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SYNTHESIS OF NEW FURAN-DERIVED N-SUBSTITUTEDAMINOMETHANEPHOSPHONATES

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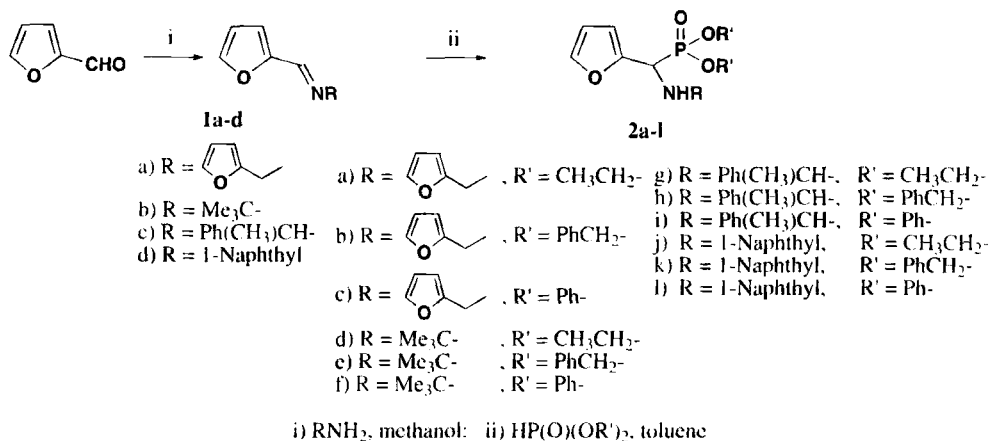
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SYNTHESIS OF NEW FURAN-DERIVED N-SUBSTITUTED AMINOMETHANEPHOSPHONATES

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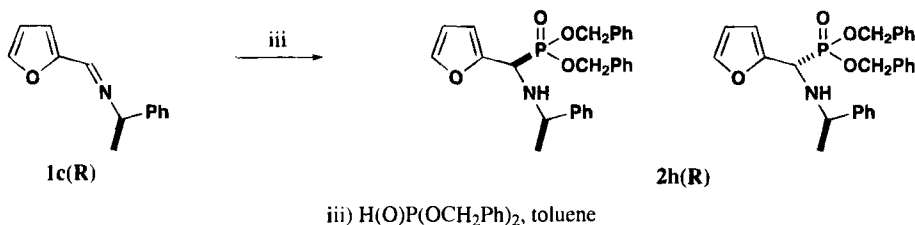
Substituted furan derivatives are important compounds,¹ as exemplified by a series of nitro-fural derived drugs,² such as the efficient anti-histamine agent the ranitidine³ or the anti-*Pneumocytis carinii* agent derived from diphenylfuran.⁴ Their importance derives also from their role as versatile synthetic intermediates.⁵ The first preparation of the phosphonic analogues of natural amino acids,⁶⁻⁸ stimulated biochemical studies,^{9,10} which confirmed that aminophosphonic and aminophosphonous acids also belong to the group of biologically active compounds.



As a part of our efforts to screen for new furanic plant protection agents, we have examined routes to new furan derived aminophosphonic acids to combine the bioactivity of these two classes of compounds. Previous papers¹¹ reported the synthesis of various new furan-containing aminophosphonates and aminophosphonites and discussed their stereochemical aspect. In this paper, we would like to report the preparation of the series of variously N-substituted (2-furyl)aminomethanephosphonates, obtained by the addition of dialkyl (or diaryl) phosphites to the azomethine bond of Schiff bases.

The general methodology for the preparation of aminophosphonic acids and esters was first worked out by Oleksyszyn *et al.*⁷ and recently described by Boduszek¹² and Hubert *et al.*¹³ Four Schiff bases N-furfurylidene-furfurylamine (**1a**), N-furfurylidene-*tert*-butylamine (**1b**), N-furfurylidene-(±)- α -methylbenzylamine (**1c**) and N-furfurylidene-1-naphthylamine (**1d**) were prepared by a slight modification of the published procedure.^{11,13} Furfural and the corresponding amine were mixed together without any solvent and stored at the room temperature for 5 hours, then the resulting Schiff bases were purified by the vacuum distillation or by column chromatography on neutral alumina. Schiff bases were then converted to aminophosphonates by the addition of dialkyl (or diaryl) phosphites to the azomethine bond. Diethyl, dibenzyl and diphenyl phosphites were chosen as model compounds, because of their commercial availability. The reactions were carried out in boiling toluene for 7 hours. The aminophosphonates were obtained in fair (50-70%) yields except for diethyl (2-furyl)-N-furfurylaminomethane phosphonate **2a**. In this case, the conversion rate was less than 60% and the isolation of this phosphonate was troublesome. Freshly prepared aminophosphonates **2b-I** were purified either by the crystallization or by column chromatography on silica gel.

We also performed the addition of phosphites to the chiral N-furfurylidene-(R)- α -methylbenzylamine **1c(R)**, which was used previously by Yuan and Cui¹⁴ to benzyl aminophosphonates. As expected,^{11,14} the reaction was stereoselective showing a 2:1 diastereoisomeric ratio. In the case of the dibenzyl phosphite addition, we succeeded in separating the product **2h(R)** into two diastereoisomers by column chromatography in 41% (the predominant isomer) and 21% (the minor isomer) yields. As both diastereoisomers were oily liquids, we could not perform the X-ray determination of the absolute configuration. Thus, the configuration remains unresolved and we are currently studying the possibility of converting these compounds into crystalline derivatives.



EXPERIMENTAL SECTION

All solvents were routinely distilled and dried prior to use. Furfurylamine, α -methylbenzylamine (Aldrich), *tert*-butylamine and 1-naphthylamine (Fluka) as well as diethyl and dibenzyl phosphites (Aldrich) and diphenyl phosphite (Fluka), were used as received. ¹H and ³¹P NMR spectra were recorded on a Varian Gemini 200 BB apparatus. Melting points were measured on a MelTemp II apparatus and were not corrected. Schiff bases were synthesized basing on modified published procedures

SYNTHESIS OF NEW FURAN DERIVED N-SUBSTITUTED AMINOMETHANEPHOSPHONATES

N-furfurylidenefurfurylamine (1a), bp. 126°/2 mm, *lit*¹⁵ bp₂: 130°/2 mm in 74% yield ¹H NMR (CDCl₃, 200 MHz): d 8.11 (s, CH=N, 1H), 7.51 (m, H⁵_{fur}, 1H), 7.38 (m, H⁵_{fur}, 1H), 6.79 (d, J = 3.4 Hz, H³_{fur}, 1H), 6.47 (dd, J = 3.4 and 1.8 Hz, H⁴_{fur}, 1H), 6.34 (d, J = 3.2 Hz, H³_{fur}, 1H), 6.29 (m, H⁴_{fur}, 1H), 4.75 (s, CH₂Fur, 2H).

N-furfurylidene-tert-butylamine (1b), bp. 95°/10 mm, *lit*¹⁶ bp. 140°/12 mm in 78% yield ¹H NMR (CDCl₃, 200 MHz): d 8.07 (s, CH=N, 1H), 7.49 (m, H⁵_{fur}, 1H), 6.69 (d, J = 3.4 Hz, H³_{fur}, 1H), 6.45 (dd, J = 3.4 and 1.6 Hz, H⁴_{fur}, 1H), 1.29 (s, CH₃, 9H).

N-furfurylidene-(±)-α-methylbenzylamine (1c), bp. 123°/2 mm, *lit*¹⁷ bp. 164-166°/13 mm in 64% yield ¹H NMR (CDCl₃, 200 MHz): d 8.06 (s, CH=N, 1H), 7.41-7.13 (m, ArH, H⁵_{fur}, 6H), 6.65 (d, J = 3.4 Hz, H³_{fur}, 1H), 6.45 (dd, J = 3.4 and 1.7 Hz, H⁴_{fur}, 1H), 4.42 (quart, J = 6.6 Hz, CHN, 1H), 1.58 (d, J = 6.6 Hz, CH₃, 3H).

N-furfurylidene-1-naphtylamine (1d), chromatographed on neutral alumina eluted with ethyl acetate to obtain yellow oily liquid in 88% yield ¹H NMR (200 MHz, CDCl₃): d 8.38-8.33 (m, H3, 1H), 8.32 (s, CH=N, 1H), 7.84-7.80 (m, H6, 2H), 7.69 (d, J = 8.2 Hz, H8, 1H), 7.63 (m, H⁵_{fur}, 1H), 7.52-7.46 (m, H5 and H7, 2H), 7.40 (d, J=8.0 Hz, H2, 1H), 7.01 (d, J = 6.6 Hz, H4, 1H), 7.00 (m, H³_{fur}, 1H), 6.55 (dd, J = 2.0 and 3.2 Hz, H⁴_{fur}, 1H).

Anal. Calcd for C₁₅H₁₁NO: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.68; H, 5.23; N, 6.24

Dialkyl (-aryl) (2-furyl)-N-alkyl (-aryl)aminomethane Phosphonates (2a-l).- To a solution of the Schiff base (5 mmol) in toluene (30 mL) heated at 40°, was added dialkyl (or -aryl) phosphite (5 mmol). The mixture was then refluxed for 7 hours and stirred for 12 hours at a room temperature, it was then evaporated and crystallized from chloroform-hexane (1:4) or chromatographed on silica gel.

Dibenzyl (2-furyl)-N-furfurylaminomethane Phosphonate (2b), mp: 63-64° in 54% yield. ¹H NMR (200 MHz, CDCl₃): d 7.41 (d, J = 1.4 Hz, H⁵_{fur}, 1H), 7.37-7.24 (m, ArH, H⁵_{fur}, 11H), 6.36 (m, H³_{fur}, H⁴_{fur}, 2H), 6.27 (m, H³_{fur}, 1H), 6.11 (m, H⁴_{fur}, 1H), 5.18-5.00 (The AB part of ABX system, ²J_{HH} = 12.1 Hz, ³J_{PH} = 8.3 Hz, ³J_{PH} = 7.2 Hz, POCH₂, 2H), 5.02-4.82 (The AM part of AMX system, ²J_{HH} = 11.8 Hz, ³J_{PH} = 7.4 Hz, ³J_{PH} = 8.0 Hz, POCH₂, 2H), 4.21 (d, ²J_{PH} = 21.4 Hz, CHP, 1H), 3.84 (d, J = 14.3 Hz, CH_αCH_β, 1H), 3.61 (d, J = 14.3 Hz, CH_αCH_β, 1H), 2.17 (s, CHN, 1H). ³¹P NMR (81 MHz, CDCl₃): d 20.87

Anal. Calcd for C₂₄H₂₄NO₅P: C, 65.90; H, 5.53; N, 3.20; P, 7.08

Found: C, 65.94; H, 5.54; N, 3.37; P, 6.81

Diphenyl (2-furyl)-N-furfurylaminomethane Phosphonate (2c), mp: 65-70° in 69% yield.

¹H NMR (200 MHz, CDCl₃): d 7.43-7.00 (m, ArH, H⁵_{fur}, H⁵_{fur}, 12H), 6.48 (t, J = 3.3 Hz, H³_{fur}, 1H), 6.39 (m, H³_{fur}, 1H), 6.30 (dd, J = 3.1 and 2.0 Hz, H⁴_{fur}, 1H), 6.17 (d, J = 3.3 Hz, H⁴_{fur}, 1H), 4.50 (d, ²J_{PH} = 21.5 Hz, CHP, 1H), 3.94 (d, J = 14.6 Hz, CH_αCH_β, 1H), 3.71 (d, J = 14.6 Hz, CH_αCH_β, 1H), 2.34 (s, NH, 1H). ³¹P NMR (81 MHz, CDCl₃): d 13.96.

Anal. Calcd for C₂₂H₂₀NO₅P: C, 64.55; H, 4.92; N, 3.42; P, 7.57

Found: C, 64.64; H, 4.94; N, 3.47; P, 7.55

Diethyl (2-furyl)-N-tert-butylaminomethane Phosphonate (2d), mp. 205-207° in 52% yield. ¹H

NMR (200 MHz, CDCl₃): δ 7.40 (m, H⁵_{fur}, 1H), 7.07 (m, H³_{fur}, 1H), 6.40 (m, H⁴_{fur}, 1H), 4.38 (d, ²J_{PH} = 18.7 Hz, CHP, 1H), 4.00-3.51 (2m, CH₂CH₃, 4H), 1.28 (s, CH₃, 9H), 1.06 and 1.00 (2t, J = 7.0 Hz, CH₂CH₃, 6H). ³¹P NMR (81 MHz, CDCl₃): δ 21.00.

Anal. Calcd for C₁₃H₂₄NO₄P: C, 53.97; H, 8.36; N, 4.84; P, 10.71

Found: C, 53.74; H, 8.16; N, 4.69; P, 10.91

Dibenzyl (2-furyl)-N-tert-butylaminomethane Phosphonate (2e), mp. 44-46° in 73% yield. ¹H NMR (200 MHz, CDCl₃): δ 7.37 (m, H⁵_{fur}, 1H), 7.37-7.24 (m, ArH, 10H), 6.33 (m, H³_{fur}, 1H); 6.30 (m, H⁴_{fur}, 1H), 5.25-5.08 (The AB part of ABX system, ²J_{HH} = 11.9 Hz, ³J_{PH} = 7.6 Hz, ³J_{PH} = 7.1 Hz, POCH₂, 2H), 5.01-4.89 (The AM part of AMX system, ²J_{HH} = 11.9 Hz, ³J_{PH} = 6.8 Hz, ³J_{PH} = 8.0 Hz, POCH₂, 2H), 4.33 (d, ²J_{PH} = 26.0 Hz, CHP, 1H), 1.54 (s, CHN, 1H), 0.97 (s, CH₃, 9H). ³¹P NMR (81 MHz, CDCl₃): δ 21.53

Anal. Calcd for C₂₃H₂₈NO₄P: C, 66.82; H, 6.83; N, 3.39; P, 7.49

Found: C, 66.36; H, 7.13; N, 3.58; P, 7.34

Diphenyl (2-furyl)-N-tert-butylaminomethane Phosphonate (2f), mp. 227-228° in 57% yield ¹H NMR (200 MHz, CDCl₃): δ 7.40-6.80 (m, ArH, H⁵_{fur}, 11H), 6.41 (m, H³_{fur}, 1H), 6.36 (m, H⁴_{fur}, 1H), 4.59 (d, ²J_{PH} = 25.8 Hz, CHP, 1H), 1.02 (s, CH₃, 9H). ³¹P NMR (81 MHz, CDCl₃): δ 13.21.

Anal. Calcd for C₂₁H₂₄NO₄P: C, 65.45; H, 6.28; N, 3.63; P, 8.04

Found: C, 65.33; H, 6.14; N, 3.59; P, 8.12

Diethyl (2-furyl)-N-(±)-α-methylbenzylaminomethane Phosphonate (2g), eluted with hexane-ethyl acetate 1:4 to obtain dark yellow oil in 59% yield. ¹H NMR (CDCl₃, 200 MHz): δ 7.45 (m, H_{5fur}, 1H), 7.28 (m, ArH, 10H), 6.37 (m, H_{3fur}, 1H), 6.32 (m, H_{3fur} and H_{4fur}, 2H), 6.27 (m, H_{4fur}, 1H), 4.18 (d, ²J_{PH} = 21.6 Hz, CHP, 1H), 4.00-3.51 (2m, CH₂CH₃, 4H), 3.87 (d, ²J_{PH} = 21.6 Hz, CHP, 1H), 3.87 (quart, J = 6.7 Hz, CHN, 1H), 3.67 (quart, J = 6.7 Hz, CHN, 1H), 1.26 (d, J = 6.7 Hz, CHCH₃, 3H), 1.16 and 1.08 (2t, J = 7.0 Hz, CH₂CH₃, 6H). ³¹P NMR (CDCl₃, 81 MHz): δ 22.23 and 22.04.

Anal. Calcd for C₁₇H₂₄NO₄P: C, 60.53; H, 7.17; N, 4.15; P, 9.18

Found: C, 60.31; H, 7.32; N, 4.34; P, 9.25

Dibenzyl (2-furyl)-N-(±)-α-methylbenzylaminomethane Phosphonate (2h), mp. 75-77° in 69% yield. ¹H NMR (CDCl₃, 200 MHz): δ 7.37-7.21 (m, ArH, H_{5fur}, 16H), 6.36 (m, H_{3fur}, 1H), 6.31 (m, H_{3fur} and H_{4fur}, 2H), 6.24 (m, H_{4fur}, 1H), 5.24-5.02 (The part of ABX system, m, OCH₂Ph, 2H), 4.97-4.73 (The part of AMX system, m, OCH₂Ph, 2H), 4.24 (d, ²J_{PH} = 21.6 Hz, CHP, 1H), 3.95 (d, ²J_{PH} = 21.6 Hz, CHP, 1H), 3.86 (quart, J = 6.7 Hz, CHN, 1H), 3.65 (quart, J = 6.7 Hz, CHN, 1H), 1.26 (d, J = 6.7 Hz, CHCH₃, 3H). ³¹P NMR (CDCl₃, 81 MHz): δ 23.18 and 22.36.

Anal. Calcd for C₂₇H₂₇NO₄P: C, 70.43; H, 5.91; N, 3.04; P, 6.73

Found: C, 70.31; H, 5.82; N, 2.89; P, 6.55

Diphenyl (2-furyl)-N-(±)-α-methylbenzylaminomethane Phosphonate (2i), mp. 205-207° in 53% yield. ¹H NMR (200 MHz, CDCl₃): δ 7.26-6.90 (m, ArH, H_{5fur}, 16H), 6.34 (m, H_{4fur}, H_{3fur}, 1H), 4.52 (d, ²J_{PH} = 23.4 Hz, CHP, 1H), 4.21 (d, ²J_{PH} = 24.8 Hz, CHP, 1H), 3.97 and 3.72 (quart, J = 6.6 Hz, CHN, 1H), 2.18 (s, NH, 1H), 1.34 and 1.31 (2d, J=6.6 Hz, CH₃, 3H). ³¹P NMR (81 MHz, CDCl₃): δ

12.26 and 12.22.

Anal. Calcd for C₂₅H₂₄NO₄P: C, 69.28; H, 5.58; N, 3.23; P, 7.15

Found: C, 69.44; H, 5.72; N, 3.01; P, 7.40

Dibenzyl (2-furyl)-*N*-(*R*)- α -methylbenzylaminomethane Phosphonate 2h(R), separated by chromatography on silica gel eluted with hexane-ethyl acetate (1:4)

Predominant Diastereoisomer, $[\alpha]_D^{20} = 6.14^\circ$ (c=1.022 MeOH) in 41% yield. IR(neat): 3280(NH); 2990(CH); 1250(P=O) cm⁻¹. ¹H NMR (CDCl₃, 200 MHz): δ 7.37-7.21 (m, H_{arom}, H_{5fur}, 16H), 6.31 (m, H_{3fur} and H_{4fur}, 2H), 5.24-5.02 (The part of ABX system, ³J_{PH} = 8.1 Hz, ³J_{PH} = 6.8 Hz, ³J_{HH} = 11.7 Hz, OCH₂Ph, 2H), 4.97-4.73 (The part of AMX system, ³J_{PH} = 8.1 Hz, ³J_{PH} = 6.4 Hz, ³J_{HH} = 11.7 Hz, OCH₂Ph, 2H), 4.24 (d, ²J_{PH} = 21.6 Hz, CHP, 1H), 3.86 (quart, J = 6.7 Hz, CHN, 1H), 1.26 (d, J = 6.7 Hz, CHCH₃, 3H). ³¹P NMR (CDCl₃, 81 MHz): δ 23.18.

Anal. Calcd for C₂₇H₂₇NO₄P: C, 70.43; H, 5.91; N, 3.04; P, 6.73

Found: C, 70.23; H, 6.01; N, 2.70; P, 6.47

Minor Diastereoisomer, $[\alpha]_D^{20} = -13.24^\circ$ (c=0.992 MeOH) in 21% yield. IR(neat): 3280(NH); 2990(CH); 1250(P=O) cm⁻¹. ¹H NMR (CDCl₃, 200 MHz): δ 7.35-7.19 (m, H_{arom}, H_{5fur}, 16H), 6.36 (m, H_{3fur}, 1H), 6.24 (m, H_{4fur}, 1H), 5.25-5.03 (The part of ABX system, ³J_{PH} = 8.0 Hz, ³J_{PH} = 6.5 Hz, ³J_{HH} = 12.1 Hz, OCH₂Ph, 2H), 5.00-4.71 (The part of AMX system, ³J_{PH} = 7.6 Hz, ³J_{PH} = 6.0 Hz, ³J_{HH} = 12.1 Hz, OCH₂Ph, 2H), 3.95 (d, ²J_{PH} = 21.6 Hz, CHP, 1H), 3.65 (quart, J = 6.7 Hz, CHN, 1H), 1.26 (d, J = 6.7 Hz, CHCH₃, 3H). ³¹P NMR (CDCl₃, 81 MHz): δ 22.66.

Anal. Calcd for C₂₇H₂₇NO₄P: C, 70.43; H, 5.91; N, 3.04; P, 6.73

Found: C, 70.63; H, 6.18; N, 2.83; P, 6.54

Diethyl (2-furyl)-*N*-1-naphtylaminemethane Phosphonate (2j), eluted with hexane-ethyl acetate to obtain yellow oily liquid in 59% yield. ¹H NMR (200 MHz, CDCl₃): δ 7.98 (m, H3, 2H), 7.76 (m, H6, 1H), 7.48 (m, H7, H8, 2H), 7.39 (m, H⁵_{fur}, 1H), 7.26 (m, H5, H2, 2H), 6.62 (m, H¹_{fur}, 1H), 6.41 (m, H4, 1H), 6.32 (m, H⁴_{fur}, 1H), 5.09 (d, ²J_{PH} = 23.3 Hz, CHP, 1H), 4.3-3.8 (m, CH₂OP, 4H), 2.08 (s, NH, 1H), 1.30 and 1.22 (2t, J = 6.8 Hz, CH₃CH₂, 6H). ³¹P NMR (81 MHz, CDCl₃): δ 19.57

Anal. Calcd for C₁₉H₂₂NO₄P: C, 63.50; H, 6.17; N, 3.90; P, 8.63

Found: C, 63.26; H, 6.10; N, 3.82; P, 8.83

Dibenzyl (2-furyl)-*N*-1-naphtylaminemethane Phosphonate (2k), mp. 86-88° in 53% yield. ¹H NMR (200 MHz, CDCl₃): δ 7.66 (m, H3, 2H), 7.78 (m, H6, 1H), 7.45 (m, H7, H8, 2H), 7.35 (m, H⁵_{fur}, 1H), 7.31-7.18 (m, ArH, H5, H2, 12H), 6.57 (dd, J = 6.7 and 1.3 Hz, H³_{fur}, 1H), 6.40 (m, H4, 1H), 6.32 (m, H⁴_{fur}, 1H), 5.11 (d, ²J_{PH} = 24.0 Hz, CHP, 1H), 5.10 (m, CH₂Ph, 2H), 5.03 (dd, ²J_{HH} = 12.0 Hz and ³J_{PH} = 7.7 Hz, CH₂H_nPh, 1H), 4.84 (dd, ²J_{HH} = 11.7 Hz and ³J_{PH} = 8.4 Hz, CH_nH_nPh, 1H), 1.25 (s, NH, 1H). ³¹P NMR (81 MHz, CDCl₃): δ 11.78

Anal. Calcd for C₂₉H₂₆NO₄P: C, 72.04; H, 5.42; N, 2.90; P, 6.41

Found: C, 72.40; H, 5.32; N, 2.80; P, 6.32

Diphenyl (2-furyl)-*N*-1-naphtylaminemethane Phosphonate (2l), mp. 119-121° in 53% yield. ¹H NMR (200 MHz, CDCl₃): δ 7.88 (m, H3, 2H), 7.81 (m, H6, 1H), 7.47 (m, H7, H8, 2H), 7.40 (m, H⁵_{fur},

1H), 7.32-7.23 (m, ArH, 6H), 7.15 (m, ArH, 4H), 7.07 (m, H5, 1H), 7.04 (m, H2, 1H), 6.70 (dd, J = 6.7 and 1.3 Hz, H³_{fur}, 1H), 6.51 (m, H4, 1H), 6.34 (m, H⁴_{fur}, 1H), 5.45 (d, ²J_{PH} = 24.4 Hz, CHP, 1H), 1.64 (s, NH, 1H). ³¹P NMR (81 MHz, CDCl₃): δ 11.78

Anal. Calcd for C₂₇H₂₂NO₄P: C, 71.20; H, 4.87; N, 3.08; P, 6.80

Found: C, 70.87; H, 4.89; N, 3.15; P, 6.83

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