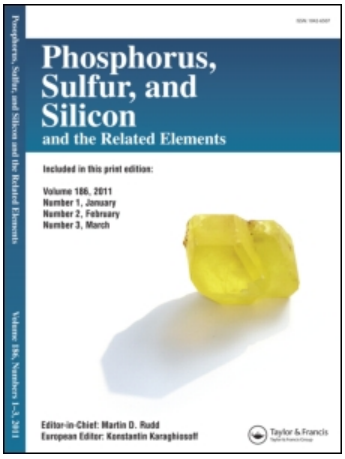

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS OF DIISOPROPYL (2-HYDROXY-3-ALKENE-1-YL) AND (5-CARBETHOXY-2-ALKENE-1-YL)PHOSPHONATES

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To cite this Article Wawrzeńczyk, Czesław , Zoń, Jerzy and Leja, Edward(1992) 'SYNTHESIS OF DIISOPROPYL (2-HYDROXY-3-ALKENE-1-YL) AND (5-CARBETHOXY-2-ALKENE-1-YL)PHOSPHONATES', Phosphorus, Sulfur, and Silicon and the Related Elements, 71: 1, 179 — 184
To link to this Article: DOI: 10.1080/10426509208034509
URL: http://dx.doi.org/10.1080/10426509208034509

Phosphorus, Sulfur, and Silicon, 1992, Vol. 71, pp. 179–184
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SYNTHESIS OF DIISOPROPYL (2-HYDROXY-3-ALKENE-1-YL) AND (5-CARBETHOXY-2-ALKENE-1-YL)PHOSPHONATES

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(Received May 5, 1992)

The synthesis of diisopropyl (2-hydroxy-3-alkene-1-yl) and (5-carbethoxy-2-alkene-1-yl)phosphonates from α,β-unsaturated aldehydes is described. The Sharpless epoxidation was applied for kinetic resolution of diisopropyl [(±)-2-hydroxy-3-pentene-1-yl]phosphonate.

Key words: Diisopropyl (2-hydroxy-3-alkene-1-yl)phosphonates; diisopropyl (5-carbethoxy-2-alkene-1-yl)phosphonates; synthesis; properties; Claisen rearrangement; Sharpless epoxidation.

INTRODUCTION

The various types of phosphonates were obtained and applied in the Wittig-Horner reaction.[1] As part of our continuing program in the synthesis of functionalized alkylphosphonates,[2] we have synthesized two new groups of phosphonates: diisopropyl (2-hydroxy-3-alkene-1-yl)phosphonates **2a–d** and diisopropyl (5-carbethoxy-2-alkene-1-yl)phosphonates **3a–d**. Phosphonates with the allyl alcohol derivative fragment as well as those with the γ,δ-unsaturated carbethoxy fragment could be very useful in organic synthesis, mainly for the carbon chain elongation and functionalization of carbonyl compounds in the Wittig-Horner reaction.

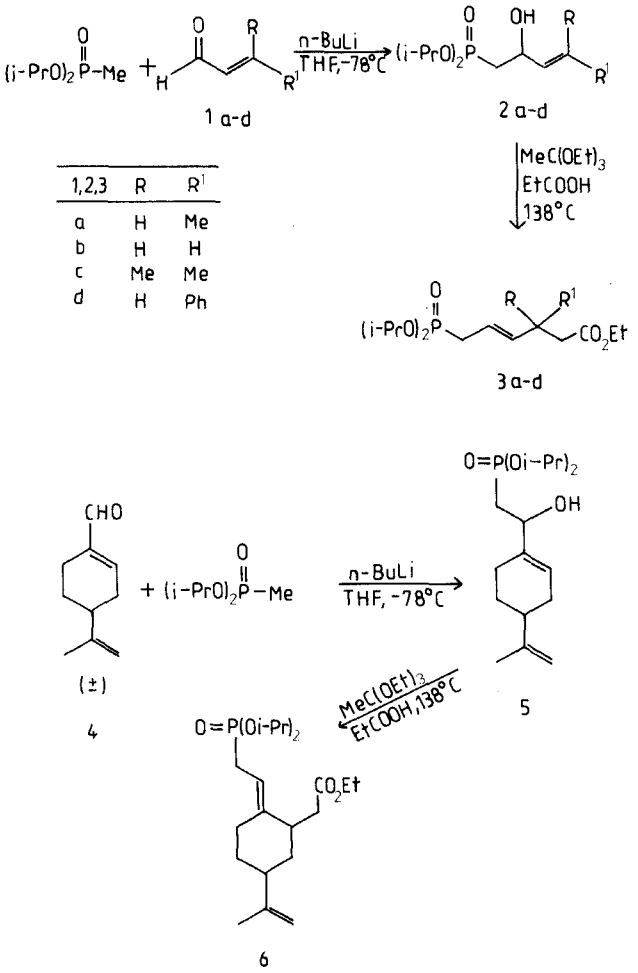
RESULTS AND DISCUSSION

The first group of phosphonates, diisopropyl (2-hydroxy-3-alkene-1-yl)phosphonates **2a–d** as well as the hydroxyphosphonate **5** were obtained by the reaction of diisopropyl lithiummethylphosphonate with the appropriate α,β-unsaturated aldehyde **1a–d** and **4** (Scheme I).

The reaction was carried out at −78°C and only products of 1,2-addition of phosphonate to the carbonyl group were isolated (yield 64–78%).

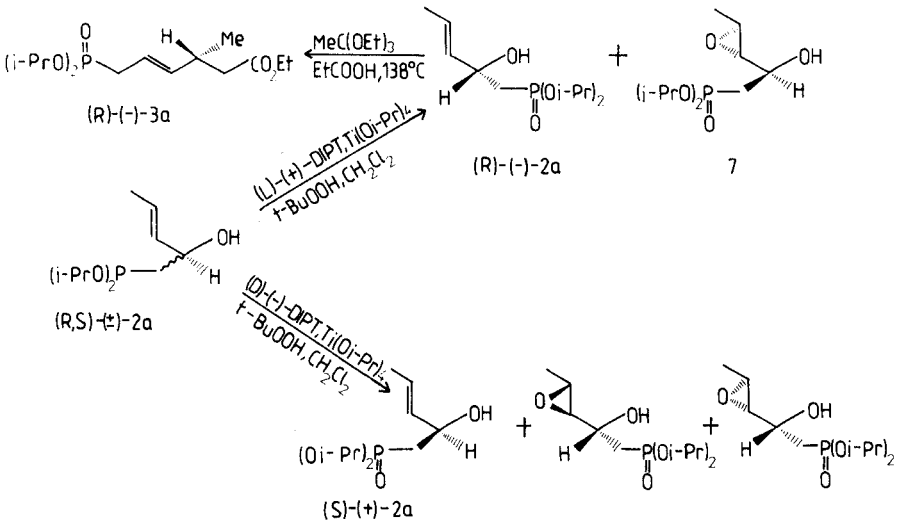
Hydroxyphosphonates were obtained in a form of optically inactive racemic mixtures. The hydroxyphosphonate obtained from perillaldehyde (**4**) was a racemic mixture of diastereoisomers. Unfortunately, neither capillary column chromatography nor ^{1}H NMR spectrum (100 MHz) afforded any data about the composition of the mixture.

The presence of the allyl alcohol derivative fragment in the molecules of hydroxyphosphonates obtained permit us to apply the enantioselective Sharpless



SCHEME I

epoxidation[3,4] in order to obtain the enantiomerically pure forms of hydroxyphosphonate **2a**. Applying the Sharpless methodology of kinetic resolution of racemic allyl alcohols,[5] both enantiomers of hydroxyphosphonate **2a** were obtained. The epoxidation reaction was carried out at $-20°C$ to $-25°C$ in methylene chloride using 1.0 equivalent of titanium tetraisopropoxide, 1.2 equivalent of diisopropyl (+) or (−) tartrate and 0.6 equivalent of *t*-butyl hydroperoxide for 1 equivalent of racemic hydroxyphosphonate **2a**. The course of the reaction was monitored by GC until 55% of the hydroxyphosphonate was consumed. The unreacted alcohol from the epoxides fraction was separated by column chromatography (silica gel, diethyl ether). The laevorotatory isomer ($[\alpha]_{578}^{20} = -13{,}6°$, CH_3OH, c 10.0) as unreacted hydroxyphosphonate **2a** was isolated from the epoxidation when diisopropyl *L*-(+)-tartrate was used as the reagent. Apart from the hydroxyphosphonate (−)-**2a** the laevoratatory ($[\alpha]_{578}^{20} = -17{,}6°$, CH_3OH, c 10.0) epoxide **7** was isolated as a pure isomer (>97% according to GC) (Scheme II). Using the Sharpless rules,[5] we ascribed the erythro structure to this isomer (Scheme II).



SCHEME II

When diisopropyl *D*-(−)-tartrate was used in the epoxidation reaction, the (+)-enantiomer of **2a** ($[\alpha]_{578}^{20}$ = +9,4°, CH_3OH, c 10.0) was isolated as unreacted isomer of hydroxyphosphonate **2a** and the mixture of threo and erythro hydroxy-epoxide was detected. According to rules proposed by Sharpless[5] *R* and *S* configurations should be assigned to the (−)- and (+)-enantiomers of hydroxyphosphonates **2a**, respectively. The configurations of these compounds were not correlated in any other way.

The enantiomeric excess (ee) of hydroxyphosphonates *R*-(−)-**2a** and *S*-(+)-**2a** was determined by converting them to the α-methoxy-α-trifluormethyl-phenylacetic acid (MTPA) esters[6] for ^1H NMR (300 MHz) analysis. The integration of the methoxy group signals ($\Delta\delta$ = 0.041 ppm) indicated that hydroxyphosphonates *R*-(−)-**2a** and *S*-(+)-**2a** were obtained in 95% and 63% of enantiomeric excess, respectively.

According to our knowledge, this is the first example of the Sharpless enantioselective epoxidation of allylic alcohols containing the dialkoxyphosphoryl group.

The second group of phosphonates, diisopropyl 5-carbethoxy-2-alkene-1-yl)phosphonates **3a–d** and **6**, were synthesized by the orthoacetate modification of the Claisen rearrangement.[7] Thus, by heating (138°C, 1–8 h) the mixture of hydroxyphosphonate (**2a–d** or **5**, 1 equiv.), triethyl orthoacetate (7 equiv.) with a catalytic amount of propionic acid (0.06 equiv.), the appropriate carbethoxyphosphonates (**3a–d** and **6**) were obtained as products in high yields (74–87%). The double bond formed in **3a–d** has the E (more than 97%) configuration.

The high steroespecifity of the Claisen rearrangement[8,9] allowed us to obtain from the *R*-(−)-hydroxyphosphonate **2a** the optically active ($[\alpha]_{578}^{20}$ = −17,1°, CH_3OH, c 1.4) *R*-(−)-carbethoxyphosphonate **3a**.

In our opinion, diisopropyl (4-methyl-5-carbethoxy-2-pentene-1-yl)phosphonate (**3a**) is a potential useful chiral building block. After further simple transformations, we plan to use it for synthesis of the monoterpenoid and sesquiterpenoid compounds via the Wittig-Horner reaction.

EXPERIMENTAL

Diisopropyl methylphosphonate was synthesized from triisopropyl phosphite and methyl iodide by the Arbuzov reaction. Crotonaldehyde, acrolein, cinnamaldehyde were purchased from Fluka. Perillaldehyde was purchased from Koch-Light Company. Butyllithium, and triethyl orthoacetate were purchased from Merck. 3,3-Dimethylacrolein, titanium (IV) isopropoxide, tert-butyl hydroperoxide, *R*-(+)-MTPA, diisopropyl *D*- and *L*-tartrate were purchased from Aldrich. ^{1}H NMR spectra were measured on a Tesla BS-497 (100 MHz) or General Electric QE 300 (300 MHz) instruments. IR spectra were recorded on a Specord IR-75 Spectrophotometer. GLC analyses were carried out on a Chromatron GCHF-18.3.4 apparatus with flame ionizing detector (FID). The steel column containing 6% QF-1 on Gas-Chrom (1–1 m, 160°C) was used. Analytical TLC was carried out on silica gel G (Merck) with different developing systems: ethyl ether, ether-methanol or hexane-acetone. Compounds were detected by spraying the plates with 7% H_2SO_4 in ethanol containing ca 0,1% of *p*-anisaldehyde, followed by heating to 120°C. Column chromatography was performed on silica gel (Kie-selgel 60, 230–400 mesch, Merck) with ethyl ether or ether-methanol, or the hexane-acetone system as eluents.

*Synthesis of β-hydroxyphosphonates (**2a–d** and **5**): General procedure:* A solution of diisopropyl methylphosphonate (0.050 mol) in dry tetrahydrofuran (50 ml) is cooled to −78°C. Then a hexane solution of butyllithium (0.055 mol) is added dropwise under nitrogen and magnetic stirring. After 15 min. the appropriate aldehyde (0.050 mol) is added dropwise at −78°C. The mixture is stirred for 40 min and then quenched by adding aqueous saturated solution of ammonium chloride (50 ml). Ether (50 ml) is added and the layers are separated. The aqueous layer is additionally extracted with ether (50 ml). The combined etheral solutions are washed with brine (2 × 50 ml) and dried over sodium sulfate. The crude products are purified by chromatography. The yields of the reaction, physical and spectral data of phosphonates obtained are given in Table I.

*Diisopropyl [(R)-(−)-2-hydroxy-3(E)-pentene-1-yl]phosphonate (**2a**):* To dry dichloromethane (50 ml) at −20 to −25°C, titanium (IV) isopropoxide (2.02 ml, 0.00679 mol) and after 5 min, diisopropyl (+)-tartrate (1.71 ml, 0.00815 mol) are added under magnetic stirring. After 5 min, diisopropyl [(±)-2-

TABLE I

Physical and spectral data of hydroxyphosphonates **2a–d** and **5**

Compound	Yield (%)	n_D^{20} or mp(°C)	Elemental anal. %P Calc.	Found	IR ν(cm^{-1})	^{1}H NMR(CDCl$_3$/TMS) δ J(Hz)
2a	64	1,4476	12,38	12,60	3360(s,b),3040(w) 1664(w),1228(s) 1124(s), 972(s)	1.29(d,J=7,12H,-OCH(CH$_3$)$_2$),1.6(d,J=7'3H,=CH-CH$_3$), 1.95(dd,J=17 and J=7,2H,-CH$_2$P(O)-),4.0(s,1H-OH), 4.26-4.86(m,3H,-CH(OH)-,-OCH(CH$_3$)$_2$),5.36-5.90(m, 2H,-CH=CH-)
2b	75.4	1,4471	13,12	13,10	3380(s,b),3064(w) 1656(w),1424(s) 1228(s),1112(s) 1004(s), 913(s)	1.3(d,J=7,12H,-CH(CH$_3$)$_2$),1.88(dd,J=17 and J=7,2H, -CH$_2$P(O)-),4.06(s,1H,-OH),4.32-4.90(m,3H,-CH(OH)- -CH(CH$_3$)$_2$),5.06(d,J=10,1H,-CH=CH$_2$cis),5.28(d,J=16, 1H,-CH=CH$_2$trans),5.72-6.08(m,1H,-CH=CH$_2$)
2c	75	1,4439	11,72	11,48	3370(br,s),1365(s) 1375(s),1245(s) 1224(s),1010(s) 992(s)	1.32(d,J=6,12H,-OCH(CH$_3$)$_2$),1.69(m,6H,=C(CH$_3$)$_2$),1.8- 2.1(m, 2H, -CH$_2$-P(O)<),3.6(s,1H,-OH),4.4-4.9(m,3H, -CH(OH),-OCH(CH$_3$)$_2$,5.15-5.32(m,1H,-CH=C(CH$_3$)$_2$)
2d	78.1	1,5092	9,92	9,80	3360(s,b),3040(w) 1668(w),1608(w) 1500(m),1456(m) 1224(s),1114(s) 972(s)750(s)700(s)	1.25(d,J=7,12H,-CH(CH$_3$)$_2$),2.05(dd,J=17 and J=7,2H, -CH$_2$-P(O)),4.3(s,-OH),4.44-4.84(m,3H,-CH(OH),-CH- (CH$_3$)$_2$),6.20(dd,J=16,J=6,1H,-CH=CHCH(OH)-),6.62(d, J=16,1H,CH=CH-CH(OH)-,7.14-7.42(m,5H,-C$_6$H$_5$)
5	67.2	45-46	9,37	9,32	3460(s,b),1652(w) 1232(s), 982(s) 896(m)	1.36(d,J=6.5,12H,-OCH(CH$_3$)$_2$),1.66(s,3H,-C(=CH$_2$)-CH$_3$), 3.70(s,1H,-OH),4.4(m,1H,-CH(OH)-),4.72(m,2H,-C(=CH$_2$) -CH$_3$),4.6-4.9(m,2H,-OCH(CH$_3$)$_2$),5.8(m,1H,>C=CH-)

hydroxy-3(*E*)-pentene-1-yl]phosphonate (**2a**, 1.7 g, 0.00679 mol) and finally, a dichloromethane solution of *t*-butyl hydroperoxide (0.004 mol, dried over magnesium sulfate) is added. The stirring is turned off and the reaction mixture is put into a freezer at −20°C–25°C. The reaction is monitored by GC. After 68 hrs, 55% of hydroxy phosphonate is converted into α,β-epoxy alcohol **7**. At that time, the reaction mixture is taken out of the freezer and quenched with 10% aqueous solution of tartaric acid (50 ml). The mixture is stirred for 1 hr, allowing it to warm to 20°C. Dichloromethane (50 ml) is added and the organic layer is washed with water (2 × 50 ml), brine (2 × 50 ml) and dried over sodium sulfate. The filtrate is evaporated to dryness yielding reaction products (3.3 g) which are subjected to column chromatography (silica gel, ether). Diisopropyl [(*R*)-(−)-2-hydroxy-3(*E*)-pentene-1-yl]phosphonate (0.53 g, 30%) is obtained: $[\alpha]_{578}^{20} = -13.60°$ (c 10.0, CH_3OH). Epoxy alcohol **7** is eluated from the column with the ether-methanol (20:1) system. Thus, diisopropyl [(−)-3,4-epoxy-2-hydroxypentane-1-yl]phosphonate (7,0, 28 g, 15%) is obtained: $[\alpha]_{578}^{20} = -17.60°$ (c 10.0, CH_3OH). ^1H NMR ($CDCl_3$, TMS), δ: 1.35–1.42 (*m*, 9H, $(C\underline{H}_3)_2CH$— and —$C\underline{H}_3$); 1.95–2.20 (*m*, 2H, $C\underline{H}_2$); 2.81–2.90 (*m*, 1H, C<u>H</u> of the oxirane); 3.04–3.18 (*m*, 1H, C<u>H</u> of the oxirane); 3.50 (bs, 1H, —<u>OH</u>); 3.80–4.00 (*m*, 1H, —<u>CH</u>(OH)—); 4.78–4.85 (*m*, 2H, —$C\underline{H}(CH_3)_2$) IR (Film) 985(s), 1015(s), 1200(s), 1375(s), 1385(s), 3360 (s, br)cm^{-1}.

*Diisopropyl [(S)-(+)-2-hydroxy-3(E)-pentene-1-yl]phosphonate (**2a**):* The reaction was carried out as for (−)-**2a** except that diisopropyl (−)-tartrate is used instead of diisopropyl (+)-tartrate. After 120 h, 54% of hydroxyphosphonate **2a** is converted into epoxyhydroxyphosphonate (mixture of diastereoisomers, GC). Diisopropyl [(*S*)-(+)-2-hydroxy-3(*E*)-pente-ne-1-yl]phosphonate: 0.52 g (30%), $[\alpha]_{578}^{20} = +9.20$ (c 10.0, CH_3OH), was obtained. In this case, diisopropyl [3,4-epoxy-2-hydroxypentane-1-yl]phosphonate was not isolated.

*Claisen rearrangement of the hydroxyphosphonates **2a–d**, and **5**. General procedure:* A mixture of hydroxyphosphonate **2a–d** or **5** (0.008 mol), ethyl orthoacetate (0.056 mol) and propionic acid (0.02 ml) is heated (138°C) for 2 h with simultaneous distilling of the ethanol formed. When TLC shows transformation of **2a–d** or **5** to be complete, the excess of orthoacetate is distilled off and the crude

TABLE II

Physical and spectral data of carbethoxyphosphonates **3a–d** and **6**

Compound	Yield (%)	n_D^{20} or mp(°C)	Elemental anal. %P Calc.	Found	IR ν(cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J(Hz)
3a	76.1	1.4429	9,67	9,40	3040(w),1748(S) 1380(s),1252(s) 974(s)	1.02(d,J=6,3H,-CH(C<u>H</u>$_3$)-),1.32(t,J=7,3H,-CH$_2$C<u>H</u>$_3$),1.36 (d,J=7,12H,-CH(C<u>H</u>$_3$)$_2$),4.10(q,J=7,2H,-OC<u>H</u>$_2$CH$_3$),4.44-4.82(m,2H,-OC<u>H</u>(CH$_3$)$_2$),5.32-5.58(m,2H,-C<u>H</u>=C<u>H</u>-),
3b	80.8	1.4455	10,12	10,00	1748(s),1256(s) 988(s)	1.28(d,J=7,12H,-CH(C<u>H</u>$_3$)$_2$),1.24(t,J=7,3H,-OCH$_2$C<u>H</u>$_3$), 2.20-2.64(m,6H,-CH$_2$- groups)4.12(q,J=7,2H,-OC<u>H</u>$_2$CH$_3$), 4.42-4.84(m,2H,-OC<u>H</u>(CH$_3$)$_2$),5.24-5.70(m,2H,-C<u>H</u>=C<u>H</u>-)
3c	77.3	1.4405	9,26	9,28	3040(w),1735(s) 1385(m),1375(m) 1250(s),1010(s) 984(s)	1.14(s,6H,-C(C<u>H</u>$_3$)$_2$-),1.30(d,J=6.5,12H,-OCH(C<u>H</u>$_3$)$_2$,1.32 (t,J=7,3H,-OCH$_2$C<u>H</u>$_3$),2.08(s,2H,-C<u>H</u>$_2$-CO$_2$-),2.5(d,J_{H-P}=22 splited on d,J=7,2H,-P-C<u>H</u>$_2$-CH=),4.11(q,J=7,-OC<u>H</u>$_2$CH$_3$), 4.68(m,2H,-OC<u>H</u>(CH$_3$)$_2$,5.38(d,J=16 splited on q,J=7,1H -P-CH$_2$-C<u>H</u>=CH),5.72(d,J=16 splited on d,J_{H-P}=4,-P-CH$_2$-CH=C<u>H</u>-)
3d	86.9	26-29	8,10	8,35	3040(w),1744(s) 1658(w),1648(w) 1612(w),1500(m) 1452(m),1256(s) 980(s),768(s) 704(s)	1.28(d,J=7,12H,-CH(C<u>H</u>$_3$)$_2$),1.12(t,J=7,3H,-OCH$_2$C<u>H</u>$_3$),2.3-2.75(m,4H),4.02(q,J=7,2H,-OC<u>H</u>$_2$CH$_3$),3.70-4.02(m,1H,-C<u>H</u>(C$_6$H$_5$)-),4.40-4.78(m,2H,-C<u>H</u>(CH$_3$)$_2$),5.20-5.90(m,2H,-C<u>H</u>=C<u>H</u>-),7.10-7.35(m,5H,-C$_6$<u>H</u>$_5$)
6	74.2	1.4760	7,71	7,52	1748(s),1652(w) 1052(w), 988(s) 896(m)	1.20(t,J=7,3H,-OCH$_2$C<u>H</u>$_3$),1.27(d,J=6.5,12H,-OCH(C<u>H</u>$_3$)$_2$), 1.68(s,3H,-C(=CH$_2$)C<u>H</u>$_3$),4.08(q,J=7,2H,-OC<u>H</u>$_2$CH$_3$,4.60 (m,2H,-OC<u>H</u>(CH$_3$)$_2$,4.68(m,2H, -C(=C<u>H</u>$_2$)CH$_3$,5.25(m,1H, >C=CH-CH$_2$-)

product is purified by column chromatography (silica gel, hexane-acetone, 3:2). The reaction yields, physical and spectral data of carbethoxy phosphonates **3a–d** and **6** are given in Table II.

ACKNOWLEDGEMENT

This work was supported by the Polish Ministry of Education (MEN). The authors are grateful to Dr. S. K. Park and Dr. I. Ujvary (SUNY, Stony Brook, USA) for ^{1}H NMR (300 MHZ) Spectra.

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