Heteroatom Chemistry
Volume 13, Number 3, 2002

Synthesis of Novel N^1-(2-Furanidyl)-5-fluorouracil Derivatives of α-Hydroxy(thio)phosphonates

Guochen Chi, Xiaodong Wang, and Ruyu Chen

Institute and National Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P. R. China

Received 10 June 2001; revised 28 August 2001

ABSTRACT: *Several* N^1*-(2-furanidyl)-5-fluorouracil derivatives of* α*-hydroxythiophosphonates were synthesized via oxidation by Moffatt's method of* N^1*-(2-furanidyl)-*N^3*-(hydroxyalkyl)-5-fluorouracil, followed by the addition of diethyl thiophosphite. The phosphonate products were obtained by the oxidation of the corresponding thiophosphonates with m-chloroperoxybenzoic acid. The crystal structure of compound* **6a** *was determined by X-ray diffraction.* © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:211–215, 2002; Published online in Wiley Interscience (www.interscience.wiley.com). DOI 10.1002/hc.10021

INTRODUCTION

N^1-(2-furanidyl)-5-fluorouracil (Tegafur) (**1**) is a potent inhibitor of mammalian cell growth in clinical use. However, undesirable side effects, such as hot sensation and pollakiuria syndrome [1] initiated our interest to develop new and better drugs. Earlier the syntheses and preliminary antitumor activities of some new types of cyclic thiophosphate derivatives of Tegafur have been reported [2–5]. In order to improve its antitumor activity and lower its toxicity, we have attempted to synthesize α-hydroxy(thio)phosphonate derivatives of Tegafur.

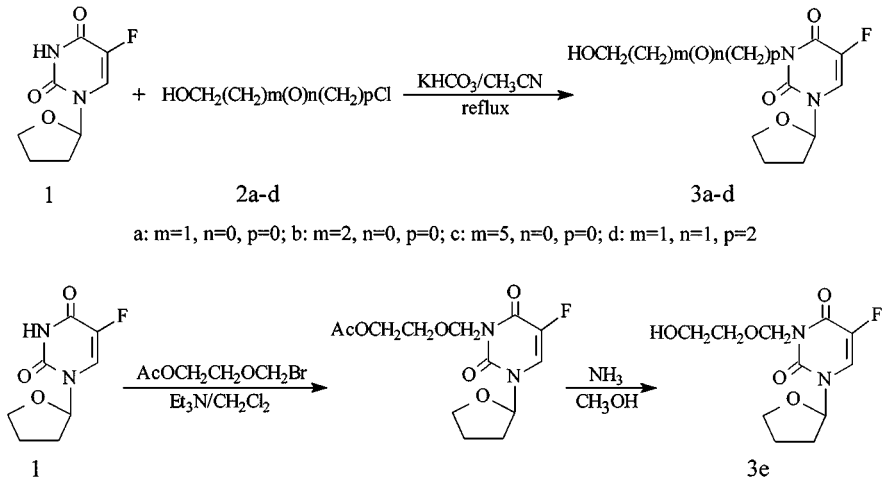
Correspondence to: Ruyu Chen; e-mail: gchchi@hotmail.com.
Contract grant sponsor: Foundation for University Key Teacher, Ministry of Education of China.
Contract grant number: GG-150-10055-1027.

RESULT AND DISCUSSION

N^1-(2-furanidyl)-N^3-(hydroxyalkyl)-5-fluorouracils **3a–d** were prepared according to the literature method [2,6], but by a modified procedure (Scheme 1). The reaction of **1** with 2-chloroethanol gave **3a** in nearly quantitative yield. The yield was lowered with increase in the length of the chain. By the reaction of **1** with 2-(acetoxyethoxy)methyl bromide, with triethylamine as the condensing reagent, and deprotection of the acetyl group, **3e** was obtained in 62.7% yield. However, the use of similar procedures that were successful for the preparation of **3a–d**, resulted in a complex mixture of products in the attempts to prepare **3e**.

Since the precursor of an N^1-(2-furanidyl)-5-fluorouracil derivative of an α-hydroxythiophosphonate is an aldehyde, which usually absorbs water or is oxidized, we designed a "one-pot" reaction using N^1-(2-furanidyl)-N^3-(hydroxyalkyl)-5-fluorouracils **3a–e** as starting materials to synthesize compounds **5a–e** (Scheme 2).

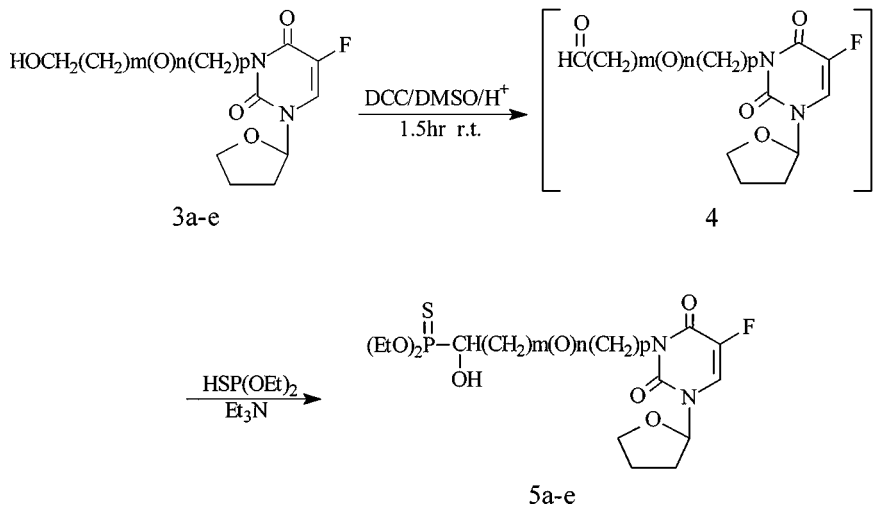
Aldehyde **4** was obtained by oxidizing **3**, using dimethylsulfoxide as the oxidizing agent as well as solvent [7,8]. The consecutive treatment of compounds **4** with O,O-diethyl thiophosphite and triethylamine afforded **5a–e**. The purification of each **5a–e** was tedious due to the difficulty in removing the dicyclohexylurea produced. More than one chromatographic separation was needed to give each pure **5a–e** in moderate yield (56.6–62.6%). Compounds **5a–e** could be converted into **6a–e** in high yields (>80%) by means of oxidation with *m*-chloroperoxybenzoic acid (*m*-CPBA) instead of



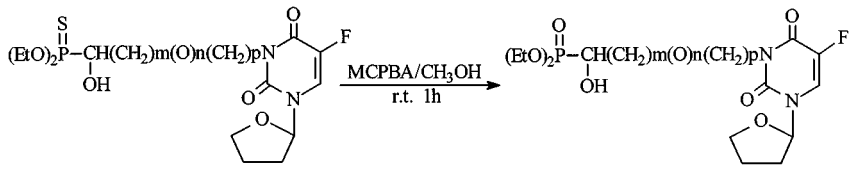
SCHEME 1

direct addition of diethyl phosphite to the corresponding aldehydes, which needs long reaction periods to give comparatively lower yields of products (for example, **6a** was obtained in only 28.9% yield by this procedure) (Scheme 3).

The structures of compounds **5** and **6** were confirmed by spectroscopic studies and elemental analyses. The structure of compound **6a** was determined by X-ray diffraction (Fig. 1). Single crystals were obtained by the slow evaporation of a petroleum ether-diethyl ether solution of the title compound at room temperature. The determination of the unit cell and the data collection were performed with Mo Kα radiation ($\lambda = 0.71073$ Å) on an BRUCKER SMART 1000 diffractometer using the ω scan mode. A total of 6807 reflections were collected in the range of $2.05^\circ < \theta < 25.02^\circ$ at 298(2) K, of which 2945 unique reflections ($R_{int} = 0.0469$) with $I > 2\sigma(I)$ were used in the successive refinements. LP-factor corrections and SADABS absorption correction were applied. The structure was solved by direct methods and expanded using difmap methods and refined on F^2 by a full-matrix least-squares method. The final refinement converged to $R = 0.0663$ and $R_w = 0.1500$. Compound **6a**, $C_{14}H_{22}FN_2O_7P$, $M_r = 587.73$, crystallizes in



SCHEME 2



5a-e 6a-e

SCHEME 3

monoclinic system, space group $C2/c$, with $a = 13.941(3)$ Å, $b = 19.866(3)$ Å, $c = 13.121(2)$ Å, $\beta = 102.760(4)^\circ$, $V = 3544(11)$ Å^3, $Z = 8$, $D_c = 1.425$ g/cm^3, $F(000) = 1600$, $\mu = 0.204$ mm^{-1}. Some important bond lengths and angles are listed in Tables 1 and 2. In the crystal, the molecules link to each other through the intermolecular hydrogen bond O(11)···H(11)···O(12d) with O(11)···O(12d) distance of 2.692 Å and an O(11)···H(11)···O(12d) angle of 177.68° (Fig. 2).

The evalaution of biological activities of the title compounds is in progress.

EXPERIMENTAL

Melting points were determined with a Thomas Hoover Capillary Melting Point Apparatus and are uncorrected. NMR spectra were measured on a Bruker AC-P200 spectrometer. Tetramethylsilane (TMS) was used as an internal standard for ^{1}H NMR spectroscopy, 85% H_3PO_4 being used as an external standard for ^{31}P NMR spectroscopy. Elementary analyses were carried out on a Yane MT-3 instrument. DMSO was dried with 4A-sieves and distilled.

*N^1-(2-Furanidyl)-N^3-[2-(2-hydroxyethoxy)ethyl]-5-fluorouracil (**3d**)*

A mixture of N^1-(2-furandiyl)-5-fluorouracil (2.00 g, 0.01 mol), 2-(2-chloroethoxy)ethanol (3.74 g, 0.03 mol), and $KHCO_3$ (3.00 g, 0.03 mol) in 20 ml of acetonitrile was refluxed for 8 h. The precipitate was filtered off and the solvent was evaporated. Purification by silica gel flash column chromatography (CH_2Cl_2/ethyl acetate 1:1 as eluant) gave 1.40 g (48.5%) of **3d** as a colorless syrup. ^{1}H NMR ($CDCl_3$): 1.99–2.08, 2.28–2.51 (m, 4H, 3′, 4′-H); 2.98 (br, 1H, —OH); 3.60–3.76 (m, 6H, $HOCH_2\underline{CH_2}O\underline{CH_2}\underline{CH_2}N$); 3.95–3.99 (m, 1H, 5′-Ha); 4.14–4.24 (m, 3H, $HO\underline{CH_2}$ 5′-Hb); 5.96 (d, br, 1H, 2′-H); 7.40 (d, 1H, 6-H, $J_{HF} = 5.35$ Hz); Elemental analysis (%): Found (Calcd.), C 50.05 (50.00), H 5.87 (5.94), N 9.50 (9.72).

Compounds **3a–c** were prepared according to the similar procedure as **3d** and the experimental data has been reported in the literature [2].

*N^1-(2-Furanidyl)-N^3-(2-hydroxyethoxy)methyl-5-fluorouracil (**3e**)*

To a stirred mixture of N^1-(2-furanidyl)-5-fluorouracil (2.00 g, 0.01 mol) and (2-acetoxyethoxy)methyl bromide (4.93 g, 0.025 mol) in 30 ml of dichloromethane at 10°C was added triethylamine (2.53 g, 0.025 mol) over 5 min. Stirring was continued for 1 h at room temperature. The solvent was evaporated. To the residue was added 30 ml of saturated

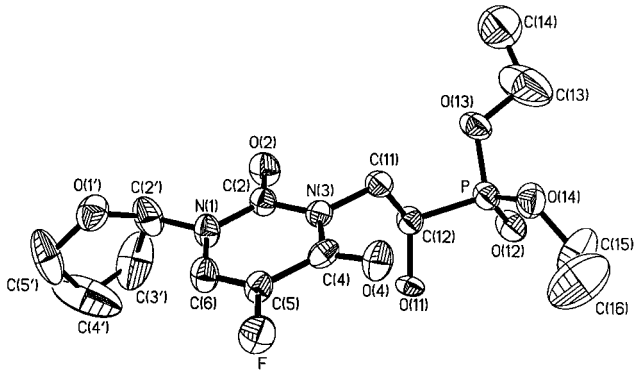


FIGURE 1 Molecular structure of compound **6a**.

TABLE 1 Selected Bond Lengths of Compound **6a**

Bond	*Length (Å)*
P—C(12)	1.780(5)
F—C(5)	1.356(5)
N(1)—C(2)	1.360(6)
N(1)—C(6)	1.383(6)
N(1)—C(2′)	1.495(7)
N(3)—C(2)	1.384(5)
N(3)—C(4)	1.406(6)
N(3)—C(11)	1.457(5)
O(11)—C(12)	1.407(5)
O(11)—O(11′)[a]	1.896(11)
O(11′)—C(12)	1.423(8)
O(2)—C(2)	1.203(5)
O(4)—C(4)	1.215(5)
C(6)—C(5)	1.292(6)
C(5)—C(4)	1.432(6)
C(11)—C(12)	1.490(6)

[a]O(11) and O(11′) of the molecule are disordered.

TABLE 2 Selected Bond Angles of Compound **6a**

Bond	*Angle (°)*
C(2)—N(1)—C(6)	121.3(4)
C(2)—N(1)—C(2′)	118.6(4)
C(6)—N(1)—C(2′)	120.0(4)
C(2)—N(3)—C(4)	125.5(4)
C(2)—N(3)—C(11)	118.0(4)
C(4)—N(3)—C(11)	116.4(4)
C(12)—O(11)—O(11′)	48.3(3)
C(12)—O(11′)—O(11)	47.6(3)
C(5)—C(6)—N(1)	121.1(4)
C(6)—C(5)—F	120.8(4)
C(6)—C(5)—C(4)	123.7(5)
F—C(5)—C(4)	115.5(4)
O(4)—C(4)—N(3)	122.6(5)
O(4)—C(4)—C(5)	125.3(5)
N(3)—C(4)—C(5)	112.1(4)
O(2)—C(2)—N(1)	122.1(4)
O(2)—C(2)—N(3)	121.8(4)
N(1)—C(2)—N(3)	116.1(4)
N(3)—C(11)—C(12)	113.8(3)
O(11′)—C(12)—O(11)	84.1(5)
O(11′)—C(12)—C(11)	124.3(6)
O(11)—C(12)—C(11)	111.9(4)
O(11′)—C(12)—P	108.3(5)
O(11)—C(12)—P	110.0(3)
C(11)—C(12)—P	114.1(3)

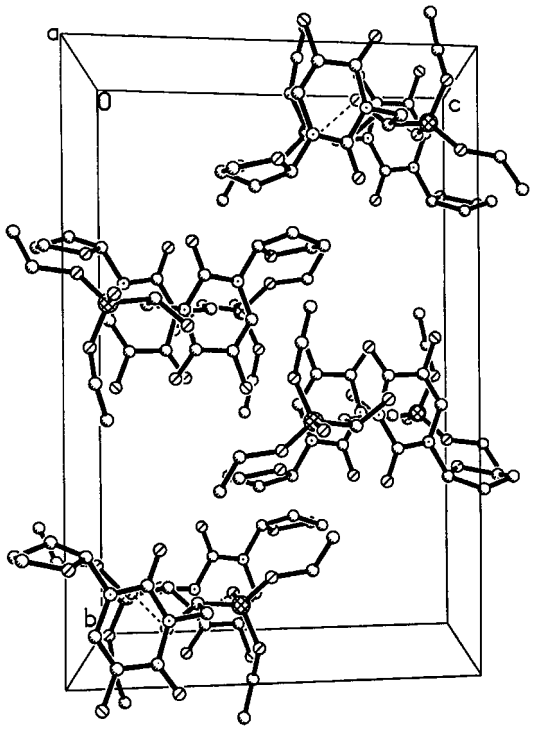


FIGURE 2 Molecular packing of compound **6a** in a unit cell.

methanolic ammonia, and the mixture was stored at 10°C for 48 h. After purification by silica gel flash column chromatography (CH_2Cl_2/ethyl acetate 1:1 as eluant), 1.72 g (62.7%) of **3e** was obtained as a colorless syrup, which solidified gradually, m.p. 58–60°C. ^{1}H NMR ($CDCl_3$): 1.90–2.06, 2.34 (m, 5H, 3′ 4′-H,—OH); 3.70 (s, 4H, $HOCH_2CH_2O$); 3.98, 4.21 (m, 2H, 5′-H); 5.44 (s, 2H, OCH_2N); 5.95 (d, br, 1H, 2′-H); 7.40 (d, 1H, 6-H, $J_{HF} = 5.56$ Hz); Elemental analysis (%): Found (Calcd.), C 47.92 (48.18), H 5.50 (5.51), N 10.05 (10.21).

General Procedure for the Synthesis of **5a–e**

Dichloroacetic acid($Cl_2CHCOOH$) (0.32 g, 2.5 mmol) was added into a solution of compound **3** (5 mmol) and dicyclohexylcarbodiimide (3.20 g, 15 mmol) in 50 ml of anhydrous DMSO. The mixture was stirred at room temperature for 1.5 h. Then, a solution of $(COOH)_2 \cdot 2H_2O$ (1.26 g, 10 mmol) in 5 ml of methanol was added dropwise to the mixture. After 10 min, triethylamine (2.02 g, 20 mmol) and diethyl thiophosphite (1.54 g, 10 mmol) were added consecutively, and the mixture was stirred at room temperature

TABLE 3 Some Experimental Data of the Compounds **5** and **6**

			Elemental analyses (%)[a]		
Compd.	*m.p. (°C)*	*Yield (%)*	*C*	*H*	*N*
5a	59–60	62.6	42.37 (42.42)	5.39 (5.59)	7.00 (7.07)
5b	Syrup	58.0	43.64 (43.90)	5.90 (5.89)	6.62 (6.83)
5c	72–73	56.6	47.79 (47.78)	6.69 (6.68)	6.22 (6.19)
5d	Syrup	75.7	43.34 (43.63)	5.75 (5.95)	6.15 (6.36)
5e	Syrup	68.6	42.16 (42.25)	5.75 (5.67)	6.85 (6.57)
6a	121–122	86.8	44.03 (44.22)	5.60 (5.83)	7.22 (7.37)
6b	93–94	88.8	45.47 (45.69)	6.11 (6.13)	6.87 (7.10)
6c	48–50	80.2	49.39 (49.54)	7.01 (6.93)	6.39 (6.42)
6d	Syrup	90.3	45.26 (45.29)	6.23 (6.18)	6.69 (6.60)
6e	Syrup	89.8	43.70 (43.91)	5.78 (5.90)	6.81 (6.83)

[a]Found and calculated (in parenthesis) values, respectively.

TABLE 4 ^{1}H NMR and ^{31}P NMR Data of Compounds **5** and **6** (δ, $CDCl_3$)

Compd.	*^{1}H NMR*	*^{31}P NMR*
5a	1.27–1.36 (m, 6H, $OCH_2\underline{CH_3}$); 1.80–2.12, 2.37 (m, 4H, 3′, 4′-H); 2.60 (br, 1H, —OH); 3.95–4.24 (m, 8H, $O\underline{CH_2}CH_3$, —CH$\underline{CH_2}$N, 5′-H); 4.49 (m, 1H, —$\underline{CH}$OH); 5.94 (d, br, 1H, 2′-H); 7.40 (d, 1H, 6-H, $J_{HF} = 5.92$ Hz).	133.53 133.65
5b	1.27 (t, 6H, $OCH_2\underline{CH_3}$); 1.78–2.20, 2.28–2.48 (m, 6H, 3′, 4′-H, —$\underline{CH_2}CH_2$N); 3.0 (br, 1H, —OH); 3.75–3.89, 4.11–4.20 (m, 9H, $O\underline{CH_2}CH_3$, —$\underline{CH}$(OH)$CH_2\underline{CH_2}$N, 5′-H); 5.96 (d, br, 1H, 2′-H); 7.39 (d, 1H, 6-H, $J_{HF} = 6.24$ Hz).	94.26
5c	1.29–1.46, 1.53–1.78, 1.93–2.18, 2.32–2.50 (m, 18H, $OCH_2\underline{CH_3}$, —$(\underline{CH_2})_4CH_2$N, 3′, 4′-H); 3.68–4.29 (m, 9H, $O\underline{CH_2}CH_3$, —$\underline{CH}$(OH)$(CH_2)_4\underline{CH_2}$N, 5′-H); 5.96 (d, br, 1H, 2′-H); 7.36 (d, 1H, 6-H, $J_{HF} = 6.26$ Hz).	96.35
5d	1.23–1.32 (m, 6H, $OCH_2\underline{CH_3}$); 1.90–2.08, 2.29–2.48 (m, 4H, 3′, 4′-H); 2.60 (br, 1H, —OH); 3.96–4.18 (m, 9H, $O\underline{CH_2}CH_3$, —$\underline{CH}$(OH)$\underline{CH_2}$O—, 5′-H); 5.46 (s, 2H, OCH_2N); 5.95 (br, 1H, 2′-H); 7.40 (d, 1H, 6-H, $J_{HF} = 5.96$ (Hz).	91.16
5e	1.27 (t, 6H, $OCH_2\underline{CH_3}$); 1.90–2.04, 2.39 (m, 4H, 3′, 4′-H); 2.92 (br, 1H, —OH); 3.72–4.17 (m, 13H, $O\underline{CH_2}CH_3$, —$\underline{CH}$(OH)$\underline{CH_2}O\underline{CH_2}CH_2$N—, 5′-H); 5.94 (d, br, 1H, 2′-H); 7.37 (d, 1H, 6-H, $J_{HF} = 6.29$ Hz).	91.16
6a	1.30–1.38 (m, 6H, $OCH_2\underline{CH_3}$); 1.84–2.13, 2.29–2.45 (m, 4H, 3′, 4′-H); 2.97 (br, 1H, —OH); 3.79–3.98, 4.16–4.27 (m, 8H, $O\underline{CH_2}CH_3$, —CH$\underline{CH_2}$N, 5′-H); 4.48 (m, 1H, —$\underline{CH}$OH); 5.95 (d, br, 1H, 2′-H); 7.41 (d, 1H, 6-H, $J_{HF} = 5.63$ Hz).	20.87
6b	1.30 (t, 6H, $OCH_2\underline{CH_3}$); 1.83–2.16, 2.30–2.48 (m, 6H, —$\underline{CH_2}CH_2$N, 3′, 4′-H); 3.65 (br, 1H, —OH); 3.71–4.28 (m, 9H, $O\underline{CH_2}CH_3$, —$\underline{CH}$(OH)$CH_2\underline{CH_2}$N, 5′-H); 5.94 (d, br, 1H, 2′-H); 7.41 (d, 1H, 6-H $J_{HF} = 6.26$ Hz).	24.20
6c	1.27–1.34, 1.52–1.78, 1.82–2.12, 2.26–2.49 (m, 18H, $OCH_2\underline{CH_3}$, —$(\underline{CH_2})_4CH_2$N, 3′, 4′-H); 2.98 (br, 1H, —OH); 3.72–4.17 (m, 9H, $O\underline{CH_2}CH_3$, —$\underline{CH}$(OH)$(CH_2)_4\underline{CH_2}$N, 5′-H); 5.95 (d, br, 1H, 2′-H); 7.35 (d, 1H, 6-H, $J_{HF} = 5.68$ Hz).	25.41
6d	1.29 (t, 6H, $OCH_2\underline{CH_3}$); 1.99, 2.38 (m, 4H, 3′, 4′-H); 3.89–4.20 (m, 9H, $O\underline{CH_2}CH_3$, —$\underline{CH}$(OH)$\underline{CH_2}$O—, 5′-H); 4.39 (br, 1H, —OH); 5.44 (s, 2H, OCH_2N); 5.94 (br, 1H, 2′-H); 7.40 (d, 1H, 6-H, $J_{HF} = 5.41$ Hz).	21.75
6e	1.26 (t, 6H, $OCH_2\underline{CH_3}$); 1.80–2.15, 2.27–2.49 (m, 4H, 3′, 4′-H); 3.67–4.17 (m, 13H, $O\underline{CH_2}CH_3$, —$\underline{CH}$(OH)$\underline{CH_2}O\underline{CH_2}CH_2$N—, 5′-H); 5.93 (d, br, 1H, 2′-H); 7.37 (d, 1H, 6-H, $J_{HF} = 5.53$ (Hz).	21.94

for another 4 h. After filtration, the filtrate was extracted with 100 ml of ethyl acetate, washed with water, and drived over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate 1:1 as eluant) to give **5a–e**. The experimental data of **5a–e** are shown in Tables 3 and 4.

General Procedure for the Synthesis of **6a–e**

A solution of **5** (1 mmol) and *m*-CPBA (2 mmol) in 10 ml of methanol was stirred at room temperature for 1 h. The solvent was evaporated and the residue was purified by silica gel flash column chromatography ($CHCl_3/CH_3OH$ 30:1 as eluant) to afford **6a–e**. The experimental data of **6a–e** are given in Tables 3–5.

TABLE 5 EIMS Data of Compounds **6** (*m/z*, %)

6a: 380 (M^+, 0.28), 310 (25.78), 138 (37.97), 71 (100)
6b: 394 (M^+, 0.16), 324 (1.15), 138 (3.77), 71 (100)
6c: 436 (M^+, 0.05), 366 (1.06), 138 (2.02), 71 (100)
6d: 424 (M^+, 0.38), 354 (3.90), 138 (8.76), 71 (100)
6e: 410 (M^+, 0.64), 340 (16.28), 138 (26.94), 71 (100)

REFERENCES

[1] Yasumoto, M.; Yamawaki, I.; Marunaka, T.; Hashimoto, S. J Med Chem 1978, 21, 738.
[2] Xu, X. H.; Chen, H. M.; Chen, R. Y. Chem J Chin Univ 2000, 21, 1410.
[3] Zhang, C. X.; Zhang, Z. B.; Chen, H. M.; Tang, C. C.; Chen, R. Y. Heteroat Chem 1998, 9, 295.
[4] He, Z. J.; Chen, W. B.; Zhang, C. X.; Zhou, Z. H.; Tang, C. C. Synth Common 2000, 30, 903.
[5] He, Z. J.; Chen, W. B.; Zhang, C. X.; Zhou, Z. H.; Tang, C. C. Phosphorus Sulfur Silicon 2000, 160, 223.
[6] Chen, H. M.; Chen, R. Y.; Li, P. Y. Phosphorus Sulfur Silicon 1997, 122, 1.
[7] Baker, D. G.; Crews, R. P.; Haskell, T. H.; Putt, S. R.; Arnett, G.; Shannon, W. M.; Reinke, M.; Katlama, N. B.; Drach, J. C. J Med Chem 1983, 26, 1530.
[8] Pfitzner, K. E.; Moffatt, J. G. J Am Chem Soc 1963, 85, 3027.