15] leading to conformations A1 or A2, and we think that conformation A1 is prefered over A2 because of an attractive van der Waals interaction between Cl and the ortho aromatic H in A1 versus a large steric hindrance between CF_3 and the ortho aromatic H in A2. Therefore, approach onto A1 from the less hindered side leads to the threo chlorohydrin as observed in the experiment.

We must also emphasize that because optically pure (*R*)- or (*S*)-1-aryl-2,2-dichloro-3,3,3-trifluoropropan-1-ols **2a**,**b** are available[8] it will now be possible to synthesize optically pure threo trifluoro chlorohidrins **5a** and **5b** in 30% and 60% overall yields.

Experimental Section

General Aspects. Reagent-grade MeOH from Carlo Erba was used without purification, and CH_2Cl_2 (Carlo Erba) was distilled over CaH_2 and stored over molecular sieves. THF was distilled under argon over Na/benzophenone and Et_2O over $LiAlH_4$. NEt_3 was distilled from KOH pellets and stored over molecular sieves. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (TBDMS triflate) from Fluka and tributyl- and triphenyltin hydride from

(11) Lazzeretti, P.; Moretti, I.; Taddei, F.; Torre, G. *Org. Magn. Reson.* **1973**, *5*, 385.

(12) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Baldwin, J. E., Ed.; Pergamon Press: New York, 1986; pp 26–32.

(13) Dupuis, J.; Giese, B.; Rüegge, D.; Fischer, H.; Korth, H. G.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 896.

(14) Korth, H. G.; Sustman, R.; Dupuis, J.; Giese, B. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1453.

(15) Dobbs, A. J.; Gilbert, B. C.; Norman, R. O. *J. Chem. Soc., Perkin Trans. 2* **1972**, 786.

Janssen were used without further purification. A 1 M solution of tetrabutylammonium fluoride (TBAF) in THF was purchased from Janssen. Melting points are uncorrected and were taken on a Reichert microscope. The IR spectra were recorded on a Perkin-Elmer 257. The ^1H and ^{13}C NMR spectra were recorded on a Bruker WP 200 SY or AC 200 (^1H, 200 MHz; ^{13}C, 50 MHz); the ^{19}F NMR spectra (376 MHz) were recorded on a Bruker AM 400. Flash chromatographies were carried out using silica gel (230–400 mesh) from Merck. Microanalyses were performed in our department.

Crystal data for **5bI**: $C_{10}H_{10}O_2F_3Cl$, mol. weight = 254, 64, monoclinic, $P2_1/n$, a = 10.001 (3) Å, b = 18.147 (5) Å, c = 13.511 Å, β = 111.38 (2)°, V = 2283 Å^3, Z = 8, D(calcd) = 1.481 g cm^{-3}, λ(Cu Kα) = 1.5418 Å (graphite monochromotor), T = −100 °C. A Philips PW1100/16 diffractometer, equipped with a local-build low-temperature device, was used to collect 2880 reflections ($3° < 2\theta < 53°$) on a colorless crystal 0.20 × 0.30 × 0.40 mm. Of these, 2180 were observed [$I > 3\ \sigma(I)$]. Empirical absorption corrections and Lorentz and polarization corrections were applied to the data. All non-hydrogen atoms were located by direct methods, and they were refined anisotropically. The hydrogen atoms, with the exception of the OH's, were included as idealized contributions. R = 0.040, R_w = 0.068, GOF = 1.50, final residual = 0.28 e Å^{-3}. All computations used MOLEN on a VAX computer.[16]

General Procedure for Protection of Alcohols 2a or 2b. To a solution of alcohol **2a** or **2b** (6 mmol) in anhydrous CH_2Cl_2 (15 mL) was added triethylamine (3 equiv) at room temperature with stirring, and the mixture was refluxed for 30 min. Then, *tert*-butyldimethylsilyl trifluoromethanesulfonate (2 equiv) was added dropwise and the new mixture refluxed overnight. The temperature was lowered to 0 °C and a saturated aqueous NH_4Cl (5 mL) was added. The CH_2Cl_2 layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layer was dried over anhydrous $MgSO_4$. The solvent was removed to give crude compound **3a** or **3b**.

3a: uncolored oil; 95% yield after purification by flash chromatography (h = 20 cm, ϕ = 5 cm, hexane, R_f = 0.65); ^1H NMR ($CDCl_3$) δ −0.21 (s, 3 H), 0.20 (s, 3 H), 0.99 (s, 9 H), 2.55 (s, 3 H), 5.69 (s, 1 H), 7.60 (m, 3 H arom), 7.90 (m, 1 H arom): ^{13}C NMR ($CDCl_3$) δ −5.4 (s, CH_3Si), −4.9 (s, CH_3Si), 18.0 (s, C, tBu), 20.1 (s, CH_3), 25.0 (s, CH_3, tBu), 71.6 (s, CHOSi), 88.3 (q, $^2J_{CF}$ = 31 Hz, CCl_2), 122.6 (q, $^1J_{CF}$ = 284 Hz, CF_3), 125.7 (s, CH arom), 128.9 (s, CH arom); 129.4 (s, CH arom), 130.0 (s, CH arom), 136.0 (s, C arom), 136.2 (s, C arom); IR (neat) no ν_{OH}. Anal. Calcd for $C_{16}H_{23}OCl_2F_3Si$: C, 49.61; H, 5.99. Found: C, 49.77; H, 6.05.

3b: uncolored oil; 96% yield after purification by flash chromatography (h = 20 cm, ϕ = 5 cm, Et_2O/hexane 5/95, R_f = 0.74); ^1H NMR ($CDCl_3$) δ −0.25 (s, 3 H), 0.12 (s, 3 H), 0.91 (s, 9 H), 3.88 (s, 3 H, OCH_3), 5.93 (s, 1 H), 6.91 (dd, 1 H arom, ^3J = 8 Hz, ^4J = 1 Hz), 7.04 (td, 1 H arom, ^3J = 8 Hz, ^4J = 1 Hz), 7.38 (td, 1 H arom, ^3J = 8 Hz, ^4J = 2 Hz), 7.79 (dd, 1 H, arom, ^3J = 8 Hz, ^4J = 2 Hz); ^{13}C NMR ($CDCl_3$) δ −5.5 (s, CH_3Si), −5.1 (s, CH_3Si), 17.9 (s, C, tBu), 25.5 (s, CH_3, tBu), 55.5 (s, CH_3O), 68.7 (s, CHOSi), 88.3 (q, $^2J_{CF}$ = 31 Hz, CCl_2), 110.2 (s, CH arom), 120.1 (s, CH arom), 122.4 (q, $^1J_{CF}$ = 284 Hz, CF_3), 126.2 (s, C arom), 130.1 (s, CH arom), 130.3 (s, CH arom), 156.9 (s, C arom); IR (neat) no ν_{OH}. Anal. Calcd for $C_{16}H_{23}O_2Cl_2F_3Si$: C, 47.72; H, 5.74. Found: C, 47.85; H, 5.12.

General Procedure for Monodechlorination of 2a, 2b, 3a, or 3b. A degassed mixture of compound **2a**, **2b**, **3a**, or **3b** (0.6 mmol) and tributyl- or triphenyltin hydride (0.6 mmol) in anhydrous ether (20 mL) was irradiated, respectively, for 5 h and for 12 h in a standard Pyrex photolysis system having a water-cooled jacket maintained at 15 °C and equipped with septum caps. Irradiation was performed using a 125-W mercury lamp (Philips HPK) located in the center of the vessel. After addition of triethylamine (10 equiv), the solvent and excess NEt_3 were removed to give, respectively, crude compounds **5a**, **5b**, **4a**, or **4b**.

5a (from **2a** and Bu_3SnH): uncolored oil; ^1H NMR ($CDCl_3$) apart from Bu_3SnCl the spectrum showed 26% of starting **2a** and 74% of **5a** as a mixture of the two diastereomers: **5aI**/**5aII** = 1/1.

5aI: δ 2.36 (s, 3 H), 2.56 (d, 1 H, OH), 4.31 (qd, 1 H), 5.50 (dd, 1 H), 7.25 (m, 3 H arom), 7.50 (m, 1 H arom).

5aII: δ 2.41 (s, 3 H), 2.45 (d, 1 H, OH), 4.41 (qd, 1 H), 5.35 (dd, 1 H), 7.25 (m, 3 H arom), 7.50 (m, 1 H arom).

5a (from **2a** and Ph_3SnH). Apart from Ph_3SnCl the ^1H NMR spectrums ($CDCl_3$) showed 27% of starting **2a** and 73% of **5a** as a mixture of the two diastereomers where **5aII** is major (65%).

5b (from **2b** and Bu_3SnH): uncolored oil; ^1H NMR ($CDCl_3$) apart from Bu_3SnCl the spectrum showed 25% of starting **2b** and 75% of **5b** as a mixture of the two diastereomers: **5bI**/**5bII** ≈ 1/1.

5bI: δ 2.90 (d, 1 H, OH), 3.88 (s, 3 H, CH_3O), 4.63 (qd, 1 H), 5.58 (dd, 1 H), 6.92 (d, 1 H arom, ^3J = 8 Hz), 7.05 (t, 1 H arom, ^3J = 8 Hz), 7.36 (td, 1 H arom. ^3J = 8 Hz, ^4J = 1 Hz), 7.46 (dd, 1 H arom, ^3J = 8 Hz, ^4J = 1 Hz).

5bII: 3.32 (d, 1 H, OH), 3.92 (s, 3 H, CH_3O), 4.67 (qd, 1 H), 5.07 (t, 1 H), 6.96 (d, 1 H arom, ^3J = 8 Hz), 7.00 (t, 1 H arom, ^3J = 8 Hz), 7.35 (d, 1 H arom, ^3J = 8 Hz), 7.37 (t, 1 H arom, ^3J = 8 Hz).

5b (from **2b** and Ph_3SnH): apart from Ph_3SnCl the ^1H NMR spectrum ($CDCl_3$) showed 13% of starting **2b** and 87% of **5b** as a mixture of diastereomers where **5bII** is major (60%).

4a (from **3a**): uncolored oil; 76% yield after purification by flash chromatography (h = 20 cm, ϕ = 3 cm, hexane, R_f = 0.46); ^1H NMR ($CDCl_3$), mixture of two diastereomers in the ratio **4aI**/**4aII** = 92/8;

4aI: δ −0.20 (s, 3 H), 0.10 (s, 3 H), 0.93 (s, 9 H), 2.36 (s, 3 H), 4.13 (qd, 1 H), 5.43 (d, 1 H), 7.25 (m, 3 H arom), 7.65 (m, 1 H arom); ^{13}C NMR ($CDCl_3$) δ −4.8 (s, CH_3Si), −4.0 (s, CH_3Si), 18.7 (s, C, tBu), 19.5 (s, CH_3), 26.3 (s, CH_3, tBu), 62.5 (q, $^2J_{CF}$ = 30 Hz, CCl_2), 124.3 (q, $^1J_{CF}$ = 282 Hz, CF_3), 126.6 (s, CH arom), 128.9 (s, CH arom), 129.0 (s, CH arom), 131.0 (s, CH arom), 138.5 (s, C arom); ^{19}F NMR ($CDCl_3$/$CFCl_3$) δ −71.2 (d, J = 7 Hz). Anal. Calcd for $C_{16}H_{24}OClF_3Si$: C, 54.46; H, 6.86. Found: C, 54.46; H, 6.96.

4aII: δ −0.25 (s, 3 H), 0.05 (s, 3 H), 0.90 (s, 9 H), 2.42 (s, 3 H), 4.29 (quint, 1 H), 5.23 (d, 1 H), aromatic H overlap with those of **4aI**.

4b (from **3b**): uncolored oil; 90% yield after purification by flash chromatography (h = 20 cm, ϕ = 3 cm, hexane, R_f = 0.31). ^1H NMR ($CDCl_3$) mixture of two diastereomers in the ratio **4bI**/**4bII** = 90.10.

4bI: δ −0.17 (s, 3 H), 0.11 (s, 3 H), 0.97 (s, 9 H), 3.88 (s, 3 H, OCH_3), 4.35 (qd, 1 H), 5.68 (d, 1 H), 6.87 (dd, 1 H arom, ^3J = 7 Hz, ^4J = 1 Hz), 7.02 (td, 1 H arom, ^3J = 7 Hz, ^4J = 1 Hz), 7.32 (td, 1 H arom, ^3J = 7 Hz, ^4J = 2 Hz), 7.57 (dd, 1 H arom, ^3J = 7 Hz, ^4J = 2 Hz); ^{13}C NMR ($CDCl_3$) δ −4.6 (s, $2CH_3Si$), 18.0 (s, (C, tBu), 25.7 (s, CH_3, tBu), 55.3 (s, CH_3O), 60.9 (q, $^2J_{CF}$ = 30 Hz, CHCl), 65.3 (q, $^3J_{CF}$ = 2 Hz, CHOSi), 109.7 (s, CH arom), 120.2 (s, CH arom), 123.8 (q, $^1J_{CF}$ = 280 Hz, CF_3), 127.8 (s, C arom), 128.9 (s, CH arom), 129.1 (s, CH arom), 154.8 (s, C arom). Anal. Calcd for $C_{16}H_{24}O_2ClF_3Si$: C, 52.09; H, 6.56. Found: C, 52.17; H, 6.55.

4bII: δ −0.3 (s, 3 H), 0.11 (overlapped with **4bI**), 0.90 (s, 9 H), ≈3.89 (s, 3 H, CH_3O), 4.50 (qd, 1 H), 5.41 (d, 1 H), aromatic H overlap with those of **4bI**.

General Procedure for Deprotection of Compounds 4a and 4b. To compound **4a** or **4b** (3.5 mmol) in anhydrous THF (20 mL) was added tetrabutylammonium fluoride (TBAF) 1 M in THF (7 mmol, 7 mL) at room temperature, and the mixture was stirred for 30 min. The mixture was filtered through silica gel 70–230 mesh (h = 3 cm, ϕ = 7 cm); the silica gel was rinsed with Et_2O (100 mL). The organic phases were combined, and the solvent was removed to give crude compound **5a** or **5b**.

5aI: uncolored oil; 50% after purification by flash chromatography (h = 20 cm, ϕ = 5 cm; Et_2O/hexane 20/80, R_f = 0.34); ^1H NMR ($CDCl_3$) only diastereomer I is observed; ^{13}C NMR ($CDCl_3$) δ 18.6 (s, CH_3), 61.5 (q, $^2J_{CF}$ = 30 Hz, CHCl), 67.2 (s, CHO), 123.5 (q, $^1J_{CF}$ = 280 Hz, CF_3), 126.2 (s, CH arom), 126.6 (s, CH arom), 128.5 (s, CH arom), 130.7 (s, CH arom), 134.0 (s, C arom), 136.7 (s, C arom); IR (neat) 3440 cm^{-1} (ν_{OH}). Anal. Calcd for $C_{10}H_{10}OClF_3$: C, 50.33; H, 4.22. Found: C, 50.35; H, 4.37.

5bI: white crystals; 80% F = 74.5 °C; X-ray see above; ^1H NMR ($CDCl_3$) (cf above the list of the signals), only diastereomer I is observed; ^{13}C NMR ($CDCl_3$) δ 56.0 (s, CH_3O), 61.3 (q, $^2J_{CF}$ = 30 Hz, CHCl), 67.4 (s, CHO), 110.9 (s, CH arom), 121.4 (s, CH arom),

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124.5 (q, $^1J_{CF}$ = 280 Hz, CF_3), 127.3 (s, C arom), 128.2 (s, CH arom), 130.2 (s, CH arom), 156.0 (s, C arom); ^{19}F NMR ($CDCl_3/CFCl_3$) δ -71.7 (d, $^3J_{HF}$ = 7 Hz); IR ($CHCl_3$) 3550 cm^{-1} (ν_{OH}). Anal. Calcd for $C_{10}H_{10}O_2ClF_3$: C, 47.17; H, 3.96. Found: C, 47.48; H, 3.80.

General Procedure for Cyclization of Chlorohydrins 5aI or 5bI. To chlorohydrin **5aI** or **5bI** (0.94 mmol) in anhydrous Et_2O (10 mL) were added powered KOH (8 equiv) and a catalytic amount of 18-crown-6. After being stirred at room temperature for 30 min, the mixture was filtered over silica gel 70-230 mesh (h = 3 cm, ϕ = 7 cm). The silica gel was rinsed with Et_2O (100 mL). The organic phases were combined, and the solvent was removed to give the crude epoxide **1a** or **1b** which was used for the next step without purification.

General Procedure for Opening of Epoxides 1a or 1b. To the crude epoxide **1a** or **1b** (0.94 mmol) in a mixture of $MeOH/H_2O$ (9/2, 10 mL) was added sodium azide (5 equiv) in one fraction. The mixture was stirred under reflux for 10 h. After concentration of the solution (half) Et_2O (100 mL) and water (20 mL) were added. The organic phase was separated and the aqueous phase extracted with Et_2O (2 × 20 mL). The combined ether layers were dried over $MgSO_4$, and the solvent was removed to give the crude compound **6aI** or **6bI**.

6aI: uncolored oil; 75% yield after purification by flash chromatography (h = 20 cm, ϕ = 3 cm, Et_2O/hexane 20/80, R_f = 0.27); ^{1}H NMR ($CDCl_3$) only one isomer was observed, δ 2.40 (s, CH_3), 3.01 (d, 1 H, OH), 4.10 (m, 1 H, CHO), 5.14 (d 1 H), 7.28 (m, 3 H arom), 7.48 (m, 1 H arom); ^{13} NMR ($CDCl_3$) δ 19.7 (s, CH_3), 60.9 (s, CHN_3), 73.0 (q, $^2J_{CF}$ = 30 Hz, CHO), 124.6 (q, $^1J_{CF}$ = 283 Hz, CF_3), 127.4 (s, CH arom), 128.0 (s, CH arom), 129.6 (s, CH arom), 131.7 (s, CH arom), 134.2 (s, C arom), 135.9 (s, C arom); ^{19}F NMR ($CDCl_3/CFCl_3$) δ -77.56 (d, $^3J_{FH}$ = 7 Hz); IR (neat) 3440 (ν_{OH}), 2180 cm^{-1} (νN_3). Anal. Calcd for $C_{10}H_{10}ON_3F_3$: C, 48.98; H, 4.11; N, 17.14. Found: C, 49.10; H, 4.32; N, 16.17.

6bI: uncolored oil; 95% yield after purification by flash chromatography (h = 20 cm, ϕ = 3 cm, Et_2O/hexane 30/70, R_f = 0.30); ^{1}H NMR ($CDCl_3$) only one isomer was observed, δ 2.88 (d, 1 H), 3.89 (s, CH_3), 4.21 (1 H), 5.35 (d, 1 H), 6.95 (d, 1 H arom, ^3J = 7.5 Hz), 7.04 (t,1 H arom, ^{3}J = 7.5 Hz), 7.36 (dd, 1 H arom, ^3J = 7.5 Hz, ^4J = 1.5 Hz), 7.44 (td, 1 H arom, ^3J = 7.5 Hz, ^4J = 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 55.4 (s, CH_3O), 58.6 (s, CHN_3), 71.2 (q, $^2J_{CF}$ = 30 Hz, CHO), 110.6 (s, CH arom), 120.9 (s, CH arom), 123.6 (s, C arom), 124.1 (q, $^1J_{CF}$ = 283 Hz, CF_3), 128.1 (s, CH arom), 130.1 (s, CH arom), 156.1 (s, C arom); IR (neat) 3440 (ν_{OH}), 2120 cm^{-1} (νN_3). Anal. Calcd for $C_{10}H_{10}O_2N_3F_3$: C, 45.98; H, 3.86; N, 16.09. Found: C, 46.19; H, 3.65; N, 15.60.

Supplementary Material Available: Tables of anisotropic thermal parameters (S1), hydrogen atomic positional parameters (S2), and bond distances (S3) and angles (S4) for **5bI** (6 pages). Ordering information is given on any current masthead page.

Phosphonate Analogues of Chorismic Acid: Synthesis and Evaluation as Mechanism-Based Inactivators of Chorismate Mutase

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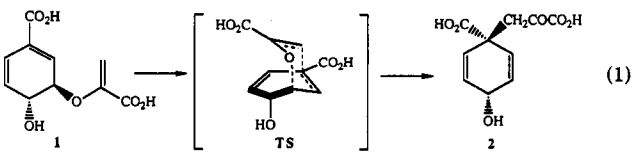
The mechanism of chorismate mutase, the enzyme which catalyzes the Claisen arrangement of chorismic to prephenic acid, remains a fascinating area for bioorganic research. This paper describes the enantioselective synthesis of phosphonochorismic acids **3** and **4**, two potential mechanism-based mutase inactivators, utilizing new transition-metal-catalyzed insertion reactions of tetraalkyl diazophosphonates. Models establish that such systems undergo smooth Claisen rearrangement and that the product acylphosphonates are good acylating agents for amines and alcohols. By contrast, thermolysis of phosphonochorismates **3** and **4** in the presence of enzyme led to *p*-hydroxybenzoic acid, with no trace of [3,3] rearrangement to the corresponding prephenates or phenylpyruvates. The half-life for elimination of **3** was 8.3 h (75° C, 2:1 CD_3OD/D_2O) while for **4** the half-life was 4.3 h. When tested over a wide range of concentrations against the *E. coli* chorismate mutases (so-called T- and P-proteins), neither **3** nor **4** interacted with the enzyme, either as a competitive inhibitor or as a substrate, perhaps reflecting the stringent demands of the rearrangment transition state. Earlier studies strongly suggest that the enol pyruvate carboxyl group is markedly tilted against the carbocyclic ring during [3,3] sigmatropy, and similar flattening of the tetrahedral phosphonate could create unfavorable steric as well as π-π interactions.

Introduction and Background

The biosynthesis of aromatic compounds in bacteria, fungi, and higher plants takes place either from acetate, by the polyketide pathway, or from glucose, by the shikimate pathway. The latter pathway commences with the condensation of erythrose-4-phosphate and phosphoenol pyruvate and proceeds via a sequence of unusually functionalized alicyclic carboxylic acids to the key branch-point intermediate, chorismic acid **1**.[1] Separate pathways from this pivotal substance lead to the aromatic amino acids (via prephenate and anthranilate), the isoprenoid quinones (via *p*-hydroxybenzoate), and folate coenzymes (via *p*-aminobenzoate).

The first committed step in the biosynthesis of phenylalanine and tyrosine involves the [3,3] sigmatropic (Claisen) rearrangement of **1** to prephenic acid **2**, a reaction which is catalyzed by the enzyme chorismate mutase (eq 1). While the nonenzymic rearrangement is unusually fast



(1)

in aqueous solution ($t_{1/2}$ for **1** = 16 h, 30 °C), chorismate mutase accelerates the process (2 × 10^6)-fold (37 °C, pH 7.5).[2] Both the enzymic[3] and nonenzymic[4,5] reactions

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