ChemComm

First synthesis of a phosphonothiashikimic acid derivative†

Montserrat Heras, Mihaela Gulea and Serge Masson*

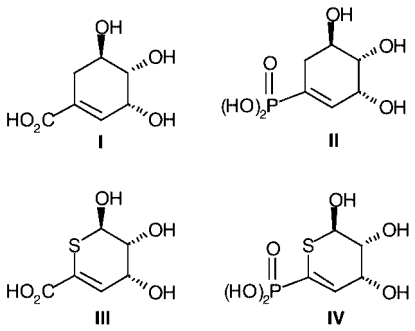
Laboratoire de Chimie Moléculaire et Thioorganique (UMR CNRS, 6507), ISMRA-Université de Caen et CNRS, 6 boulevard du Maréchal Juin, F-14050 Caen, France. E-mail: serge.masson@ismra.fr

Received (in Cambridge, UK) 30th January 2001, Accepted 21st February 2001
First published as an Advance Article on the web 13th March 2001

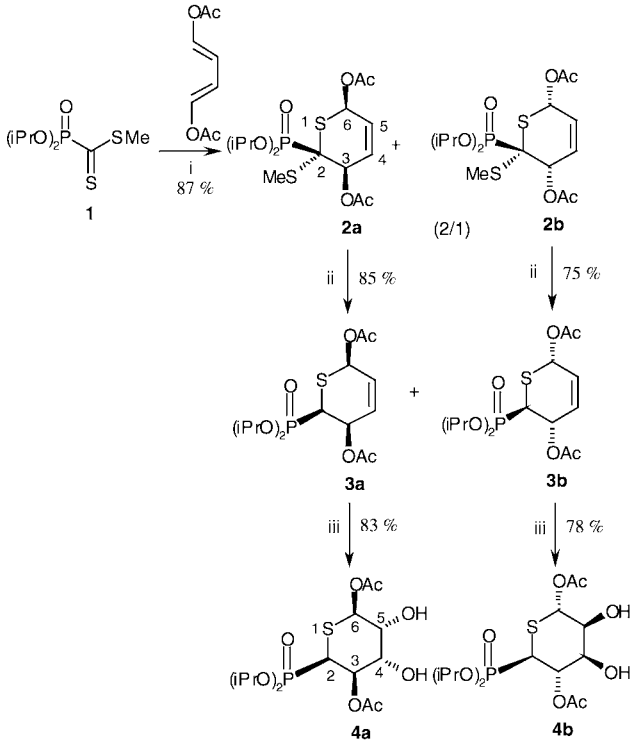
A new phosphono and thio analogue of shikimic acid ester has been synthesised from a thiopyranic derivative obtained *via* a [4 + 2] cycloaddition involving a phosphonodithioformate as heterodienophile.

Shikimic acid[1] **I** (Scheme 1) is an important intermediate in the biosynthesis of aromatic amino acids from carbohydrates in plants and microorganisms. Therefore, increasing effort has been directed towards the synthesis of its analogues as potential enzyme inhibitors in this biological pathway. Several modifications of the shikimic acid structure were described, including the functionalisation of the cyclohexene ring,[2] the substitution of the carboxylic function by a phosphono group[3] (phosphono shikimic acid **II**) or the replacement of the methylene group involved in the shikimate pathway by a sulfur atom (thiashikimic acid **III**). We report here the first synthesis of a new racemic derivative of compound **IV** which is both a phosphono and thio analogue of shikimic acid.

As for the preparation of thiashikimic acid ester,[4] we used a hetero Diels–Alder cycloaddition for the first step of our synthesis (Scheme 2). However, instead of the unknown and probably very unstable thioaldehyde-phosphonate (analogue of a thioxoacetate) we used a very stable and readily accessible phosphonodithioformate **1** (very recently described by our group as a new heterodienophile[5]). Although relatively slow (7 days), the reaction of (*E*,*E*)-1,4-diacetoxybutadiene with this dithioester in refluxing THF led to the functionalized dihydrothiopyranic derivative **2** as a mixture of diastereomers **2a** and **2b** in a 2 : 1 ratio and 87% yield (use of a Lewis acid to accelerate the reaction[5] was excluded because it induced some undesirable degradation of the cycloadduct). These isomers were easily separated by chromatography on silica gel. By comparison with the reaction of the thioxoacetate,[4] we could expect for the major isomer **2a** (58%) resulting from a preferential phosphonyl-*endo* cycloaddition, a *cis* configuration as far as the two acetoxy and the phosphono groups are concerned. The structures assumed for **2a** and **2b** were indeed found in accordance with the observed coupling constants between phosphorus and protons on C_3 and C_6: large equatorial–equatorial or axial–axial coupling (torsion angle $\Phi \sim 0$ or $\sim 180°$) and almost null equatorial–axial coupling ($\Phi \sim 90°$)[6] (Scheme 3).

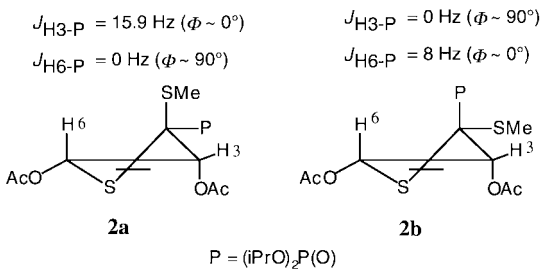


Scheme 1



Scheme 2 *Reagents and conditions*: i: THF, rt, 7 d; ii: Bu_3SnH–AIBN, refluxing benzene, 2 h; iii: OsO_4–Py, rt, 2 h.

Each isomer was then desulfanylated using Bu_3SnH–AIBN in refluxing benzene and, as expected from our preliminary study,[5] the heterocyclic sulfur atom is not affected by the reaction. A mixture of 2,3-*cis* **3a** and 2,3-*trans* **3b** isomers was respectively obtained in a 2 : 1 ratio from **2a** (85%) and in a 5 : 3 ratio from **2b** (75%). The favoured formation of isomer **3a** could be explained by the preferential reduction of the anomeric radical on the opposite side to the C_3 acetoxy groups through an axial attack.[7] The stereochemistry of these diastereomers was deduced from the $^3J_{H2–H3}$ = 6.1 (for **3a**) and 10.7 Hz (for **3b**) coupling constants.



Scheme 3 Relative configurations of cycloadducts **2** (one conformer of each isomer is represented).

† Electronic supplementary information (ESI) available: experimental. See http://www.rsc.org/suppdata/cc/b1/b101050f/

DOI: 10.1039/b101050f

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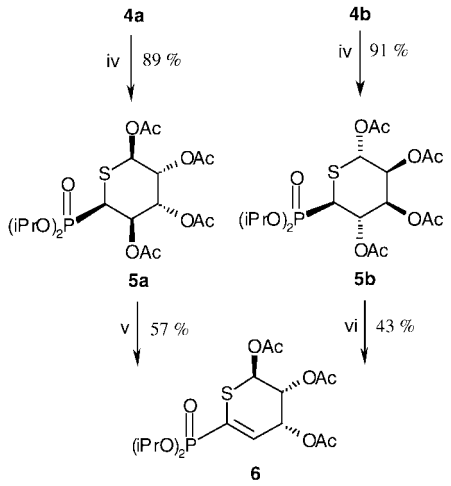
After separation of these isomers by flash column chromatography on silica gel they were dihydroxylated by osmium tetroxide in pyridine. Compound **3a** gave the corresponding *cis*-diol **4a** (83%) as a single isomer, by attack from the less hindered side of the molecule. Under the same conditions, the dihydroxylation of isomer **3b** gave diol **4b** (78%). To avoid the possible 1,2-migration of an acetyl group[4] from O–C_3 to O–C_4, diols **4a** and **4b** were protected as acetylated derivatives **5a** and **5b** before performing a basic elimination of acetic acid (Scheme 4). From tetraacetate **5a**, this 1,2-elimination occurred in hot pyridine to give the phosphonothiashikimic derivative **6** in 57% yield after purification. As expected, for the epimer **5b**, in which the relevant proton and acetoxy group are not in a *trans* configuration, the elimination failed in similar conditions. However, using a stronger base (NaH in THF), **5b** led to the same expected compound **6** in 43% yield. In this way, both *Diels–Alder* isomeric cycloadducts were used for the synthesis of the target molecule **6**. The observed *J* values ($^3J_{H5–H6}$ = 4.6, $^3J_{H5–H4}$ = 3.3 Hz) for the acetoxy derivative of phosphonoshikimate **6** are consistent with the attributed structure and in good agreement with that of its carboxylic analogue.[4]



Scheme 4 *Reagents and conditions*: iv: $(AcO)_2O$–Py, 80 °C, 12 h; v: Py, reflux, 36 h; vi: 3 equiv. NaH, THF, rt, 36 h.

The search of an efficient enantioselective version of this synthesis is now under investigation. Besides, the preparation of other thiapyranic derivatives, from the phosphonodithioformate **1** and various functionalized dienes by the same sequence, cycloaddition–desulfanylation–dihydroxylation, are in progress and will be the subject of a full publication.

We thank the Réseau Inter-Régional Normand de Chimie Organique Fine (RINCOF, Contrat de Plan Etat-Bassin Parisien-Régions Haute-Normandie-Basse-Normandie) for financial support to M. Heras.

Notes and references

1 Review: S. Jiang and G. Singh, *Tetrahedron*, 1998, **54**, 4697.
2 (*a*) S. Jiang, G. Singh, D. J. Boam and J. R. Coggins, *Tetrahedron: Asymmetry*, 1999, **10**, 4087; (*b*) J. K. Sutherland, W. J. Watkins, J. P. Bailey, A. K. Chapman and G. M. Davies, *J. Chem. Soc., Chem. Commun.*, 1989, 1385; (*c*) J. K. Sutherland, R. C. Whitehead and G. M. Davies, *J. Chem. Soc., Chem. Commun.*, 1993, 464.
3 S. Mirza and J. Harvey, *Tetrahedron Lett.*, 1991, **32**, 4111.
4 D. Adam, A. A. Freer, N. W. Isaacs, G. W. Kirby, A. Littlejohn and M. S. Rahman, *J. Chem. Soc., Perkin Trans. I*, 1992, 1261.
5 B. Heuze, R. Gasparova, M. Heras and S. Masson, *Tetrahedron Lett.*, 2000, **41**, 7327.
6 E. Ôhler, E. Haslinger and E. Zbiral, *Chem. Ber.*, 1982, **115**, 1028 and references therein.
7 For examples of selective axial trapping of anomeric radicals see: (*a*) M. Gulea, J. M. Lopez-Romero, L. Fensterbank and M. Malacria, *Org. Lett.*, 2000, **2**, 2591; (*b*) B. Giese, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 969; (*c*) H. Togo, W. He, Y. Waki and M. Yokoyama, *Synlett*, 1998, 700.