Pergamon

Tetrahedron Letters 43 (2002) 3061–3065

TETRAHEDRON LETTERS

Asymmetric cyclopropanation of chiral (1-dimethoxyphosphoryl-2-phenyl)vinyl *p*-tolyl sulfoxide: a new synthesis of enantiomerically pure 2-amino-3-phenyl-1-cyclopropane-phosphonic acid—a constrained analog of phaclofen

Wanda H. Midura and Marian Mikołajczyk*

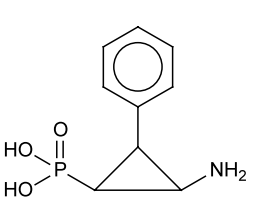
Centre of Molecular and Macromolecular Studies, Department of Heteroorganic Chemistry, Polish Academy of Sciences, 90-363 Łódź, Sienkiewicza 112, Poland

Received 2 January 2002; revised 28 January 2002; accepted 21 February 2002

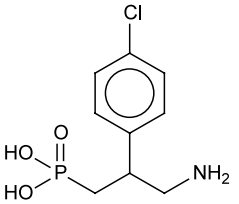
Abstract—*E*-(*S*)-(1-Dimethoxyphosphoryl-2-phenyl)vinyl *p*-tolyl sulfoxide **3** was found to undergo cyclopropanation with sulfur ylides [dimethyl(oxo)sulfonium methylide, diphenyl sulfonium isopropylide and ethyl (dimethylsulfuranylidene)acetate (EDSA)] in a highly diastereoselective manner. The major diastereomer obtained in the reaction of *E*-(*S*)-**3** with EDSA was converted into enantiopure (2*R*)-amino-(3*R*)-phenyl-(1*R*)-cyclopropane-phosphonic acid, a constrained analog of the $GABA_B$ antagonist, phaclofen. © 2002 Published by Elsevier Science Ltd.

Aminoalkylphosphonic acids are important surrogates for aminoalkylcarboxylic acids in which the planar carboxylic group is replaced by a phosphonic acid or related moiety having a tetrahedral configuration. Aminophosphonic acids, both natural and synthetic, have attracted considerable attention because of their diverse and useful biological activities.[1] Intensive research aimed at the synthesis of phosphonic acid analogs of protein and non-protein amino acids resulted in new classes of drugs and other bioactive compounds with a great variety of commercial applications, ranging from agriculture to medicine.

Thus, amino phosphonic acids display promising antibiotic and anti-cancer properties. They are strong neuromodulators, plant growth regulators and herbicides. This class of compounds also includes metal-sequestering drugs, radiopharmaceuticals and NMR imaging agents. Since the design and synthesis of conformationally constrained peptidomimetics has recently been an important strategy in modern drug discovery processes[2] and the cyclopropyl group is found as a basic structural unit in a wide range of naturally occurring compounds, both in plants and microorganisms,[3] we turned our attention to aminocyclopropanephosphonic acids which are conformationally constrained analogs of 1-, 2- and 3-aminoalkanephosphonic acids. Although many articles have been published on the preparation of this class of compounds, particularly on 1-aminocyclopropanephosphonic acids,[4] the first and only asymmetric synthesis of the enantiomerically pure 2-amino-3-phenyl-1-cyclopropane-phosphonic acid **1**, a constrained analog of the $GABA_B$ antagonist, phaclofen **2**, has recently been reported by Hanessian and co-workers.[5]



1



2

Encouraged by our results on the asymmetric synthesis of 1-amino- and 2-aminoalkylphosphonic acids mediated by a chiral sulfinyl auxiliary,[6] as well as on asymmetric cyclopropanation of chiral α-phosphorylvinyl

Keywords: asymmetric cyclopropanation; chiral α-phosphorylvinyl sulfoxides; aminocyclopropanephosphonic acid.

* Corresponding author. Fax: (+48-42) 684-71-26; e-mail: marmikol@bilbo.cbmm.lodz.pl

0040-4039/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4039(02)00374-X

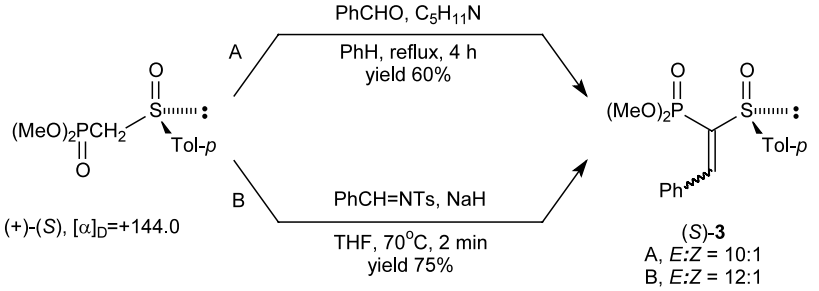
sulfoxides,[7] we decided to develop a new approach to the synthesis of the enantiomerically pure **1**. Our method, is based on the highly diastereoselective cyclopropanation of chiral *E*-(*S*)-(1-dimethoxyphosphoryl-2-phenyl)vinyl *p*-tolyl sulfoxide **3**.

The starting reagent **3** was easily prepared in 60% yield by treatment of (+)-(*S*)-dimethoxyphosphorylmethyl *p*-tolyl sulfoxide[8] with benzaldehyde in the presence of piperidine (route A) or in 75% yield by reacting with *N*-tosylsulfonyl benzylimine in the presence of a catalytic amount of sodium hydride (route B)[9] (Scheme 1). Both geometrical isomers of (*S*)-**3** formed in these reactions were separated by column chromatography [*E*-(*S*)-**3**: $[\alpha]_D = +3.2$ (*c* 3.2, acetone), $\delta_P = 12.8$ ppm; *Z*-(*S*)-**3**: $[\alpha]_D = -367.0$ (*c* 2.6, benzene), $\delta_P = 16.4$ ppm].[10]

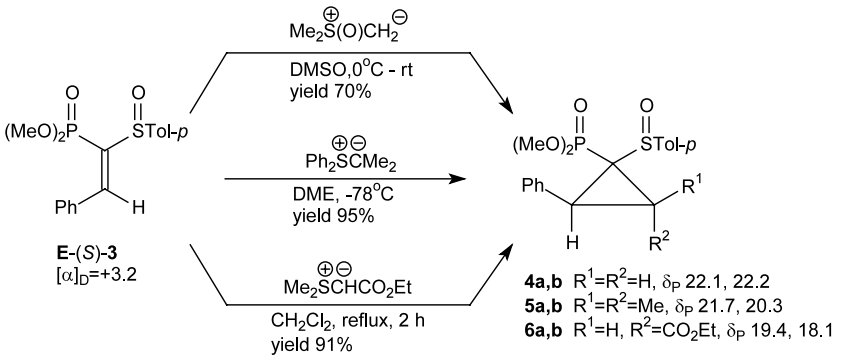
In the preliminary experiments (Scheme 2) the cyclopropanation reaction was performed with two sulfur ylides, namely dimethyl(oxo)sulfonium methylide and diphenylsulfonium isopropylide. The corresponding cyclopropanes **4** and **5** were obtained as mixtures of only two diastereomers. However, while the cyclopropane **4** was formed with moderate stereoselectivity (3:1 ratio), in the case of **5** a high level of asymmetric induction was observed leading to a 92:8 mixture of two diastereomers. The high level of diastereoselectivity observed in the latter reaction prompted us to carry out the cyclopropanation reaction of *E*-(*S*)-**3** with ethyl (dimethylsulfuranylidene)acetate (EDSA) in which three new centers of chirality should be formed under the control of the chiral *p*-toluenesulfinyl group. It was gratifying to find that the cyclopropane **6** was formed as a mixture of only two diastereomers in an 8:1 ratio. The major diastereomer of **6a** ($\delta_P = 19.4$ ppm), isolated by column chromatography was converted into the corresponding methyl ester **6a**′ ($\delta = 19.5$ ppm) in quantitative yield by transesterification with methanol under basic conditions.

Analysis of the ^{1}H and ^{13}C NMR spectra of the products **4**–**6**[11] revealed that the *cis*-relationship between the phosphoryl group and phenyl substituent in the starting *E*-(*S*)-**3** is preserved in the cyclopropane ring and the methoxycarbonyl group is *trans*-oriented to both of them. Especially conclusive was the ^{13}C NMR spectrum of **6a**′ where a $^3J_{CP}$ coupling constant of 5.1 Hz for the phenyl carbon and 2.0 Hz for the methyl ester carbonyl carbon was observed indicating *cis*- and *trans*-orientations, respectively, between phosphorus and the two carbon nuclei.[12] The relative configuration ascribed to **6a**′ is in good agreement with the transition state model for cyclopropanation of chiral α-phosphorylvinyl sulfoxides proposed by us earlier,[7] in which the approach of EDSA to the carbon–carbon double bond in *E*-(*S*)-**3** takes place preferentially from the less hindered diastereotopic face occupied by the lone electron pair of sulfur (Scheme 3). Therefore, the two diastereomers of **6** obtained differ only in the configuration at the methoxycarbonyl bearing carbon atom. Moreover, based on this transition state model it is possible to assign the absolute stereochemistry to the cyclopropane ring in **6a** and **6a**′ as (1*S*,2*R*,3*R*). The correctness of this assignment was confirmed by the conversion of **6a**′ into (2*R*)-amino-(3*R*)-phenyl-(1*R*)-cyclopropanephosphonic acid **1** outlined below (Schemes 4 and 5).

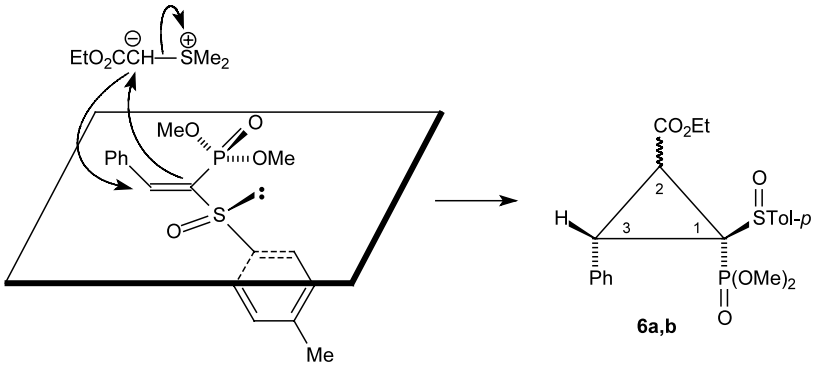
In the first step of the synthesis of **1**, the cyclopropane **6a**′ was treated with sodium amalgam in order to



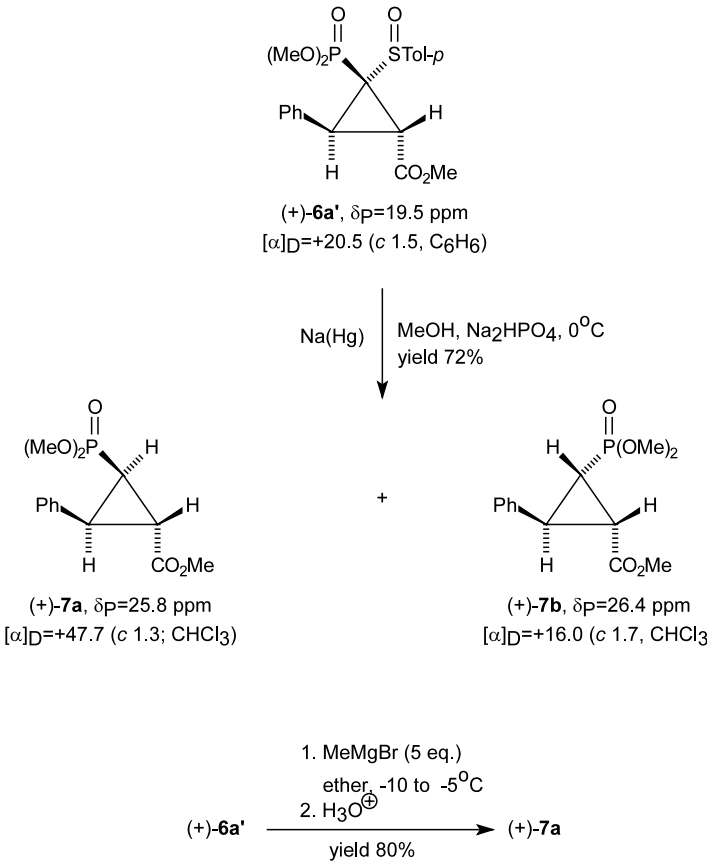
Scheme 1.



Scheme 2.



Scheme 3.

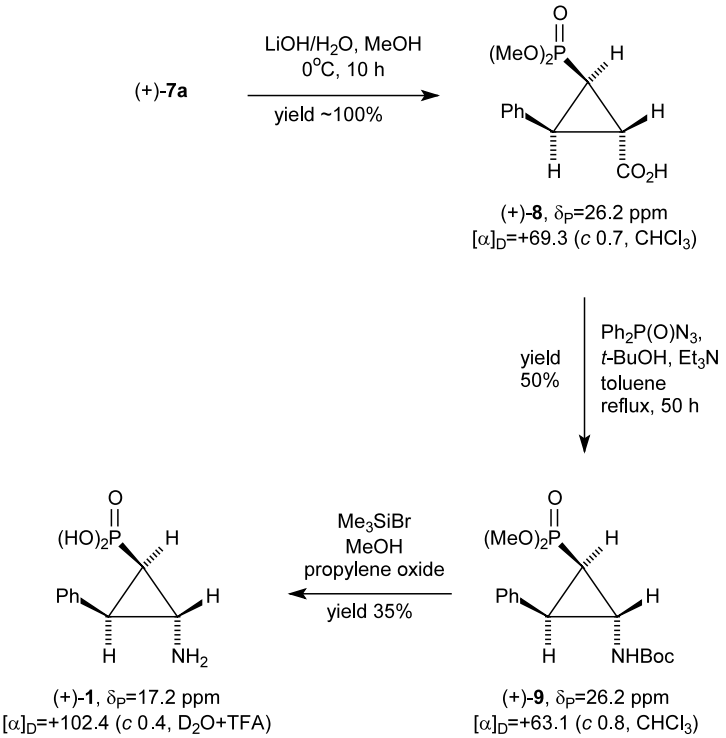


Scheme 4.

remove the chiral sulfinyl moiety via reduction of the carbon–sulfur bond. Under the reaction conditions applied (Scheme 4), the cyclopropanephosphonate **7** was obtained as a 3:1 mixture of two diastereomers **7a** and **7b**, which were easily separated by column chromatography.

Based on the three-bond carbon–phosphorus coupling constants as well as on the NOE measurements,[13] cyclopropane phosphonates **7** were found to have a different configuration at the α-phosphonate carbon atom,[14] the major diastereomer (+)-**7a** being formed with retention of configuration. From the synthetic point of view, it is relevant to emphasize that (+)-**6a**′ was converted exclusively into (+)-**7a** in 80% yield upon treatment with methylmagnesium iodide at ca. −10 to −5°C. The ester group in (+)-**7a** was then hydrolyzed to the corresponding carboxylic acid (+)-**8**, which was in turn converted by the well-known literature procedure[15] into the desired *N*-Boc derivative (+)-**9**. Final deprotection of the amino and phosphonate groups afforded the enantiomerically pure (+)-(2*R*)-amino-(3*R*)-phenyl-(1*R*)-cyclopropanephosphonic acid **1**.

Our synthesis afforded the dextrorotatory enantiomer of **1** and in this way is complementary to the asymmetric synthesis of the enantiomeric (−)-**1** described by Hanessian and co-workers[5] involving the conjugate addition of chiral α-chlorophosphonamide anions to α,β-unsaturated esters. The synthesis of other optically



Scheme 5.

active isomers of **1** is currently being studied in our laboratory.

Acknowledgements

Partial financial support by the State Committee for Scientific Research (Grant No Z-005/t09/99) is gratefully acknowledged.

References

1. *Aminophosphonic and Aminophosphinic Acids, Chemistry and Biological Activity*; Kukhar, V. P.; Hudson, H. R., Eds.; John Wiley & Sons: Chichester, 2000.
2. (a) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244–1267; (b) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699–1720.
3. (a) Reissig, H. U. In *The Chemistry of the Cyclopropyl Group*; Patai, S.; Rappaport, Z., Eds.; John Wiley & Sons: New York, 1978; (b) Salaün, J.; Baird, M. S. *Curr. Med. Chem.* **1995**, *2*, 511.
4. Jászay, Z.; Keserü, G. M.; Clementis, G.; Petneházy, I.; Kováts, K.; Töke, L. *Heteroat. Chem.* **2000**, *12*, 90–96 and references cited therein.
5. Hanessian, S.; Cantin, L.-D.; Roy, S.; Andreotti, D.; Gomtsyan, A. *Tetrahedron Lett.* **1997**, *38*, 1103–1106.
6. (a) Mikołajczyk, M.; Łyżwa, P.; Drabowicz, J.; Wieczorek, M. W.; Błaszczyk, J. *Chem. Commun.* **1996**, 1503–1504; (b) Mikołajczyk, M.; Łyżwa, P.; Drabowicz, J. *Tetrahedron: Asymmetry* **1997**, *8*, 3991–3994.
7. Midura, W. H.; Krysiak, J. A.; Wieczorek, M. W.; Majzner, R.; Mikołajczyk, M. *Chem. Commun.* **1998**, 1109–1110.
8. Mikołajczyk, M.; Midura, W. H.; Grzejszczak, S.; Zatorski, A.; Chefczyńska, A. *J. Org. Chem.* **1978**, *43*, 473–478.
9. For this new procedure of the Horner–Wittig reaction of α-phosphoryl sulfoxides see: Shen, J.; Jing, G.-F. *Synthesis* **2000**, 99–102.
10. *E*-(*S*)-**3**: $[\alpha]_D=+3.2$ (*c* 3.2, acetone); ^{31}P NMR ($CDCl_3$): 12.8 ppm; ^1H NMR (500 MHz, $CDCl_3$): 2.39 (s, 3H), 3.28 (d, 3H, $J=11.6$ Hz), 3.47 (d, 3H, $J=11.7$ Hz), 7.27–7.29 (m, 3H), 7.41–7.43 (m, 2H), 7.65–7.67 (m, 2H), 7.75–7.77 (m, 2H), 8.09 (d, 1H, $J=41.7$ Hz). Calcd for $C_{17}H_{19}O_4PS$: C, 58.28; H, 5.47. Found: C, 58.37; H, 5.42. *Z*-(*S*)-**3**: $[\alpha]_D=-367.0$ (*c* 2.6, C_6H_6); ^{31}P NMR ($CDCl_3$): 16.4 ppm; ^1H NMR (200 MHz, $CDCl_3$): 2.38 (s, 3H), 3.26 (d, 3H, $J=11.5$ Hz), 3.80 (d, 3H, $J=11.6$ Hz), 7.25–7.29 (m, 2H), 7.42–7.49 (m, 5H), 7.65–7.70 (m, 2H), 8.18 (d, 1H, $J=21.8$ Hz).
11. **6a′**: ^1H NMR (200 MHz, $CDCl_3$): 2.45 (s, 3H), 3.02 (d, 3H, $J=11.4$ Hz), 3.42 (dd, 1H, $J=8.3$, 16.9 Hz), 3.54 (d, 3H, $J=11.1$ Hz), 3.78 (dd, 1H, $J=8.3$, 13.4 Hz), 3.82 (s, 3H), 7.15–7.37 (m, 7H), 7.70–7.74 (m, 2H); ^{13}C NMR (50.3 Hz) 21.48, 25.53, 31.91, 47.96 (d, $J=174.2$ Hz), 52.63 (d, $J=24.5$ Hz), 61.79 (d, $J=42.7$ Hz), 127.26, 127.94, 128.97, 129.1, 133.0, (d, $J=5.1$ Hz), 139.3, 142.3, 166.62 (d, $J=2.0$ Hz). Calcd for $C_{20}H_{23}O_6PS$: C, 56.87; H, 5.49. Found: C, 56.65; H, 5.52.
12. For the spectral criteria used for the determination of the relative configuration in cyclopropylphosphonates see:

Jubault, P.; Goumain, S.; Feasson, C.; Collignon, N. *Tetrahedron* **1998**, *54*, 14767–14778 and references cited therein.

13. For (+)-**7a**: $^{3}J_{\mathrm{Carom-P}}=6.25$ Hz, $^{3}J_{\mathrm{C(O)-P}}=3.62$ Hz; NOE: $H^{1}\rightarrow H^{3}$ 6.5%.
For (+)-**7b**: $^{3}J_{\mathrm{Carom-P}}=3.2$ Hz, $^{3}J_{\mathrm{C(O)-P}}=8.55$ Hz; NOE: $H^{1}\rightarrow H^{2}$ 5.75%.
14. The desulfurization with sodium amalgam performed in MeOD gave the cyclopropane **7** with deuterium incorporated at the α-phosphonate carbon atom. No exchange of hydrogen by deuterium at the other cyclopropane carbon atoms was observed.
15. Charette, A. B.; Côté, B. *J. Am. Chem. Soc.* **1995**, *117*, 12721–12732.