Stereoselective Synthesis of Highly-Functionalized Cyclohexene Derivatives Having a Diethoxyphosphoryldifluoromethyl Functionality from Cyclohex-2-enyl-1-phosphates

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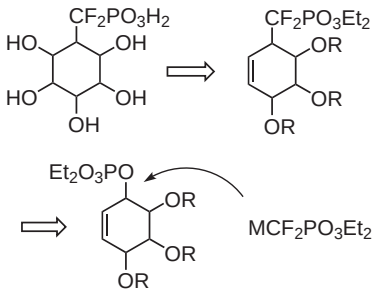
Abstract: Reaction of diethoxyphsphoryldifluoromethylzinc bromide ($BrZnCF_2PO_3Et_2$) with highly functionalized cyclohex-2-enyl-1-phosphates in the presence of CuBr in THF was examined. The reaction provides a facile method for introducing a difluoromethylenephosphonate unit to the allylic position within a cyclic array in a stereo- and regioselective manner.

Key words: diastereoselectivity, regioselectivity, phosphonates, fluorine

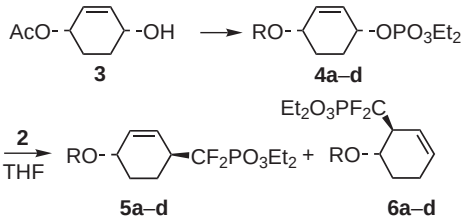
Naturally occurring phosphate derivatives play pivotal roles in various cellular processes including signal transduction.[1] Non-hydrolyzable phosphate mimetics have been studied for the design of potential enzyme inhibitors and probes for elucidation of biochemical processes. Extensive studies have been devoted to synthesis and biological evaluation of (α,α-difluoromethylene)phosphonic acid (DFMPA) derivatives, a non-hydrolyzable mimetic of phosphates.[2,3] While many useful methods for synthesis of DFMPA-based mimetics of phosphorylated amino acids, sugars and nucleic acids have been reported,[3] stereoselective synthesis of DFMPA-derived cyclic compounds that may act as hydrolytically stable analogues of naturally-occurring inositol phosphates remains a challenging issue.[4]

We examined organometalic-mediated allyl-coupling of α,α-difluoromethylphosphonate to cyclohex-2-enyl-1-phosphates to give the DFMPA-derived cyclohexene derivatives, potentially useful intermediates for the synthesis of the DFMPA-based mimetics of inositol phosphates[5] (Scheme 1). In this paper, we describe the allyl-coupling reaction of the copper species **2**,[6,7] generated from zinc reagent **1** and copper(I) bromide in THF, with cyclohex-2-enyl-1-phosphates gave highly-oxygenated cyclohexene derivatives having a DFMPA-ester in a high degree of diastereo- and regioselectivity.

First, we examined the reaction of 4-oxygeneated cyclohex-2-enyl-1-phosphates **4a**–**d** with the copper species **2** to investigate the regio- and diastereoselectivity (Scheme 2). The phosphates **4a**–**d** were synthesized in an optically active form from (+)-(1*R*,4*S*)-4-hydroxycyclohex-2-en-1-yl acetate **3**, $[\alpha]_D^{25}$ +77.0 (*c* 1.0, $CHCl_3$), obtained by lipase PS (Amano)-catalyzed desymmetrization of the corresponding diacetate according to the method of Sih.[8] Treatment of **3** with diethyl chlorophosphate in pyridine gave **4a**. Hydrolysis (K_2CO_3, MeOH) of **4a** and subsequent pivaloylation (PivCl, pyridine) or silylation (TBDPSCl, imidazole, DMF) of the resulting alcohol **4b** yielded **4c** and **4d**, respectively. Compounds **4a**–**d** were treated with **2** at room temperature for 16 hours to give the results summarized in Table 1.



Scheme 1 $MCF_2PO_3Et_2$, **1**: M = BrZn, **2**: M = $Br_2Zn{\cdot}Cu$



a: R=Ac; **b**: R=H; **c**: R=Piv; **d**: R=TBDPS

Scheme 2

When the acetyl-protected derivative **4a** was treated with **2**, installation of the DFMPA-ester occurred at the α- and γ-carbon to give **5a** and **6a** in a ratio of 63:27 in 62% yield. Diastereomeric excess (de) of **5a** was determined to be 72% (entry 1). In the reaction of non-protected derivative **4b**, a mixture of **5b** and **6b** was formed in a ratio of 43:57 and formation of γ-alkylated product **6b** was slightly preferred. De of **5b** was found to be 61% (entry 2). The reaction with pivaloyl-protected derivative **4c** afforded a mixture of **5c** and **6c** in virtually the same ratio as for the acetate **4a**, but de of both adducts increased to 85% (entry 3). Though the yield of adducts was quite poor, the reaction of TBDPS-protected derivative **4d** resulted in prefer-

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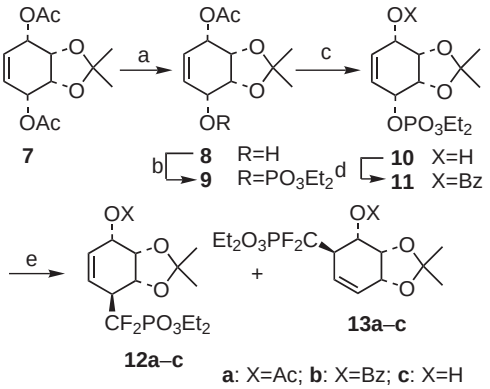
Table 1 Reaction of Cyclohex-2-enyl-1-phosphates **4a**–**d** with **2** in THF[a]

Entry	Phosphate (*R*)	Yield (%)[b]	**5**:**6**[c]	De (%) of **5**	De (%) of **6**
1	**4a** (Ac)	62	63:27	72	ND[d]
2	**4b** (H)	82	43:57	61	ND[d]
3	**4c** (Piv)	91	65:35	85	>85[e]
4	**4d** (TBDPS)	54	25:75	94	99

[a] All reactions were carried out at r.t. for 16 h.
[b] Combined yield of **5** and **6**.
[c] The ratio was determined by ^{31}P NMR analysis.
[d] Not determined.
[e] The de could not be precisely determined.



Scheme 3 (a) Lipase PS, phosphate buffer (pH = 7.0), r.t., 12 h (90%); (b) $ClPO_3Et_2$, pyridine, cat. DMAP (95%); (c) K_2CO_3, MeOH (85%); (d) BzCl, pyridine, cat. DMAP (98%); (e) **2**, THF–HMPA, r.t., 16 h.

able formation of γ-alkylated product **6d** to α-alkylated product **5d**. Furthermore, de of **5d** and **6d** was found to be 94% and 99%, respectively (entry 4). On consideration of these results, the reaction pathway could not be accounted for by an S_N2/S_N2' substitution mechanism.[9] The reaction would involve a process in which leaving of the phosphate group occurs prior to the carbon-carbon bond formation.[10]

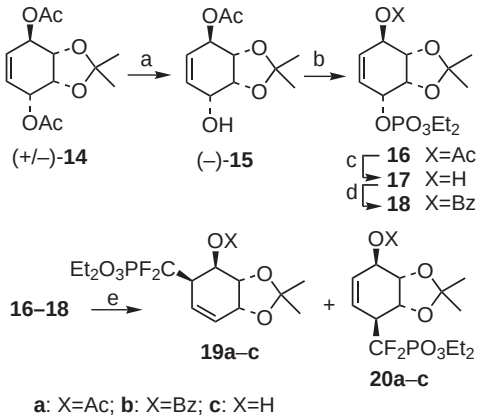
The regioisomers **5d** and **6d** were not readily separated by column chromatography on silica gel.[11] However, treatment of a mixture of **5d** and **6d** with 1.0 equivalent of tetrabutylammonium fluoride in THF at room temperature for 12 hours gave **5b** by selective desilylation and **6d** remained unchanged. Thus, diasteromerically pure **5b** and **6d** were readily isolated in 24% and 71% yield,[12] by chromatography on silica gel, respectively. The 2D-NMR (500 MHz, $CDCl_3$) analyses of the *p*-bromobenzoate derived from **5b**, including HMBC, HMQC, COSY and NOESY, cleanly demonstrated the relative stereochemistry to be *trans*.[13] The stereochemistry of **6d** was also ascertained to be *trans* by two-dimensional heteronuclear NOE (HOESY) experiments between ^{31}P and ^{1}H.[14] In the HOESY spectrum, a diagnostic HOESY-correlation between the phosphorus atom and the proton adjacent to the TBDPSO-functionality was observed.

To access highly-oxygenated cyclohexene derivatives having a DFMPA-ester, we next examined reaction with cyclohex-2-enyl-1-phosphates **9**–**11** fused to the 1,3-dioxolane ring. In these ring systems, stereoselective installation of a DFMPA-ester could be expected, since the attack of the copper reagent from the α-face is sterically hindered by the 1,3-dioxolone ring and the oxygenated substituent at the 4-position, forcing attack of the reagent from the convex face. Compounds **9**–**11** were prepared from *meso*-diacetate **7** as shown in Scheme 3. Desymmetrization of **7**, derived from the corresponding known diol,[15] in a phosphate buffer (pH = 7.0) in the presence of lipase PS at room temperature for 12 hours gave **8**,[16] $[\alpha]_D^{25}$ –57.5 (*c* 1.08, $CHCl_3$), in 90% yield. Enantiomeric excess of **8** was determined to be >98% on analyzing the MTPA-esters. Treatment of **8** with diethyl chlorophosphate in pyridine gave **9**, which was transformed to the phosphates **10** and **11**, through hydrolysis of the acetate and benzoylation of the resulting alcohol, respectively.

When the acetyl-protected derivative **9** was treated with **2** in THF at room temperature for 16 hours, virtually no reaction occurred and a significant amount of the starting **9** was recovered unchanged. Treatment of **9** with **2** in the presence of HMPA (4.0 equiv) as a co-solvent gave a mixture of α- and γ-alkylated products **12a** and **13a** in 10% yield, along with large amounts of unidentified products. The reaction of benzoyl-protected derivative **11** with **2** in THF gave a mixture of **12b** and **13b** in 17% yield, along with the recovered **11**. However, when the reaction was carried out in the presence of HMPA (4.0 equiv), the yield (70%) significantly increased to give a 17:83 mixture of **12b** and **13b**.[17] In this reaction, diastereomeric isomers of **12b** and **13b** were not detected. The reaction between the non-protected derivative **10** and **2** in THF containing HMPA gave a mixture (45:55) of **12c** and **13c** in 65% yield and their diastereoisomers were not detected. The solvent and the protecting group at the 4-hydroxy were found to play critical role to get the products with high regioselectivity and good yield.

We next examined the steric influence of the substituent at the 4-position. We expected the β-oriented substituent would suppress approach of the copper species **2** to the γ-position and the α-alkylated products would be formed preferably. We prepared the allylic phosphates **16**–**18** in an optically active form from (–)-**15**, $[\alpha]_D^{25}$ –204.4 (*c* 1.0, $CHCl_3$), obtained by lipase PS-catalyzed resolution of (±)-**14**[18] according to the procedure of Chung[19] (Scheme 4).

Treatment of the acetyl-protected derivative **16** with **2** in the presence of HMPA (4.0 equiv) in THF at room temperature for 16 hours gave a separable mixture of **19a** and **20a** in a ratio of 89:11 in 67% yield and their diastereomeric isomers were not detected. The major adduct was proved to be, unexpectedly, a γ-alkylated product, whose structure was confirmed by careful analysis of the 2D NMR spectrum (HMQC, HMBC, COSY and NOESY). The reaction of benzoyl-protected derivative **18** also gave **19b** as an isolable product in 42% yield. In contrast to the



Scheme 4 (a) Lipase PS, phosphate buffer (pH = 7.0), r.t., 3 h; (b) $ClPO_3Et_2$, pyridine, cat. DMAP (86%); (c) K_2CO_3, MeOH (85%); (d) BzCl, pyridine, cat. DMAP (98%); (e) **2**, THF–HMPA, r.t., 16 h.

reactions with **16** and **18**, the reaction of non-protected derivative **17** with **2** gave α-alkylated product **20c**[20] in 48% yield, along with a trace amount of a γ-alkylated product **19c**. It is interesting that the regiochemical outcome of the allyl-coupling reaction can be controlled by either using acyl-protected or non-protected derivatives as a substrate, but we cannot explain clearly these phenomena at the moment.

In summary, we have demonstrated a new and simple procedure for stereoselective synthesis of highly oxygenated cyclohexene derivatives having diethoxyphosphoryldifluoromethyl functionality, which would be valuable intermediates for stereoselective synthesis of analogous compounds of inositol phosphates.

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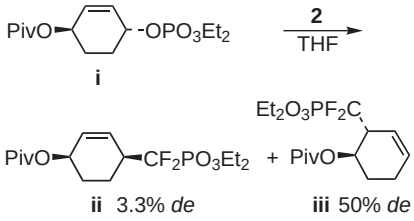
(9) Burton discussed mechanisms for reaction between **2** and allychlorides and proposed that the reaction may proceed through an S_N2/S_N2' substitution mechanism.[7b]
(10) *trans*-Isomer **i** of **4c** reacted with **2** under the same conditions to give a 62:38 mixture of α-alkylated product **ii** and γ-alkylated product **iii** in 71% yield (Scheme 5). The α-alkylated product showed virtually no de. However, the γ-alkylated product showed modest de preferable to 1,2-*trans*-stereochemistry showing that the reaction proceeded from the less-hindered *syn*-face of the phosphate to avoid the bulky pivaloyl group. These results also support that the reactions would involve a process for leaving the phosphate group prior to the carbon–carbon bond formation.



Scheme 5

(11) Compounds **5c** and **6c** were not readily separated on column chromatography on silica gel. However, these products were also separated by using the difference in their chemical reactivity; selective deprotection of the Piv functional group of **5d** occurred to give **6b** upon treatment with ethylmagnesium bromide in diethyl ether at –15 °C.
(12) All new compounds gave satisfactory spectroscopic and analytical data. Compound **5b** obtained as a colorless oil, $[\alpha]_D^{25}$ +55.2 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.94 (1 H, d, *J* = 10.6 Hz), 5.87 (1 H, dd, *J* = 10.6, 1.2 Hz), 4.31–4.22 (4 H, m), 3.01–2.85 (1 H, m), 2.21–2.12

(1 H, m), 2.10–2.01 (1 H, m), 1.80–1.69 (3 H, m), 1.52–1.40 (1 H, m), 1.39 (3 H, t, J = 7.0 Hz), 1.38 (3 H, t, J = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 123.13 (t, J_{CF} = 4.3 Hz), 120.79 (dt, J_{CF} = 262.2 Hz, J_{CP} = 211.0 Hz), 115.36, 77.20, 66.04, 64.56 (d, J_{CP} = 6.9 Hz), 64.38 (d, J_{CP} = 6.9 Hz), 40.93 (dt, J_{CF} = 19.9 Hz, J_{CP} = 15.4 Hz), 31.04, 20.15, 16.27. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 7.09 (t, J_{PF} = 107.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –51.07 (1 F, ddd, J_{FF} = 300.8 MHz, J_{FP} = 107.9 Hz, J_{FH} = 16.2 Hz), –53.04 (1 F, ddd, J_{FF} = 300.8 MHz, J_{FP} = 107.9 Hz, J_{FH} = 13.9 Hz). IR (film): 3433, 1632, 1263 cm^{-1}. MS (ESI): *m/z* = 307 [M + Na]$^+$. HRMS (ESI) calcd for $C_{11}H_{19}O_4F_2NaP$: 307.0887. Found: 307.0876. Compound **6d** obtained as a colorless oil, $[\alpha]_D^{25}$ –23.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.66 (4 H, m), 7.40–7.36 (6 H, m), 6.06 (1 H, dd, J = 10.3, 1.9 Hz), 5.72 (1 H, d, J = 8.8 Hz), 4.55 (1 H, s), 4.56–4.07 (4 H, m), 2.99–2.85 (1 H, m), 2.38–2.25 (1 H, m), 1.68–1.60 (m), 1.30–1.26 (6 H, m), 1.10 (3 H, s), 1.07 (3 H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.8, 135.3, 132.0, 129.6, 123.0–116.0 (m), 118.0, 65.1, 64.3, 47.1 (dt, J_{CF} = 19.1 Hz, J_{CP} = 19.1 Hz), 27.3, 26.9, 26.5, 20.3, 19.1, 19.0, 16.2 (d, J_{CP} = 5.4 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 7.00 (t, J_{PF} = 110.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –47.13 (1 F, ddd, J_{FF} = 298.9 Hz, J_{FP} = 110.4 Hz, J_{FH} = 11.3 Hz), –51.87 (1 F, ddd, J_{FF} = 298.9 Hz, J_{FP} = 110.4 Hz, J_{FH} = 24.8 Hz). IR (film): 1657, 1271 cm^{-1}. MS (EI): *m/z* = 523 [M$^+$ + 1]. Anal. Calcd for $C_{27}H_{37}F_2O_4PSi$: C, 62.05; H, 7.14. Found: C, 61.58; H, 6.99. Compound **13b** obtained as an oil, $[\alpha]_D^{25}$ –51.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.12 (2 H, d. J = 7.3 Hz), 7.57 (1 H, dd, J = 7.3, 7.3 Hz), 7.44 (2 H, dd, J = 7.3, 7.3 Hz), 5.95 (1 H, d with small splits, J = 10.6 Hz), 5.92 (1 H, d, J = 10.6 Hz), 5.70 (1 H, dd, J = 8.8, 2.3 Hz), 4.72–4.71 (1 H, m), 4.64–4.62 (1 H, m), 4.28–4.15 (4 H, m), 3.64–3.55 (1 H, m), 1.37 (3 H, s), 1.33 (3 H, s), 1.29 (6 H, t, J = 7.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.73, 133.13, 130.06, 129.15, 128.30, 124.00–116.00 (m), 121.59, 110.04, 73.52, 72.58, 67.72 (d, J = 3.7 Hz), 64.81 (t, J = 5.6 Hz), 42.03 (dt, J = 15.3, 20.2 Hz), 27.51, 26.52, 16.24 (d, J = 5.7 Hz), 16.25 (d, J = 4.9 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 6.12 (t, J_{PF} = 106.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –47.73 (2 F, dd, J_{FP} = 106.7 Hz, J_{FH} = 15.8 Hz). IR (film): 1723, 1602, 1451, 1271 cm^{-1}. MS (ESI): *m/z* = 483 [M + Na]$^+$. HRMS (ESI) calcd for $C_{21}H_{27}O_7F_2NaP$: 483.1360. Found: 483.1316. Compound **19a** obtained as an oil, $[\alpha]_D^{25}$ –72.6 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.03 (2 H, broad s), 5.46 (1 H, dd, J = 5.8, 4.3 Hz), 4.63 (1 H, dd, J = 6.0, 2.4 Hz), 4.45 (1 H, t, J = 6.1 Hz), 4.32–4.23 (5 H, m), 3.48–3.39 (1 H, m), 2.07 (3 H, s), 1.40 (3 H, s), 1.37 (3 H, t, J = 6.9 Hz), 1.37 (3 H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.35, 128.96, 124.00–116.00 (m), 122.17, 109.61, 72.57, 71.53, 69.53, 64.63 (dt, J_{CF} = 22.1 Hz, J_{CP} = 6.8 Hz), 39.90 (dt, J = 15.3, 19.8 Hz), 27.60, 25.90, 21.00, 16.30. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 6.25 (t, J_{PF} = 105.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –48.79 (1 F, ddd, J_{FF} = 280.5 Hz, J_{FP} = 105.5 Hz, J_{FH} = 12.0 Hz), –50.22 (1 F, ddd, J_{FF} = 280.5 Hz, J_{FP} = 105.5 Hz, J_{FH} = 23.7 Hz). IR (film): 1750, 1372, 1271, 1233 cm^{-1}. MS (ESI): *m/z* = 421 [M + Na]$^+$. Anal. Calcd for $C_{16}H_{25}F_2O_7P$: C, 48.24; H, 6.33. Found: C, 48.51; H, 6.41. Compound **20c** obtained as an oil, $[\alpha]_D^{25}$ +3.85 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.05 (1 H, d with small splits, J = 10.0 Hz), 5.81 (1 H, ddd, J = 10.0, 3.1, 2.1 Hz), 4.63 (1 H, dd, J = 6.5, 4.3 Hz), 4.35–4.24 (4 H, m), 4.19–4.16 (1 H, m), 4.15–4.07 (2 H, m), 3.08–2.92 (1 H, m), 1.46 (3 H, m), 1.40–1.31 (9 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.1, 121.0, 108.9, 78.7, 70.0, 68.0, 47.3 (t, J_{CF} = 11.8 Hz), 27.6, 25.4, 16.3, 16.1. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 6.74 (dd, J_{PF} = 108.8, 102.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –47.25 (1 F, ddd, J_{FF} = 303.4 Hz, J_{FP} = 102.9 Hz, J_{FH} = 16.2 Hz), –49.91 (1 F, ddd, J_{FF} = 304.4 Hz, J_{FP} = 108.8 Hz, J_{FH} = 16.2 Hz). IR (film): 3419, 1645, 1445, 1263 cm^{-1}. MS (ESI): *m/z* = 379 [M + Na]$^+$. HRMS (ESI) calcd for $C_{14}H_{23}O_6F_2NaP$: 379.1098. Found: 379.1081.

(13) Compound **5b** was chemically correlated to **5a** and **5c** to determine their *trans*-stereochemistry in the usual manner (Ac_2O, pyridine, PivCl, pyridine).
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(19) See the reference in note 16.
(20) Stereo- and regiochemistry of **20c** was confirmed by 2D-NMR including HMBC, HMQC, COSY and NOESY.