Allylations of [(Diethoxyphosphinyl)difluoromethyl]zinc Bromide as a Convenient Route to 1,1-Difluoro-3-alkenephosphonates

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The reaction of [(diethoxyphosphinyl)difluoromethyl]zinc bromide, $(EtO)_2P(O)CF_2ZnBr$, with allylic halides was found to be catalyzed by CuBr and represents a synthetically viable and convenient route to the title phosphonates. However, the reaction could not be readily extended to allyl acetate. Propargyl chloride gave predominantly an allenic product, diethyl 1,1-difluoro-2,3-butadienephosphonate (4). The regiochemistry of the allylation reactions is controlled by steric factors such that the $(EtO)_2P(O)CF_2$ moiety is bound to the least sterically hindered allylic terminus. Evidence is presented for an S_N2 vs S_N2' type mechanistic interpretation, rather than the involvement of a symmetrical (π-allyl)Cu(III) intermediate and an oxidative addition/reductive elimination type mechanism.

The preparation of a majority of the numerous reported organic phosphonates has been accomplished by the general and versatile Michaelis–Arbuzov reaction. The beauty of the Michaelis–Arbuzov reaction is that it serves as a simple, one-step method to directly introduce a carbon–phosphoryl bond into an organic compound. However, the generality of the Michaelis–Arbuzov reaction is lost with regard to the preparation of α,α-difluorinated alkanephosphonates, as fluorocarbons do not generally undergo the necessary S_N2 type reaction.

Some α,α-difluorinated alkanephosphonates have been synthesized directly via the radical oligomerization of tetrafluoroethene and dialkyl phosphite,[2] as well as by the reaction of trimethyl phosphite and 2,3-dichloro-1,1,3,3-tetrafluoropropene.[3] The formation of a phosphoryl–difluoromethyl bond has also been effected through the oxidation of trivalent organofluorine phosphorus compounds. The diiodo(*F*-alkyl)phosphines (formed in the reaction of metallic phosphorus and iodo-*F*-alkanes) were converted to *F*-alkanephosphonic acids by sequential oxidation and hydrolysis.[4-7] The oxidation of trivalent *F*-alkanephosphonites also yielded the *F*-alkanephosphonates.[8]

A number of α,α-difluorinated methanephosphonates have been reported.[9,10] Many of these phosphonates are conveniently prepared from an admixture of trialkyl phosphite and a halogenated fluoromethane. While the process superficially resembles the Michaelis–Arbuzov reaction, a more complicated mechanistic pathway is believed to be involved.[11] There is little credible evidence to suggest that longer chain fluorocarbons may be used in an extension of this reaction.

Organometallic reagents derived from α,α-difluorinated methanephosphonates were used in the preparation of chain-extended phosphonates. The alkylations[12] and acylations[13] of diethyl lithiodifluoromethanephosphonate were necessarily conducted at low temperature in order to prevent the anticipated thermal dissociation of the phosphonate anion.[14] The organocadmium reagent **1** is remarkably stable at room temperature and reacted with a variety of electrophiles such as 3-chloropropene to yield 1,1-difluoro-3-butenephosphonate **3**.[15] The organozinc reagent **2** behaves in a manner similar to that of other perfluorinated alkylzinc halides. It will react only with strong electrophiles such as some acyl halides,[16] halogens, and mineral acids and is not readily hydrolyzed with water. We subsequently found that the reactivity of **2** with acyl halides could be enhanced under the influence of a catalytic amount of cuprous halide salts.[17]

$$(RO)_2P(O)CF_2Br + M \rightarrow (RO)_2P(O)CF_2MX$$

1: M = Cd; X = Br, $CF_2P(O)(OR)_2$

2: M = Zn; X = Br

We now report that the CuBr-augmented organozinc reagent **2** reacts readily with allylic halides, and this reaction constitutes a synthetically viable and convenient route to 1,1-difluorinated 3-alkenephosphonates.

Results

The zinc reagent **2** by itself reacts only slowly with 3-bromo-1-propene (allyl bromide). A solution of **2** and 3-bromo-1-propene gave only minor conversion to **3** after 18 h at room temperature. Complete conversion of **2** was achieved after heating of the same solution for 13 h at 55 °C.

In contrast to the above results, **2** reacts readily with 3-bromo-1-propene in the presence of a catalytic amount of cuprous bromide to yield phosphonate **3**. The reaction was vigorously exothermic, but could be conducted easily on a 0.25-mol scale. Although the allylation was carried out in the absence of a coordinating cosolvent, none of the

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(2) Brace, N. O. *J. Org. Chem.* **1961**, *26*, 3197.
(3) Bisseg, J. E.; Goldwhite, H.; Roswell, D. G. *J. Org. Chem.* **1967**, *32*, 1542–6.
(4) (a) Bennett, F. W.; Emele'us, H. J.; Haszeldine, R. N. *J. Chem. Soc.* **1954**, 3598. (b) Emele'us, H. J.; Haszeldine, R. N. *J. Chem. Soc.* **1955**, 563. (c) Emele'us, H. J.; Smith, J. D. *J. Chem. Soc.* **1959**, 375–81.
(5) Brecht, H.; Hoffmann, D. *Ger. Offen.* 2,110,767 Sept 28, 1972.
(6) Mahler, W.; Burg, A. B. *J. Am. Chem. Soc.* **1958**, *80*, 6161.
(7) Mahmood, T.; Shreeve, J. M. *Inorg. Chem.* **1986**, *25*, 3128–31.
(8) Kato, M.; Yamabe, M. *J. Chem. Soc., Chem. Commun.* **1981**, 1173–4.
(9) (a) Burton, D. J.; Flynn, R. M. *J. Fluorine Chem.* **1977**, *10*, 329–32. (b) Burton, D. J.; Flynn, R. M. *Synthesis* **1979**, 615.
(10) Soborovskii, L. Z.; Baina, N. F. *J. Gen. Chem. USSR* **1959**, *29*, 1144–6 (Engl. transl. 1115–7).
(11) Burton, D. J.; Naae, D.; Flynn, R. M.; Smart, B. E.; Brittelli, D. R. *J. Org. Chem.* **1983**, *48*, 3616–8.
(12) Obayashi, M.; Kondo, K. *Tetrahedron Lett.* **1982**, *23*, 2323–6.
(13) Blackburn, G. M.; Brown, D.; Martin, S. J. *J. Chem. Res., Synop.* **1985**, 92–3.
(14) Burton, D. J.; Flynn, R. M. *J. Fluorine Chem.* **1980**, *15*, 263.
(15) Burton, D. J.; Shin-ya, S.; Takei, R. *J. Fluorine Chem.* **1981**, *18*, 197–202.
(16) Burton, D. J.; Ishihara, T.; Maruta, M. *Chem. Lett.* **1982**, 755–8.
(17) (a) Burton, D. J.; Sprague, L. G. *J. Org. Chem.* **1988**, *53*, 1523–7. (b) Burton, D. J.; Sprague, L. G.; Pietrzyk, D. J.; Edelmuth, S. H. *J. Org. Chem.* **1984**, *49*, 3437–8.

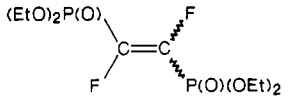
0022-3263/89/1954-0613$01.50/0

Table I. Cuprous Bromide Catalyzed Reaction of $(EtO)_2P(O)CF_2ZnBr$ with Selected Allylic Halides

entry no.	allylic halide	product	yield, %
1	$ClCH_2CH{=}CH_2$	$(EtO)_2P(O)CF_2CH_2CH{=}CH_2$, **3**	– (87)[a]
2	$BrCH_2CH{=}CH_2$	$(EtO)_2P(O)CF_2CH_2CH{=}CH_2$, **3**	47
3	$BrCH_2CBr{=}CH_2$	$(EtO)_2P(O)CF_2CH_2CBr{=}CH_2$, **6**	52
4	$BrCH_2CH{=}CHCH_3$	$(EtO)_2P(O)CF_2CH_2CH{=}CHCH_3$, **7**	49
5	$CH_2{=}CHCHClCH_3$	$(EtO)_2P(O)CF_2CH_2CH{=}CHCH_3$, **7**	76
6	$ClCH_2CH{=}C(CH_3)_2$	$(EtO)_2P(O)CF_2CH_2CH{=}C(CH_3)_2$, **9**	43
7	$ClCH_2CH{=}CHPh$	$(EtO)_2P(O)CF_2CH_2CH{=}CHPh$, **10**	55
8	$BrCF_2CH{=}CH_2$	$(EtO)_2P(O)CF_2CH_2CH{=}CF_2$, **11**	55
9	$ClCD_2CH{=}CH_2$	$(EtO)_2P(O)CF_2CH_2CH{=}CD_2$, **14**	– (69)[a]
		$(EtO)_2P(O)CF_2CD_2CH{=}CH_2$, **15**	– (28)[a]

[a] ^{19}F NMR spectroscopic yield vs benzotrifluoride.

dimeric decomposition product, (*E*)- or (*Z*)-1,2-difluoroethenediylbisphosphonate, was observed.



Allylic chlorides also proved to be efficacious reaction substrates. Little or no qualitative difference between the reactions of **2** with allylic bromides or allylic chlorides was apparent. The reaction of 3-chloro-1-propene with **2** in the presence of cuprous bromide also yielded phosphonate **3** (Table I).

$$2 + XCH_2CR{=}CH_2 \xrightarrow{CuBr} (EtO)_2P(O)CF_2CH_2CR{=}CH_2$$

3: X = Br, Cl; R = H
6: X = R = Br

Allyl acetate proved to be a very poor reactant with the CuBr-catalyzed organozinc **2**. Even with the addition of DMF as a coordinating cosolvent, which allylic halides did not require, the reaction was largely incomplete after 25 h. The addition of 10% of an equivalent of CuBr had only effected a 5% yield to phosphonate **3** after 25 h, while 20% of an equivalent of CuBr had effected a 9% yield to **3** in the same amount of time.

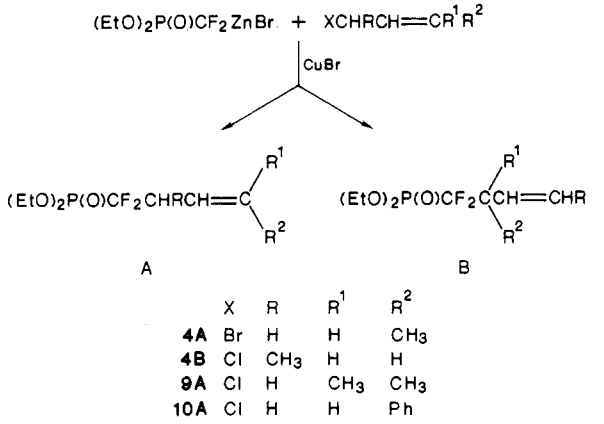
Propargyl chloride reacted readily with organozinc **2** in the presence of a catalytic amount of CuBr to yield a reaction mixture that contained 86% diethyl 1,1-difluoro-2,3-butadienephosphonate (**4**) and 6% diethyl 1,1-difluoro-3-butynephosphonate (**5**). The first product was produced by an S_N2 type reaction. Neither product could be isolated as the reaction mixture decomposed violently on attempted distillation, a phenomenon also associated with other fluorinated allenes.[18]

$$2 + HC{\equiv}CCH_2Cl \xrightarrow{CuBr} \underset{\mathbf{4}}{(EtO)_2P(O)CF_2CH{=}C{=}CH_2} + \underset{\mathbf{5}}{(EtO)_2P(O)CF_2CH_2C{\equiv}CH}$$

2,3-Dibromo-1-propene reacted with **2** in the presence of a catalytic amount of cuprous bromide to yield only diethyl 1,1-difluoro-3-bromo-3-butenephosphonate (**6**). None of the isomer resulting from substitution at the vinylic position was observed. This result indicates that the reaction of cuprous bromide catalyzed **2** occurs much faster with an allylic halide than with a vinylic halide.

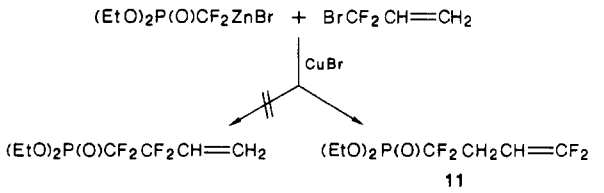
The products **3** and **6** are incapable of yielding any regiochemical information on the reaction of **2** with allylic halides. In the cases studied where meaningful regiochemical data could be collected, only one regioisomer was formed. The regioisomer that was formed in all of the cases studied is the one that results from the substitution of the (difluoromethylene)phosphoryl moiety onto the least substituted carbon atom of the allylic system, as illustrated in Scheme I.

Scheme I



	X	R	R^1	R^2
4A	Br	H	H	CH_3
4B	Cl	CH_3	H	H
9A	Cl	H	CH_3	CH_3
10A	Cl	H	H	Ph

Scheme II



Comparison of the products obtained from the reaction of 3-chloro-1-butene or 1-bromo-2-butene with **2** and catalytic cuprous bromide did show that the products obtained from these reactions, diethyl 1,1-difluoro-3-pentenephosphonate (**7**), were identical. The other possible regioisomer, diethyl 1,1-difluoro-2-methyl-3-butenephosphonate (**8**), was not observed.

1-Chloro-3-methyl-2-butene reacted with **2** in the presence of catalytic CuBr to produce diethyl 1,1-difluoro-4-methyl-3-pentenephosphonate (**9**). Similarly, the reaction of **2** and (*E*)-cinnamyl chloride in the presence of catalytic CuBr yielded diethyl (*E*)-1,1-difluoro-4-phenyl-2-butenephosphonate (**10**).

The ^{19}F NMR characterization of **10** did show a doublet of triplets at −110.8 ppm with a $^2J_{F,P}$ coupling constant of 106 Hz, and a vicinal $^3J_{F,H}$ constant of 18 Hz. The ^1H NMR spectroscopic coupling constant of 15.9 Hz between the vinylic hydrogens establishes the *E* stereochemistry.[19]

The organozinc reagent **2** reacted with 3-bromo-3,3-difluoropropene in the presence of catalytic CuBr to yield only one regioisomer, diethyl 1,1,4,4-tetrafluoro-3-bu-

(18) Coe, P. L.; Milner, N. E. *J. Organomet. Chem.* **1974**, *70*, 147–52.

(19) Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon Press: New York, 1969; Chapter 4.

tenephosphonate (11) (Scheme II). None of the other regioisomer, diethyl 1,1,2,2-tetrafluoro-3-butenephosphonate, was observed in the reaction mixture by ^{19}F NMR spectroscopic analysis.

The phosphonate 11 was unambiguously characterized by a combination of spectral techniques and provided a satisfactory elemental analysis. The ^{19}F NMR spectrum showed the $-P(O)CF_2-$ resonance as a doublet of triplets at −112.1 ppm. The phosphorus–fluorine coupling constant was observed as 106 Hz, with a vicinal fluorine–hydrogen coupling constant of 19 Hz. Two additional fluorine resonances were observed at −84.8 and −88.6 ppm and are attributable to nonequivalent vinyl fluorines. In the infrared spectrum, a strong absorption band was observed at 1745 cm^{-1}, in agreement with the presence of the $CH{=}CF_2$ group.[20]

Discussion

A possible mechanistic explanation for the above results invokes an S_N2 vs S_N2' type mechanism. The steric demands of the organometallic reagent may make it so cumbersome that nucleophilic attack must be on the requisite least sterically hindered allylic carbon. In the case of 1-bromo-2-butene, an S_N2 attack of **2** on the primary carbon that bears the halogen would yield the observed product **7**, while an S_N2' attack at the olefinic carbon to yield **8** is excluded. The complementary reaction of **2** with 3-chloro-1-butene also yields **7** due to steric constraints.

Reactions of organocopper reagents with allylic substrates have been generally rationalized in terms of an S_N2 vs an S_N2' type reaction.

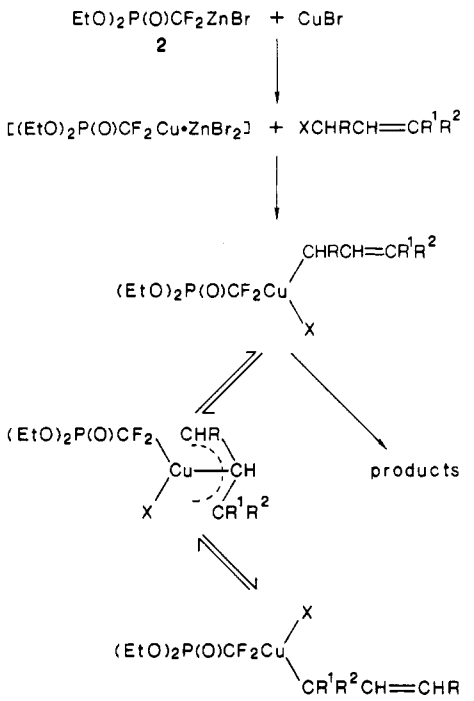
In most cases, reaction of an organocopper reagent with an allylic electrophile may result in two different regioisomeric products[21] in contrast to the results reported here.

Similar stereoselective results have been described by Savignac and co-workers[22] in a report with [(diethoxyphosphinyl)methyl]copper, $(EtO)_2P(O)CH_2Cu$ (**12**). The difference in reactivity between the fluorinated and nonfluorinated cuprous salt augmented organometallic reagents would be expected to be electronic in nature rather than steric, given that hydrogen and fluorine atoms bonded to carbon are roughly sterically equivalent.

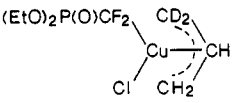
The regiochemical results of the reactions of **12** or cuprous bromide mediated **2** with the same allylic systems are identical. These results would support any mechanism in which steric factors maintain an important role. As differences between two bimolecular nucleophilic substitution reactions seem to be due chiefly to steric factors rather than electronic factors, these results would especially support a nucleophilic substitution type reaction.

A mechanistic interpretation other than a highly discriminatory nucleophilic substitution is possible. Currently, oxidative addition/reductive elimination mechanisms are popular in the explanation of organocopper chemistry. Symmetrical (π-allyl)copper(III) complexes have been postulated as reaction intermediates.[23] Oxidative addition of an allylic halide to an intermediate cuprous complex would yield a d^{10} allylic complex which would be expected to exist in a number of η^1 and η^3 isomeric structures, as illustrated in Scheme III. Reductive elimination of two organic ligands from an n^1 isomer would result in the observed products.

Scheme III



In order to test this hypothesis, we reacted **2** and 3-chloro-*3,3-d*$_2$-propene with a catalytic amount of CuBr. If the reaction proceeded through (π-allyl)copper intermediate **13**, then the difluoromethylene moiety would not be



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able to discriminate significantly between the terminal allylic carbons based on either steric or electronic effects. It should be expected that the product distribution from this experiment would consist of a 50:50 mixture of isomeric d_2-butenephosphonates.

The experimentally determined distribution was found to be 29:71 respectively, in a 97% ^{19}F NMR spectroscopic yield. Examination of the reaction mixture by ^2H NMR spectroscopy revealed two very broad resonance signals (~15 Hz at half-height) with normalized integration of 65% and 35%, respectively. The larger of these signals was recorded at 4.67 ppm and was assigned to **14**. The smaller of the two signals was recorded at 2.35 ppm and was assigned to **15**.

$$(EtO)_2P(O)CF_2ZnBr + ClCD_2CH{=}CH_2 \xrightarrow{CuBr} (EtO)_2P(O)CF_2CH_2CH{=}CD_2 + (EtO)_2P(O)CF_2CD_2CH{=}CH_2$$

14, 71% **15**, 29%

These results are similar to those obtained by Magid and Welch[24] who reported that the nucleophilic reaction of phenyllithium with 3-chloro-*3,3-d*$_2$-1-propene yielded a

(20) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*; John Wiley & Sons: New York, 1981; pp 108–9.

(21) (a) Ochiai, H.; Tamaru, Y.; Tsubaki, K.; Yoshida, Z. *J. Org. Chem.* **1987**, *52*, 4418–20. (b) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 2318–25. (c) Alexakis, A.; Cahiez, G.; Normant, J. F. *Synthesis* **1979**, 826–30. (d) van Mourik, L.; Pabon, H. J. J. *Tetrahedron Lett.* **1978** 2705–8. (e) Bourgain-Commercon, M.; Normant, J. F.; Villieras, J. *J. Chem. Res., Synop.* **1977**, 183.

(22) Savignac, P.; Breque, A.; Mathey, F. *Synth. Commun.* **1979**, 487–96.

(23) (a) Keinan, E.; Bosch, E. *J. Org. Chem.* **1986**, *51*, 4006–16. (b) Goering, H. L.; Tseng, C. C. *J. Org. Chem.* **1983**, *48*, 3986–90. (c) Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1984**, *49*, 422–6.

(24) (a) Magid, R. M.; Welch, J. G. *J. Am. Chem. Soc.* **1968**, *90*, 5211–7; (b) *Ibid.* **1966**, *88*, 5681–2.

24:76 ratio of α- to γ-substituted products. This similarity of their results to our own suggests that a common mechanistic process is involved. Thus, the role of an oxidative addition/reductive elimination type mechanism must necessarily be ruled out, and this indicates that substitution at the γ-allylic carbon is favored over α-substitution.

In conclusion, we present a convenient and practical regiospecific synthesis of a variety of 1,1-difluoro-3-alkenephosphonates. The reaction provides substitution of the phosphoryl functionality onto the least sterically hindered allylic carbon and is proposed to involve an S_N2/S_N2' type mechanism.

Experimental Section

General. The reaction flasks and other glass equipment were stored in an oven at 130 °C overnight and assembled in a stream of dry nitrogen. All boiling points were determined during fractional distillation by means of a partial immersion thermometer and are uncorrected. NMR spectra were recorded on a JEOL FX90-Q multinuclear spectrometer or, where noted, on a Bruker WM360X spectrometer. ^{19}F NMR spectra are referenced against internal $CFCl_3$, ^1H NMR spectra against internal tetramethylsilane, and ^{31}P NMR spectra against an external 85% H_3PO_4 capillary. ^{31}P NMR spectra were broadband decoupled from hydrogen nuclei. IR spectra were recorded as thin films on a Beckman Acculab 8 grating IR spectrometer.

Materials. Diethyl bromodifluoromethanephosphonate was prepared by the method of Flynn.[9a] Monoglyme (MG) was obtained from the Ansul Chemical Co., Marinette, WI, and was purified and dried by distillation from a sodium benzophenone ketyl. Cuprous bromide was obtained from Aldrich Chemical Co. and was purified by a method similar to that of Osterlof.[25] Zinc powder was activated by washing with dilute HCl and then distilled water and dried in vacuo overnight at 120 °C.

[(Diethoxyphosphinyl)difluoromethyl]zinc Bromide (2). A 250-mL round-bottomed flask equipped with a reflux condenser, a nitrogen bubbler, and a Teflon-coated spin bar was placed in a water bath. The flask was charged with acid-washed zinc powder (16.3 g, 0.25 g-atom) and 125 mL of dry monoglyme. Then 66.7 g (0.25 mol) of diethyl bromodifluoromethanephosphonate was added slowly via a constant addition funnel in order to avoid a vigorous exothermic reaction. After being stirred overnight at room temperature, the solution was filtered through a Schlenk funnel (medium frit) to remove any excess zinc powder, leaving [(diethoxyphosphinyl)difluoromethyl]zinc bromide: ^{19}F NMR (MG) −126.1 ppm (d, $^2J_{F,P}$ = 89 Hz); ^{31}P NMR (MG) 14.1 ppm (t); ^{13}C NMR (MG, undecoupled) 16.04 (d, CH_3, $^1J_{C,H}$ = 127 Hz), ~58–59 (CH_2O, masked by monoglyme solvent), 140.51 ppm (td, CF_2, $^1J_{C,F}$ = 290 Hz, $^1J_{C,P}$ = 119 Hz).

Diethyl 1,1-Difluoro-3-butenephosphonate (3). In a representative reaction, a round-bottomed flask was connected to a nitrogen bubbler and was equipped with a Teflon-coated spin bar. To the flask was added a Schlenk-filtered (medium frit) solution of [(diethoxyphosphinyl)difluoromethyl]zinc bromide which had been prepared via the above procedure. To this solution was added CuBr (0.14 g, 0.001 mol), followed by 3-bromopropene (22 mL, 31 g, 0.25 mol) in two equal portions in order to prevent a vigorous exotherm. After stirring at room temperature for 12 h, the volume of the solution was reduced to approximately one-half by rotary evaporation. The reaction mixture was washed with 100 mL of water, and the water layer was extracted thrice with 100 mL of CH_2Cl_2. The organic phases were combined, dried over anhydrous Na_2SO_4, decanted, concentrated by rotary evaporation, and flash distilled. Redistillation give 26.6 g (0.116 mol, 47%, 97% GLPC purity) of diethyl 1,1-difluoro-3-butenephosphonate: bp 34 °C (0.02 mmHg); n^{24} = 1.4083; ^{19}F NMR −111.7 ppm (dt, $^2J_{F,P}$ = 107 Hz, $^3J_{F,H}$ = 20 Hz); ^{31}P NMR 6.62 ppm (t); ^1H NMR 1.36 (t, CH_3CH_2O), $^3J_{H,H}$ = 7.0 Hz), 2.81 (m, CF_2CH_2), 4.25 (dq, 5 lines, CH_2O), 5.17 (br s, vinylic hydrogen), 5.33 (br s, vinylic hydrogen), 5.63–6.09 ppm (m, vinylic hydrogen); IR (neat) 3010 (m), 1650 (w), 1460 (w), 1420 (w), 1395 (w), 1290 (s, P=O), 1180 (s), 1050 (s, ROP), 915 (w), 820 (m), 770 cm^{-1} (w). The physical and spectral data are in agreement with that previously reported.[15]

Anal. Calcd for $C_8H_{15}F_2O_3P$: C, 42.11; H, 6.63. Found: C, 41.96; H, 6.65.

Diethyl 3-bromo-1,1-difluoro-3-butenephosphonate (6): 52% yield (97% GLPC purity); bp 68–69 °C (0.05 mmHg); n^{26} = 1.4435; ^{19}F NMR −112.4 ppm (dt, $^2J_{F,P}$ = 105 Hz, $^3J_{F,H}$ = 18 Hz); ^{31}P NMR 5.90 ppm (t); ^1H NMR 1.38 (t, CH_3CH_2O, $^3J_{H,H}$ = 6.8 Hz), 3.24 (td, CF_2CH_2, $^4J_{H,H}$ = 4.0 Hz), 4.27 (dq, $^3J_{H,H} \sim {}^3J_{P,H}$ = 7.5 Hz), 5.75 (s, vinylic hydrogen), 5.89 ppm (s, vinylic hydrogen); IR (neat) 3010 (m), 2980 (w), 2970 (w), 1630 (m, C=C), 1480 (w), 1445 (w), 1425 (w), 1390 (w), 1370 (w), 1275 (s, P=O), 1175 (s), 1145 (s), 1085 (s), 1035 (vs), 1010 (vs), 980 (s), 790 cm^{-1} (m).

Diethyl 1,1-difluoro-3-pentenephosphonate (7): bp 46–50 °C (0.10 mmHg); n^{24} = 1.4142; ^{19}F NMR −110.4 ppm (dt, $^2J_{P,F}$ = 117 Hz, $^3J_{F,H}$ = 20 Hz); ^{31}P NMR 5.57 ppm (t); ^1H NMR (360 MHz) 1.3762 (t, CH_3CH_2O, $^3J_{H,H}$ = 7.0 Hz), 1.7173 (dtd, 8 lines, C=CHCH_3, $^3J_{H,H}$ = 6.4 Hz, $^4J_{H,H} \sim {}^5J_{H,H}$ = 1.3 Hz), 2.5767 (m, CF_2CH_2), 4.25 (dq, 5 lines, CH_2O, $^3J_{P,H} \sim {}^3J_{H,H}$ = 7.5 Hz), 5.4522 (dtq, CH_2CH=, $^3J_{H,H}$ = 15.3 Hz, $^3J_{H,H}$ = 7.1 Hz, $^4J_{H,H}$ = 1.7 Hz), 5.6804 ppm (dqt, =CHCH$_3$, $^3J_{H,H}$ = 15.3 Hz, $^3J_{H,H}$ = 6.4 Hz, $^4J_{H,H}$ = 1.3 Hz); IR (neat) 2990 (m), 2970 (w), 2960 (w), 1420 (w), 1380 (w), 1350 (w), 1250 (s), 1140 (m), 1080 (w), 950 cm^{-1} (s).

Anal. Calcd for $C_9H_{17}F_2O_3P$: C, 44.63; H, 7.08. Found: C, 44.72; H, 6.76.

Diethyl 1,1-Difluoro-4-methyl-3-pentenephosphonate (9). A round-bottomed flask was connected to a nitrogen bubbler and was equipped with a Teflon-coated spin bar. To the flask was added a Schlenk-filtered solution of [(diethoxyphosphinyl)difluoromethyl]zinc bromide which had been prepared from diethyl bromodifluoromethanephosphonate (26.7 g, 0.10 mol), acid-washed zinc powder (6.6 g, 0.10 g-atom), and 50 mL of dry monoglyme. To the mixture was added CuBr (0.2 g, 0.001 mol) followed by 1-chloro-3-methyl-2-butene (10.7 g, 0.10 mol) in a dropwise manner. The reaction mixture turned dark after $^1/_2$ h and was stirred at room temperature overnight. The mixture was filtered through a fritted-glass (medium frit) funnel under aspirator pressure and poured into 100 mL of water, the organic layer separated, and the aqueous layer extracted twice with 50 mL of CH_2Cl_2.

The organic phases were combined and dried over anhydrous Na_2SO_4, decanted, concentrated by rotary evaporation, and flash distilled. Redistillation through a B/R 8T 8-in. spinning band column gave 11.1 g (0.043 mol, 43%, 97% GLPC purity) of diethyl 1,1-difluoro-4-methyl-3-pentenephosphonate and 1.56 g of a sample enriched in an unknown [^{19}F NMR −112.3 ppm (dt, $^2J_{F,P}$ = 110 Hz, $^3J_{F,H}$ = 18 Hz); ^{31}P NMR 6.91 ppm (t)].

Diethyl 1,1-difluoro-4-methyl-3-pentenephosphonate (9): bp 84–88 °C (0.17 mmHg); n^{27} = 1.4224; ^{19}F NMR −111.2 ppm (dt, $^2J_{F,P}$ = 110 Hz, $^3J_{F,H}$ = 20 Hz); ^{31}P NMR 7.27 ppm (t); ^1H NMR (360 MHz) 1.378 (t, 6 H, CH_3CH_2O, $^3J_{H,H}$ = 7.0 Hz), 1.664 (s, 3 H, allylic methyl), 1.767 (s, 3 H, allylic methyl), 2.788 (m, 2 H, CF_2CH_2), 4.258 (dq, 4 H, CH_2O, $^3J_{H,H} \sim {}^3J_{P,H}$ = 7.3 Hz), 5.214 ppm (t, 1 H, vinyl hydrogen, $^3J_{H,H}$ = 6.7 Hz); IR (neat) 3000 (m), 1280 (s, P=O), 1180 (s), 1060 (s), 1040 (s, POR), 990 (w), 920 (w), 820 (w), 780 cm^{-1} (w).

Anal. Calcd for $C_{10}H_{19}F_2O_3P$: C, 46.88; H, 7.47. Found: C, 47.02; H, 7.51.

Diethyl (*E*)-1,1-difluoro-4-phenyl-3-butenephosphonate (10): 55% yield (98% GLPC purity); bp 144–149 °C (0.01 mmHg); n^{22} = 1.4950; ^{19}F NMR −110.8 ppm (dt, $^2J_{F,P}$ = 106 Hz, $^3J_{F,H}$ = 18 Hz); ^{31}P NMR 6.67 ppm (t); ^1H NMR (360 MHz) 1.328 (t, CH_3CH_2O, $^3J_{H,H}$ = 7.1 Hz), 2.980 (tdd, CF_2CH_2, $^3J_{H,H}$ = 7.3 Hz, $^3J_{P,H}$ = 6.2 Hz), 4.239 (dq, 5 lines, CH_2O, $^3J_{P,H} \sim {}^3J_{H,H}$ = 7.2 Hz), 6.185 (dt, CH_2HC=C, $^3J_{H,H}$ = 15.9 Hz), 6.557 (d, C=CHPh), 7.281 ppm (s, C=CHC$_6H_5$); IR (neat) 3010 (m), 2990 (w), 2980 (w), 1500 (w), 1450 (m), 1420 (w), 1395 (m), 1370 (w), 1270 (s, P=O), 1160 (s), 1020 (s, ROP), 965 (s), 740 (m), 690 cm^{-1} (m).

Anal. Calcd for $C_{14}H_{19}F_2O_3P$: C, 55.26; H, 6.29. Found: C, 55.50; H, 6.40.

Diethyl 1,1,4,4-tetrafluoro-3-butenephosphonate (11): 55% yield (97% GLPC purity); bp 110–112 °C (13 mmHg); ^{19}F NMR −84.8 (d, *cis*-HC=CF_2, $^2J_{F,F}$ = 36.6 Hz), −88.6 (dd, *trans*-HC=CF_2, $^3J_{F,H}$ = 23 Hz), −112.1 ppm (dt, CF_2, $^2J_{F,P}$ = 106 Hz, $^3J_{F,H}$ = 19

(25) Osterlof, J. *Acta Chem. Scand.* **1950**, *4*, 375–85.

Hz); ^{31}P NMR 6.29 ppm (t); ^{1}H NMR (360 MHz) 1.390 (t, CH_3, $^{3}J_{H,H}$ = 7.5 Hz), 2.702-2.824 (m, CF_2CH_2), 4.283 (dq, 5 lines, CH_2O, $^{3}J_{H,H} \sim {}^{3}J_{H,P}$ = 7.3 Hz), 4.344 ppm (vinyl H, partially overlapped by resonance at 4.283 ppm); ^{13}C NMR (100 MHz) 15.79 (d, CH_3, $^{3}J_{C,P}$ = 5.6 Hz), 28.02 (tdd, CF_2CH_2, J = 30.7, 11.4, 5.2 Hz), 64.12 (d, CH_2O, $^{2}J_{C,P}$ = 7.0 Hz), 68.51-69.11 (m CH=C), 118.47 (td, CF_2CH_2, $^{1}J_{C,F}$ = 260.7 Hz, $^{1}J_{C,P}$ = 216.2 Hz), 157 ppm (t, C=CF_2, $^{1}J_{C,F}$ = 288.4 Hz); IR (neat) 2995 (m), 2965 (w), 1765 (vs, C=CF_2), 1485 (w), 1455 (w), 1410 (w), 1385 (w), 1290 (s, P=O), 1220 (m), 1180 (s), 1050 (vs, POR), 1000 (m), 880 (w), 815 cm^{-1} (m).

Anal. Calcd for $C_8H_{13}F_4O_3P$: C, 36.38; H, 4.96; F, 28.77. Found: C, 36.44; H, 5.08; F, 28.21.

Reaction of [(Diethoxyphosphinyl)difluoromethyl]zinc Bromide with CuBr and 3-Chloro-3,3-d_2-propene. A hot, oven-dried NMR tube was flushed with dry nitrogen until cool and charged with 0.33 mL (0.3703 g, ~0.0007 mol) of a Schlenk funnel filtered (medium frit) solution of [(diethoxyphosphinyl)difluoromethyl]zinc bromide which had been prepared from diethyl bromodifluoromethanephosphonate (2.67 g, 0.01 mol), acid-washed zinc powder (0.7 g, 0.01 g-atom), and 5 mL of dry monoglyme. To the NMR tube were also added 3-chloro-3,3-d_2-propene[26] (0.0206 g, 0.0003 mol) and CuBr (0.0155 g, 0.0001 mol). The NMR tube was capped and shaken vigorously. An exothermic reaction resulted which lasted for only 5 min. After $2^1/_2$ h, benzotrifluoride was added to the reaction mixture, and the yields of allylated products were determined by ^{19}F NMR spectroscopy to be 69% $(EtO)_2P(O)CF_2CH_2CH{=}CD_2$ and 28% $(EtO)_2P(O)CF_2CD_2CH{=}CH_2$. ^{2}H NMR spectral integration revealed the ratio of products to be 65%/35%, respectively.

Diethyl 1,1-difluoro-4,4-d_2-butenephosphonate (14): ^{19}F NMR (MG) -111.08 ppm (dt, $^{2}J_{F,P}$ = 114.9 Hz, $^{3}J_{F,H}$ = 19.8 Hz); ^{31}P NMR 5.30 ppm (t); ^{2}H NMR (MG) 4.67 ppm (br s).

(26) Magid, R. M.; Fruchey, O. S.; Johnson, W. L. *Tetrahedron Lett.* **1977**, 2999-3003.

Diethyl 1,1-difluoro-2,2-d_2-butenephosphonate (15): ^{19}F NMR (MG) -111.10 ppm (br d, $^{2}J_{F,P}$ = 115.3 Hz); ^{31}P NMR 5.30 ppm (t); ^{2}H NMR (MG) 2.85 ppm (br s).

Reaction of [(Diethoxyphosphinyl)difluoromethyl]zinc Bromide with 3-Chloro-1-propyne (Propargyl Chloride). A round-bottomed flask was connected to a nitrogen bubbler and was equipped with a Teflon-coated spin bar. To the flask was added a Schlenk-filtered (medium frit) solution of [(diethoxyphosphinyl)difluoromethyl]zinc bromide which had been prepared from diethyl bromodifluoromethanephosphonate (53.4 g, 0.20 mol), acid-washed zinc powder (13.1 g, 0.20 g-atom), and 100 mL of dry monoglyme. To this solution were added 3-chloro-1-propyne (14.5 mL, 15 g, 0.20 mol, Aldrich Chemical Co., and CuBr (1.1 g, 0.01 mol). The reaction mixture was stirred for 24 h at room temperature. Analysis by ^{19}F NMR spectroscopy indicated that the mixture consisted of 86% (normalized) diethyl 1,1-difluoro-2,3-butadienephosphonate, 6% diethyl 1,1-difluoro-3-propynephosphonate, and 8% diethyl difluoromethanephosphonate. The inorganic salts were removed by filtration through a fritted-glass funnel (medium frit) under aspirator vacuum; $3^1/_2$ mL of water was added to the filtrate, and the solution was concentrated by rotary evaporation. The attempted flash distillation of the mixture did not yield any distillate, but violently converted the contents of the flask into a black dry solid.

Diethyl 1,1-difluoro-2,3-butadienephosphonate (4): ^{19}F NMR (MG) -105.3 ppm (ddt, $^{2}J_{F,P}$ = 121 Hz, $^{3}J_{F,H}$ = 12 Hz, $^{5}J_{F,H}$ = 7 Hz); ^{31}P NMR 4.20 ppm (t).

Diethyl 1,1-difluoro-3-propynephosphonate (5): ^{19}F NMR (MG) -110.0 ppm (dt, $^{2}J_{F,P}$ = 120 Hz, $^{3}J_{F,H}$ = 18 Hz); ^{31}P NMR 4.60 ppm (t).

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Synthesis of the Cyclodepsipeptide Nordidemnin B, a Cytotoxic Minor Product Isolated from the Sea Tunicate *Tridemnum cyanophorum*[1]

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Nordidemnin B (3), a cyclodepsipeptide isolated from a sea tunicate, was prepared by following a segment strategy which will permit further structural modifications. The non-proteinogenic D-Val-ψ(CHOH)-Gly-HIP subunit was elaborated sequentially by using a β-keto ester preparation via lithium enolate condensation with 2-acyl-3,5-dioxo-4-methyl-1,2,4-oxadiazolidine (acyl-MODD) derivatives. Isopropenyl chlorocarbonate activation was employed for depsipeptide bond formation. Coupling of this subunit with the tetradepsipeptide Z-Thr-(Leu-Pro-MeTyr(Me))-OAll made use of the CuI-promoted *tert*-butyl thioester activation. Macro ring closure was carried out by using BOP reagent and sodium bicarbonate. The total synthesis of nordidemnin B was achieved by coupling the dipeptidyl unit Lac-Pro-D-MeLeu (25) to the cyclic fragment 21 by using BOP methodology. The synthetic compound was identical in every respect with the natural nordidemnin B (3).

Numerous cyclopeptides and linear peptides of natural origin that contain non-proteinogenic amino acids exhibit various important biological activities.[2,3] Didemnins are a family of cyclodepsipeptides first extracted from a Caribbean tunicate during a systematic study of marine natural products to identify antimicrobial and antiviral activity.[4]

(1) Abbreviations and symbols follow the recommendations of IUPAC-IUB Joint Commission on Biochemical Nomenclature (*Eur. J. Biochem.* **1984**, *138*, 9.) In addition, the following abbreviations are used: All, allyl; BOP, (1*H*-1,2,3-benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate; BOP-Cl, *N,N'*-bis(2-oxo-3-oxazolidinyl)phosphonic chloride; COMODD, 2,2'-carbonylbis(3,5-dioxo-4-methyl-1,2,4-oxadiazolidine; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCC, *N,N*-dicyclohexylcarbodiimide; DIEA, diisopropylethylamine; DMAP, 4-(dimethylamino)pyridine; DPPA, diphenyl phosphorazidate; EDCI, 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride; HIP, (2*S*,4*S*)-2,5-dimethyl-3-oxo-4-hydroxyhexanoic acid; Hyv, L-α-isovaleric acid; IPCC, isopropenyl chlorocarbonate; Lac, L-lactic acid; MODD, 3,5-dioxo-4-methyl-1,2,4-oxadiazolidine; TEA, triethylamine; TFA, trifluoroacetic acid.

(2) (a) Wasylyk, J. M.; Biskupiak, J. E.; Costello, C. E.; Ireland, C. M. *J. Org. Chem.* **1983**, *48*, 4445. (b) Zabriskie, T. M.; Klocke, J. A.; Ireland, C. M.; Marcus, A. H.; Molinski, T. F.; Faulkner, D. J.; Xu, C.; Clardy, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 3123. (c) Ishida, T.; Tanaka, M.; Nabae, M.; Inoue, M. *J. Org. Chem.* **1988**, *53*, 107.

(3) Petit, G. R.; Kamano, Y.; Herald, C. L.; Tuinman, A. A.; Boettner, F. E.; Kizu, A.; Schmidt, J. M.; Baczynskyj, L.; Tomer, K. B.; Bontems, R. J. *J. Am. Chem. Soc.* **1987**, *109*, 6863.

(4) Rinehart, K. L., Jr.; Shaw, P. D.; Shield, L. S.; Gloer, J. B.; Harbour, G. C.; Moustapha, E. S.; Samain, S.; Schwartz, R. E.; Tymiak, A. A.; Weller, D. L.; Carter, G. T.; Munro, M. H.; Hugues, R. G., Jr.; Renis, H. E.; Swynenberg, E. B.; Stringfellow, D. A.; Vavra, J. J.; Coats, J. H.; Zurenco, G. E.; Kuentzel, S. L.; Li, L. H.; Bakus, G. J.; Brusca, R. C.; Craft, L. L.; Young, D. N.; Connor, J. L. *Pure Appl. Chem.* **1981**, *53*, 795.

0022-3263/89/1954-0617$01.50/0