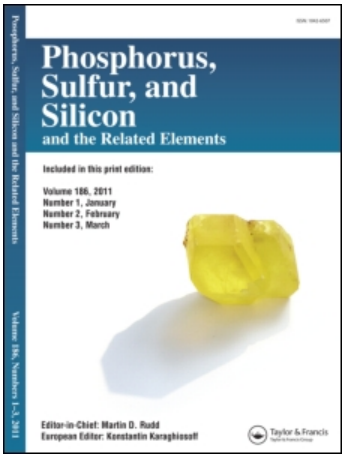


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Synthesis of Enantiomers of Some Aminophosphonate Derivatives

Hieu T. Phan[a]; Vinh V. Diep[a]; Raymond Azoulay[a]; Ln M. Nguyen[a]
[a] Symphar SA, Geneva, Switzerland

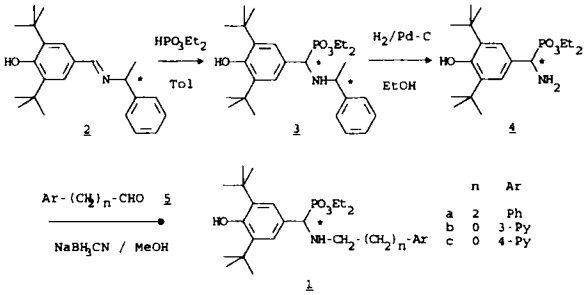
To cite this Article Phan, Hieu T. , Diep, Vinh V. , Azoulay, Raymond and Nguyen, Ln M.(1999) 'Synthesis of Enantiomers of Some Aminophosphonate Derivatives', Phosphorus, Sulfur, and Silicon and the Related Elements, 147: 1, 315
To link to this Article: DOI: 10.1080/10426509908053638
URL: http://dx.doi.org/10.1080/10426509908053638

Phosphorus, Sulfur and Silicon, 1999, Vol. 147, pp. 315-315
Reprints available directly from the publisher
Photocopying permitted by license only

Synthesis of Enantiomers of Some Aminophosphonate Derivatives

HIEU T. PHAN, VINH V. DIEP, RAYMOND AZOULAY and LÂN M. NGUYEN

Symphar SA, 243 route des Fayards, 1290 Versoix (Geneva), Switzerland



Racemic diethyl α-(3,5-di-tert-butyl-4-hydroxyphenyl)-N-(arylakyl)aminomethylphosphonates 1 have been demonstrated to possess potent cholesterol lowering and antioxidant activities in the mouse and dog [1]; therefore it is of interest to determine if this pharmacological effect is due to one of its individual enantiomers. We wish to report the synthesis of enantiomer pairs of the three compounds 1(a,b,c). The synthetic route is based on the preparation of the enantiomers of the key primary amine 4. Condensation of 3,5-di-tert-butyl-4-hydroxybenzaldehyde with R(+)- and S(-)-α-methylbenzylamine gave the corresponding imine 2 to which was added diethyl phosphite. In each case, the major diastereomer of the aminophosphonates 3 formed were purified by crystallization and catalytically hydrogenated to yield an optically active primary aminophosphonate 4. In agreement with the literature [2][3], it was found that the major diastereomer 3 obtained from R(+)-α-methylbenzylamine gave, on hydrogenation, the levorotatory enantiomer 4, while the major diastereomer 3 from S(-)-α-methylbenzylamine yielded the dextrorotatory isomer 4 ($[\alpha]_{D\,22}$ -12.12° (c 1.65, $CHCl_3$) and $[\alpha]_{D\,22}$ +11.32° (c 1.71,$CHCl_3$))

The target enantiomers 1(a,b,c) were obtained by reacting each enantiomer 4 with an appropriate aldehyde 5 under reductive amination conditions
1a = $[\alpha]_{D\,22}$+ 31.09° (c1 9,$CHCl_3$). mp=99-100°C and -33.09° (c2 0,$CHCl_3$). mp=99-100°C
1b = $[\alpha]_{D\,22}$+42.88° (c1 6,$CHCl_3$): mp=116-119°C and -10.91°(c1 7,$CHCl_3$). mp=118-120°C
1c = $[\alpha]_{D\,22}$+43.03° (c2 0, $CHCl_3$): mp=67-70°C and -44.05°(c2 0, $CHCl_3$),mp=66-69°C

Direct three dimensional x-ray diffraction studies on two enantiomers of differently substituted analogues of aminophosphonate esters 1 revealed that (+)-enantiomer is of absolute R configuration and (-)-enantiomer corresponds to S configuration. These findings are consistent with the literature[3]

References

[1] Symphar SA, US Patent 5'424'303 (1995). H.T. Phan, L.M. Nguyen, E. Niesor, Y. Guyon-Gellin and C.L. Bentzen.
[2] W.F. Gilmore and H.A. McBride, J.Amer.Chem.Soc., **94,** 4361,(1972).
[3] T. Gloviak, W. Sawka-Dobrowolska, J. Kowalik, P. Mastalerz, M Soroka and J. Zón, THL, **1977,** 3965–3968.