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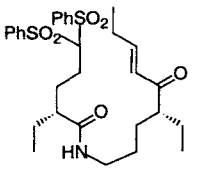
[6] Since the base/oxidant ratio should not exceed 1:1, the amount of hydroxide resulting from the initial oxidation of $K_2[OsO_2(OH)_4]$ to Os^{VIII}, releasing two equivalents of base, was taken into account.

[7] The use of isopropyl cinnamates instead of the methyl esters is preferable in terms of greater stability towards hydrolysis and enhanced regioselectivity under the reaction conditions. As in the case of compounds **1** and **2**, which are quite soluble in the reaction medium, the use of more than 50% (v/v) water may result in slightly increased regioselectivities.



3

[8] H. Becker, K. B. Sharpless, *Angew. Chem.* **1996**, *108*, 447–449; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 448–451: Corrigendum: The Experimental Procedure in this paper should include the following: "Asymmetric dihydoxylations of entries 1–8, and 16 in Tables 1 and 2 were run under buffered conditions in which the reaction is performed as desribed except that $NaHCO_3$ (252 mg, 3 mmol) was added at the beginning of the reaction". Also, in the syntheses of the ligands $(DHQD)_2AQN$ and $(DHQ)_2AQN$, it should be noted that the dihydroquinidine and dihydroquinine were dried over P_2O_5 under vacuum before use. Both $(DHQ)_2AQN$ and $(DHQD)_2AQN$ are commercially available (Aldrich); an improved synthesis will be reported elsewhere.

[9] K. L. Reddy, G. Li, K. B. Sharpless, unpublished results. See also ref. [1d].

[10] Preliminary experiments with other substrates indicate that a reversal of regiochemistry occurs when anthraquinone-derived ligands are used instead of phthalazines.

[11] So far, only a few exceptions to our mnemonic device for the AD have been reported: a) K. J. Hale, S. Manaviazar, S. A. Beak, *Tetrahedron Lett.* **1994**, *35*, 425–428; b) D. J. Krysan, *ibid.* **1996**, *37*, 1375–1376; c) D. L. Boger, J. A. McKie, T. Nishi, T. Ogiku, *J. Am. Chem. Soc.* **1996**, *118*, 2301–2302; d) P. Salvadori, S. Superchi, F. Minutolo, *J. Org. Chem.* **1996**, *61*, 4190–4191; e) K. P. M. Vanhessche, K. B. Sharpless, *ibid.* **1996**, *61*, 7987–7979.

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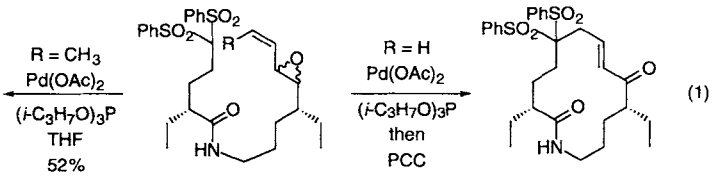
Palladium-Catalyzed Additions of Alkenyl Epoxides to Pronucleophiles: A Synthesis of the Macrolactam Aglycone of Fluviricin B1**

Barry M. Trost,* Marco A. Ceschi, and Burkhard König

The additions of alkenyl epoxides with pronucleophiles catalyzed by palladium constitutes a promising approach for constructing complex molecules.[1–3] However, the facility by which the palladium catalysts effect epoxide rearrangements,[4] which are intramolecular processes, makes their intermolecular capture a challenge. Macrocyclizations, which resemble intermolecular reactions, illustrate the delicate balance [Eq. (1)].



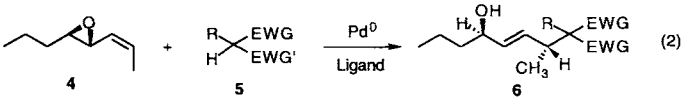
1a, R = H
1b, R = CH_3
2

(1)

Whereas, the simple vinyl epoxide **1a** cyclized smoothly to form the 14-membered ring **2**, addition of a methyl group at the terminus completely suppressed cyclization and led to isomerization of this alkenyl epoxide to the enone **3**.

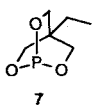
The importance of such terminally substituted alkenyl epoxides stems from their use for chirality transfer to control relative configurations of distal centers. We therefore studied the characteristics of the pronucleophiles that would allow reaction with alkenyl epoxides, in order to provide a synthesis of the aglycone of fluviricin B1[5, 6] that exemplified their use in controlling stereochemistry of distal centers.

To explore the effect of substitution on the palladium-catalyzed addition of pronucleophiles to alkenyl epoxides, we chose the propenyl derivative **4** [Eq. (2)]. The unsubstituted bis(sul-



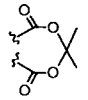
4 **5** **6**

(2)



7

a, R = H, EWG = EWG' = $PhSO_2$
b, R = C_2H_5, EWG = EWG' = $PhSO_2$
c, R = H, EWG = $PhSO_2$, EWG' = CH_3CO
d, R = CH_3, EWG = $PhSO_2$, EWG' = CN
e, R = C_2H_5, EWG, EWG' =



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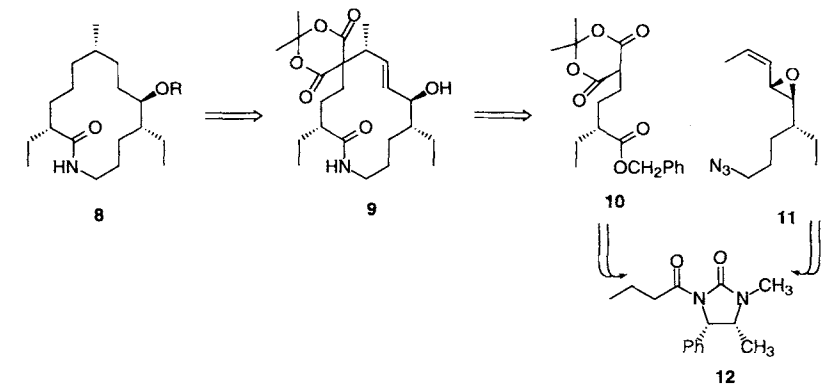
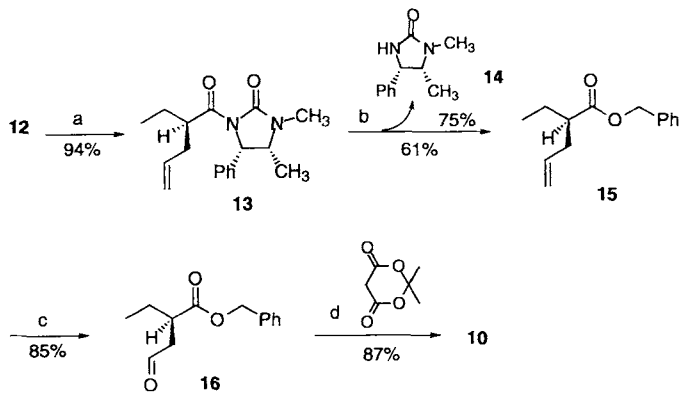
fone) **5a** as pronucleophile reacted smoothly to give the desired alkylation product **6a**[7] ([$(Ph_3P)_4Pd$], THF, reflux, 62%), whereas the monoalkylated derivative **5b** gave none of its corresponding dialkylated derivative **6b**. The unsubstituted ketosulfone **5c** underwent smooth alkylation to afford **6c**[7] ([$(dba)_3Pd_2]\cdot CHCl_3$, **7**, THF, reflux, 55%). More significantly, the substituted cyanosulfone **5d** also participated quite well, yielding the monoalkylated product **6d**[7] ($Pd(OAc)_2$, (i-$C_3H_7O)_3P$, THF, reflux, 55%). The best reaction involved use of a substituted Meldrum's acid (**5e**) as the pronucleophile: alkylation proceeded at room temperature to form the alkylated product **6e**[7] ($Pd(OAc)_2$, (i-$C_3H_7O)_3P$, THF, room temperature, 75%). In each of these cases NMR analysis reveals only one diastereomer, indicating good control of chirality transfer by the palladium catalyst.

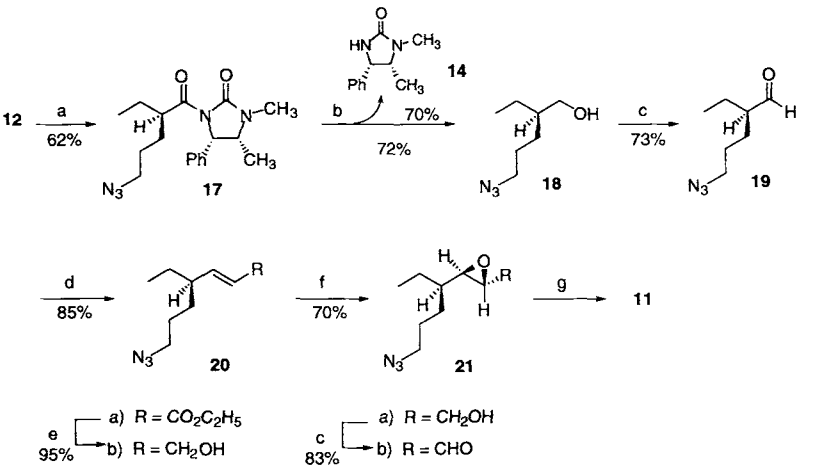
We therefore chose to use Meldrum's acid as the pronucleophile for the synthesis of fluviricin B1 aglycone **8** as outlined in Scheme 1. This target is representative of the fluviricins (macrolactams active against influenza A virus as well as against pathogenic fungi). To use the concept of stereochemical relay via π-allylpalladium species to create the proper configuration at C-5, we required macrocycle **9** as synthetic precursor: bis-decarboxylation and reduction would create **8**. Splitting **9** into **10** and **11** yields two fragments that can both be synthesized from the imidazolidinone **12**, as revealed in Schemes 2 and 3.



Scheme 1. Retrosynthetic analysis of fluviricin B_1 (**8**, R = H).



Scheme 2. Asymmetric synthesis of the pronucleophile **10**. a) Lithium diisopropylamide (LDA), THF, −78 °C, $H_2C{=}CHCH_2Br$; b) $PhCH_2OH$, n-C_4H_9Li, THF, 0 °C; c) O_3, CH_2Cl_2, −78 °C, then Ph_3P; d) NaTeH ($NaBH_4$ + Te), C_2H_5OH, piperidine, HOAc, −30 °C → room temperature.



Scheme 3. Synthesis of the propenyl epoxide **11**. a) LDA, THF, −78 °C, $ICH_2CH_2CH_2N_3$; b) $LiAlH_4$, THF, 0 °C; c) $(COCl)_2$, DMSO, CH_2Cl_2, $(C_2H_5)_3N$, −78 °C; d) NaH, $(C_2H_5O)_2P(O)CH_2CO_2C_2H_5$, NaH, THF, room temperature; e) DIBAL-H, THF, −78 °C; f) 13.5 mol % Ti (Oi-$C_3H_7)_4$, 21 mol % diethyl tartrate ((−)-DET), 4 Å MS, CH_2Cl_2, 0 °C; g) $Ph_3PCH_2CH_3Br$, $KN(SiMe_3)_2$, THF, −78 °C → room temperature.

The stable imidazolidinone **12** was chosen as the chiral auxiliary because of its ease of access from ephedrine and its excellent diastereoselectivity in alkylations.[8] The alkylations to form **13**[7] and **17**[7] gave only one diastereomer detectable by NMR spectroscopy (>95% *de*). Either deacylation with lithium benzyloxide to **15**[7] or, remarkably, reduction with $LiAlH_4$ returned the chiral auxiliary **14**[7] in good yields. The monosubstituted Meldrum's acid **10** was best prepared by reductive alkylation of aldehyde **16** with sodium hydrogen telluride, generated in situ, under Knoevenagel conditions.[9]

For the azide half, direct reduction of **17** to aldehyde **19** could be accomplished with diisobutylaluminum hydride (DIBAL-H), but significant racemization accompanied the reduction—consequently, the two-step sequence via alcohol **18** was preferable. Asymmetric epoxidation[10] of the olefination product **20b** required larger amounts of catalyst for good yields, which suggests a low turnover number. On the other hand, only a single diastereomeric epoxide (**21a**) was observed. Olefination of the aldehyde **21b** under standard conditions gave a 7:1 (*Z*):(*E*) ratio of alkenes.

The key Pd-catalyzed alkylation employed a precatalyst generated by mixing [$(dba)_3Pd_2\cdot CHCl_3$] (1.5 mol %) and phosphite **7** (20 mol %) in THF. Sequential addition of equimolar quantities of the alkenyl epoxide **11** and Meldrum's acid **10** gave, after 12 h at room temperature, a 75% yield of the alkylation product **22** (Scheme 4) as a single diastereomer. Thus, chirality transfer occurred completely within experimental error. The assignment of the stereochemistry derived from mechanistic considerations[11] and the successful completion of the total synthesis.

Numerous attempts to effect both alkene hydrogenation and hydrogenolysis of the benzyl ester and azide proved futile. On the other hand, hydrogenolysis of the latter two functionalities did occur with ammonium formate in the presence of Pd/C;[12] though various protocols for the subsequent macrolactamization of the amino acid to give **23** failed, including the use of the Yamaguchi reagent,[13] bromotripyrrolidinophosphonium hexafluorophosphate[14] successfully effected macrolactamization in what may be a generally applicable procedure. The initial

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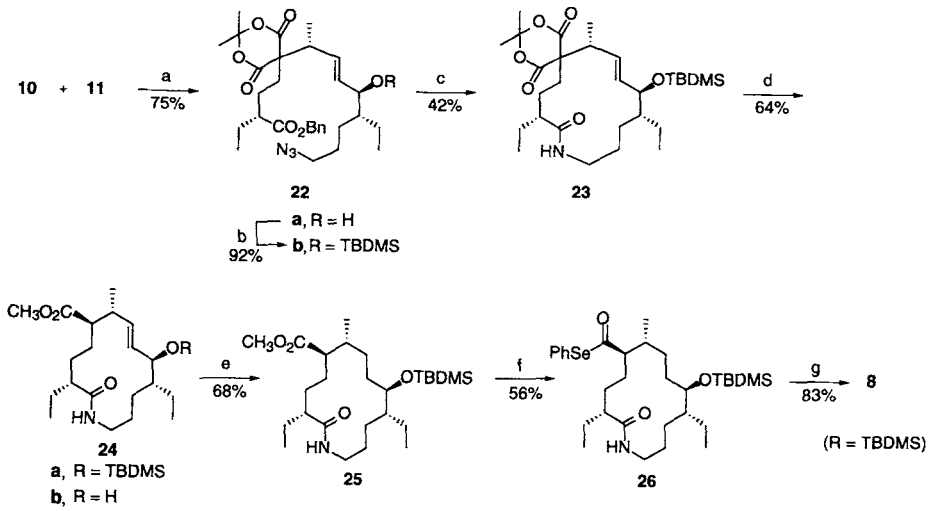
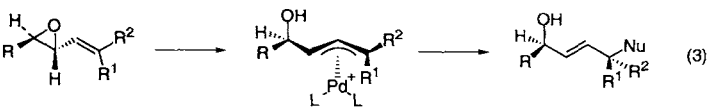


Scheme 4. Synthesis of the fluviricin B_1 aglycon **8**, R = TBDMS. a) See text; b) $TBDMSOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2, 0 °C; c) 1.5% Pd/C, HCO_2NH_4, H_2O, 4 kbar, room temperature, 2. PyBroP, $(iC_3H_7)_2NC_2H_5$, 4-dimethylaminopyridine (DMAP), $PhCH_3$, 83 °C; d) LiOH, CH_3OH, H_2O, 4 kbar, room temperature, then DMSO, 120 °C; e) tetra-*n*-butylammonium fluoride (TBAF), THF, 0 → 40 °C, H_2 (1 atm), 10% Pd/C, C_2H_5OH, room temperature; $TBDMSOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2, 0 °C; f) LiOH, KCN, CH_3OH, H_2O, THF, room temperature; $PhOP(O)Cl_2$, $(C_2H_5)_3N$, THF, 0 °C, then PhSeH, $(C_2H_5)_3N$, THF, 0 °C; g) $(C_4H_9)_3SnH$, azobisisobutyronitrile (AIBN), xylene, 175 °C.

decarboxylation gave a single diastereomeric monoester (**24a**, assigned based upon molecular modeling).[15] The double bond in silyl ether **24a** proved resistant to hydrogenation; however, allyl alcohol **24b** was reduced smoothly to give **25** after resilylation. Inability to form the ester from *N*-hydroxypyridine-2-thione[15] led to an alternative to decarboxylation for the removal of the remaining ester.[16] The acyl selenide **26** underwent a smooth decarbonylation[17] to the silyl ether of fluviricin B1, which was identical in every respect to an authentic sample (for physical data see Table 1). The monosilyl ether **8** (R = TBDMS) has previously been desilylated to fluviricin B1 aglycone **8** (R = H).

This reaction of terminally substituted vinyl epoxides provides a useful approach to chirality transfer. The selection of the pronucleophile is more critical than for unsubstituted vinyl epoxides. For a trisubstituted anion, steric hindrance appears to be the dominating influence as illustrated by the success of cyano-stabilized anions or those derived from Meldrum's acid. The stereochemical memory derives from its temporary storage as the π-allylpalladium species [Eq. (3)]. In this way, vicinal stereochemistry readily translates into 1,4-stereochemistry. The synthesis of the aglycone of the fluviricin family illustrates the utility of this methodology. The sequence also demonstrates some of the unusual properties of this ring system. The difficulty in hydrolyzing and decarboxylating the Meldrum's acid unit and in hydrogenating of the double bond illustrate two interesting aspects. In addition, the functionality present allows access to analogues. This convergent strategy in which the two halves are joined by a palladium-catalyzed alkylation and an amide formation may prove to be generally useful.



(3)

Table 1. Selected physical data of the important compounds.

8: (R = TBDMS) $[\alpha]_D^{25}$ +12 (c = 0.02, CH_2Cl_2). M.p. 187–188 °C. IR (neat): $\tilde{\nu}$ = 3448, 1633, 1553, 1463, 1381 cm^{-1}; ^1H NMR (400 Hz, C_6D_6): δ = 4.38 (dd, J = 8.7, 3.0 Hz, 1H), 3.77 (dddd, J = 23.7, 11, 4, 2 Hz, 1H), 3.51 (m, 1H), 2.44 (m, 1H), 1.98–1.10 (m, 21H), 1.04 (s, 9H), 0.97 (d, J = 7 Hz, 3H), 0.89 (t, J = 7.4 Hz, 3H), 0.82 (t, J = 7.5 Hz, 3H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ = 174.8, 73.1, 50.9, 42.9, 38.6, 34.8, 34.2, 31.5, 28.6, 27.0, 26.2, 25.9, 25.2, 24.4, 21.1, 20.9, 18.4, 12.5, 9.5, 8.1, 5.7, 4.7.

10: $[\alpha]_D^{25}$ 1.97 (c = 1.59, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 1780, 1730 (broad), 1610, 1595, 1500, 1457 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.43–7.30 (m, 5H), 5.18 (s, 2H), 3.53 (t, J = 9.3 Hz, 1H), 2.48–2.32 (m, 2H), 2.19–2.03 (m, 2H), 1.75 (d, J = 9.3 Hz, 6H), 1.95–1.50 (m, 2H), 0.90 (t, J = 12.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.5, 165.3, 136.1, 128.3, 128.3, 105.0, 66.4, 47.1 46.1, 28.6, 26.8, 25.2, 24.1, 11.7.

11: $[\alpha]_D^{25}$ −10.5 (c = 0.74, $CHCl_2$). IR (neat): $\tilde{\nu}$ = 2096, 1650, 1480, 1380 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.77 (m, 1H), 5.05 (m, 1H), 3.39 (dd, J = 7.1, 2.0 Hz, 1H), 3.27 (m, 2H), 2.61 (dd, J = 8.1, 2.2 Hz, 1H), 1.81 (dd, J = 7.0, 1.8 Hz, 3H), 1.75–1.20 (m, 7H), 0.95 (t, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 131.3, 128.3, 63.6, 53.9, 51.9, 42.6, 28.1, 27.0, 25.5, 13.5, 11.2.

22a: $[\alpha]_D^{25}$ +13.3 (c = 0.8, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3528, 2099, 1770, 1737, 1456 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35 (m, 5H), 5.68–5.48 (m, 2H), 5.10 (s, 2H), 4.10 (bs, 1H), 3.25 (t, J = 7.5 Hz, 2H), 2.80 (m, H), 1.90 (m, 2H), 1.70 (s, 3H), 1.63 (s, 3H), 1.62–1.12 (m, 12H), 1.10 (d, J = 7.3 Hz, 3H), 0.88 (t, J = 7 Hz, 3H), 0.83 (t, J = 7 Hz, 3H) (J = 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.2, 169.0, 168.2, 136.5, 135.3, 131.2, 129.1, 128.8, 120.8, 106.3, 74.1, 66.8, 58.7, 52.3, 47.3, 47.2, 45.6, 33.6, 31.4, 29.6, 28.2, 27.5, 27.0, 25.2, 22.7, 17.6.

23: $[\alpha]_D^{25}$ +32 (c = 0.5, CH_2Cl_2). M.p. 139 °C. IR (neat): $\tilde{\nu}$ = 1783, 1735, 1671 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.52 (dd, J = 16.8, 10 Hz, 1H), 5.32 (dd, J = 16.8, 10 Hz, 1H), 5.30 (m, 1H), 3.88 (m, 1H), 3.77 (t, J = 9.6 Hz, 2H), 2.93 (m, 1H), 2.75 (m, 1H), 2.1 (dt, J = 14, 4.8 Hz), 1.72 (s, 3H), 1.75 (s, 3H), 1.40 (d, J = 7 Hz, 3H), 0.85 (s, 9H), 0.80 (m, 6H), 0.0 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.3, 172.6, 168.8, 139.9, 133.5, 108.1, 59.9, 52.8, 50.5, 46.7, 40.8, 38.3, 33.1, 31.4, 31.2, 29.1, 28.5, 27.9, 26.9, 21.6, 20.2, 19.5, 14.2, 10.4, −1.3, −2.7.

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Keywords: allylic alkylations · asymmetric synthesis · chirality transfer · macrolactamization · palladium

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The Surprising Crystal Packing of Chlorinefluoride**

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Dedicated to Professor Günter Schmid on the occasion of his 60th birthday

Interhalogen compounds are of special interest both from the synthetic and the theoretical standpoint. They are widely used as very strong oxidizing agents, and some of them, for example halogen fluorides, are typical amphoteric systems that exhibit Lewis acid Lewis base interactions in the liquid and solid states.[1, 2] As ions or neutral species they have become important objects of numerous structural investigations as they serve as model compounds in the studies of the chemical bond.[3, 4] Thus, the molecular structures of XF_3, XF_5 (X = Cl, Br, I), and some other polyhalogens are often considered as typical examples for the application of the VSEPR (Valence Shell Electron Pair Repulsion) model for describing molecular geometry.[4]

Strong intermolecular interactions between the halogen atoms (F···Cl, F···Br) were found in the crystals of neutral halogen fluorides, for example in the two polymorphic modifications of ClF_3[5] and BrF_3.[6] However, no short F···F contacts were observed in these structures. In most cases fluorine atoms act as bridging atoms, or do not participate in the intermolecular (interionic) interactions.

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In general, X-ray diffraction studies of neutral interhalogen compounds are rather rare, because most of them are reactive and low-melting compounds, which causes difficulties in obtaining single crystals. Nevertheless, these studies are of great interest because they provide access to important information about the electronic nature of the intermolecular interactions between halogen atoms.

We report herein the molecular and crystal structure of the simplest interhalogen compound, chlorine monofluoride, ClF, at −188 °C. To the best of our knowledge, the solid-state structure of ClF is the only structure of the well-known family of halogen monofluorides that has ever been determined. There are a few objective reasons for this. Halogen monofluorides have very low melting and boiling points (e.g. ClF: −155.6 and −100.1 °C, respectively), and together with their very high oxidizing activity and moisture sensitivity this makes these compounds extremely difficult to handle. For example, ClF reacts readily with glass, so its storage and crystal growth in the usual thin-walled glass capillaries from the melt is very difficult. Furthermore, the crystallization point, which is essentially lower than the melting point, is almost at the limit of liquid nitrogen low-temperature devices for single-crystal diffractometers. All this was considered as a challenge to our developments in crystallization and low-temperature techniques. For the crystal packing of ClF we expected something similar to that observed for α-,[7] β-ICl[8] or IBr,[9] that is zigzag or herringbone patterns, governed by the intermolecular dipole interactions, with chlorine atoms surrounded by one or more fluorine atoms.

Surprisingly, the X-ray data show that in the crystal individual ClF molecules form infinite planar ribbons along the screw axis (space group $P2_1/c$), which are characterized by very short intermolecular Cl···Cl contacts (3.070(1) Å) between neighboring molecules (Figure 1). The ribbon planes are inclined to

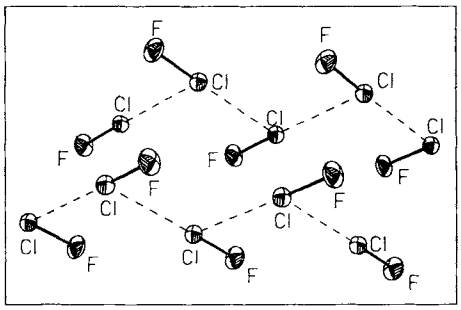

Figure 1. Perspective view of the crystal structure of ClF (ellipsoid plot (50%)), showing two rows of molecules, arranged along the screw axis.

the *a*, *b*, and *c* crystal axes by 74.7, 90, and 179.6°, respectively, and along the *c* axis they are antiparallel. In the ribbon the Cl atoms are arranged in a zigzag fashion, so each atom participates in two (symmetry equivalent) Cl···Cl contacts; the Cl···Cl···Cl angle is 87.5(1)°. One contact is directed along the prolongation of the F–Cl bond (the F–Cl···Cl angle is 178.8(1)°), and the other one is perpendicular to the same F–Cl bond (the corresponding angle is 93.5(1)°) (Figure 2). Between the ribbons there are only F···F contacts for which the shortest distance is 2.92 Å, which is a normal value for a van der Waals interaction.[10]

To our knowledge, the Cl···Cl contacts in the crystal of ClF are the shortest among the known Cl···Cl intermolecular distances in molecular crystals. In a recent study[10] a value of 3.50 Å is assumed as a typical distance for Cl···Cl contacts. In