Tetrahedron Letters 51 (2010) 2717–2719

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

New aspects of the Hunsdiecker–Barton halodecarboxylation—syntheses of phospha-shikimic acid and derivatives

Benoit Carbain, Peter B. Hitchcock, Hansjörg Streicher *

Department of Chemistry and Biochemistry, University of Sussex, Brighton, BN1 9QG, UK

ARTICLE INFO

Article history:
Received 21 January 2010
Revised 2 March 2010
Accepted 12 March 2010
Available online 17 March 2010

Keywords:
Shikimic acid
Hunsdiecker–Barton reaction
Cyclohexenephosphonates
Inhibitors

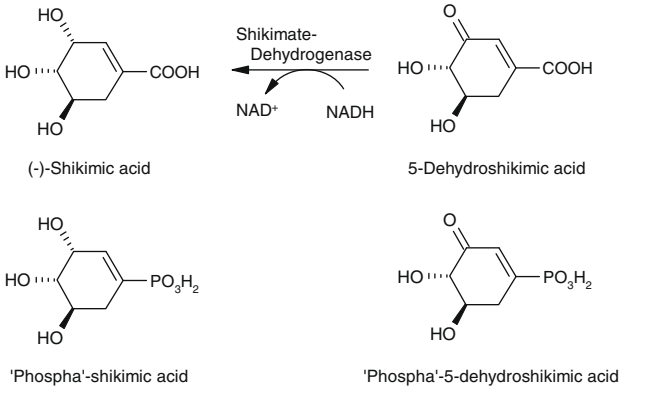
ABSTRACT

We report an efficient synthetic approach to phospha-isosteres of important intermediates of the shikimic acid pathway by the application of the Hunsdiecker–Barton halodecarboxylation to cyclohexenylcarboxylic acids. As examples, phospha-shikimic acid, its 3-dehydro derivative and the respective monomethyl esters were synthesized. The approach has proven equally useful in the synthesis of isosteres of the antiviral agent oseltamivir.

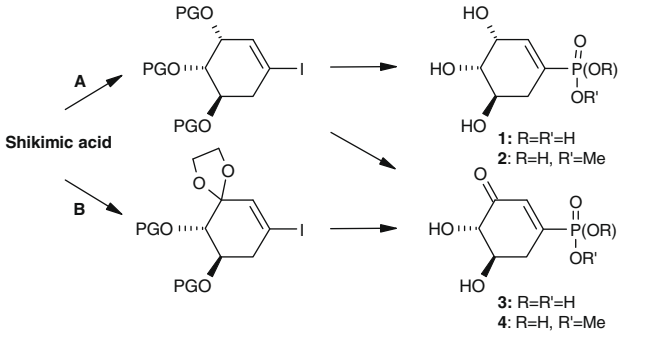
Non-aromatic carbocycles such as cyclohexanes and cyclohexenes play important roles in biological systems with inositols as second messengers, aminocyclitol entities in antibiotics and shikimate derivatives in the biosynthesis of amino acids being some prominent examples.[1] In addition, carbocycles, and in particular cyclohexene derivatives such as valienamine or oseltamivir, have served well as mimetics of bioactive carbohydrates and inhibitors of respective metabolic processes.[2,3] Consequently, interest in new synthetic approaches towards such compounds has remained intense.[4] We recently introduced a variable approach to *xylo*-configured cyclohexenephosphonates as sialylmimetics starting from D- and L-xylose, respectively, with the phosphonate group being of particular importance as a modifiable mimetic of a carboxylate.[5] The latter approach contains both the phosphonate introduction via nucleophilic substitution as well as a cyclization reaction leading to only moderate yields. Therefore, we sought a more straightforward chiral pool based access to cyclohexenephosphonates with shikimic acid being a particularly interesting starting material as it is both an important metabolite, and a starting material for anti-influenza drug synthesis (Scheme 1).[6]

The most effective way to achieve this would be the halodecarboxylation of shikimic acid followed by conversion of the resulting vinyl halide into the respective phosphonate diester (Scheme 2).[7]

Route **A** is based on halodecarboxylation of protected shikimic acid followed by phosphonylation (and oxidation if required). Route **B**, which has the oxidation step placed prior to the halodecarboxylation, was investigated to assess the effects of protecting



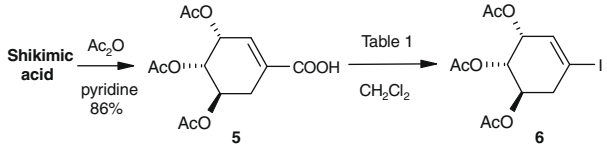
Scheme 1. Biosynthesis of (−)-shikimic acid and its phospha-isosteres envisaged in this study.



Scheme 2. Strategies towards phospha-shikimic acids. PG = protecting group.

* Corresponding author. Tel.: +44 1273 602205; fax: +44 1273 876687.
E-mail address: h.streicher@sussex.ac.uk (H. Streicher).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.03.044

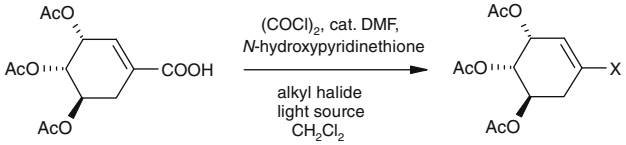


Scheme 3. Halodecarboxylation of acetylated shikimic acid.

groups and to improve final deprotection of the dehydro derivative. The classical Hunsdiecker reaction and its Kochi variant,[8] particularly in its metal-free version introduced by Barton,[9] is well-established for the conversion of carboxylic acids into halides via a radical mechanism.

It came as a surprise to us that, although well-investigated for aryl- and alkylcarboxylic acids,[8–10] very little has been reported on vinyl carboxylic acids.[11] Vinyl halides, especially iodides, are very useful substrates in a variety of organic reactions, namely C–C coupling reactions. We therefore started with a study on suitable conditions for the halodecarboxylation of acetylated shikimic acid **5** (Scheme 3 and Table 1).[12]

Table 1
Conditions for the halodecarboxylation of acetylated shikimic acid



Entry	Alkyl halide	Equiv	Light source[b]	Time (h)	Yield (%)
1	CF_3CH_2I	5	250 W e.f.	1.5	64
2	CF_3CH_2I	11	250 W e.f.	1	57
3	CF_3CH_2I	11	250 W e.f.	4	28
4	CF_3CH_2I	11	125 W UV	1	27
5	CF_3CH_2I	5	400 W UV	1	17
6	CF_3CH_2I/ ICH_2CH_2I	2 3.5	250 W e.f.	1.5	20
7	ICH_2CH_2I	11	250 W e.f.	2	5
8	CBr_4	11	250 W e.f.	1.1	36
9	CCl_4[a]	11	250 W e.f.	1	23
10	CCl_4[a]	11	125 W UV	1	8

[a] Entries 9 and 10: Alkyl halide as solvent.
[b] e.f. = electric floodlamp; UV = medium pressure Hg-vapour lamp.

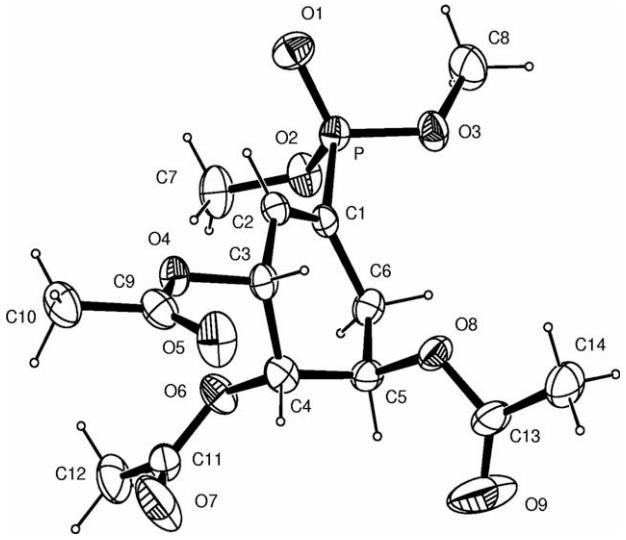
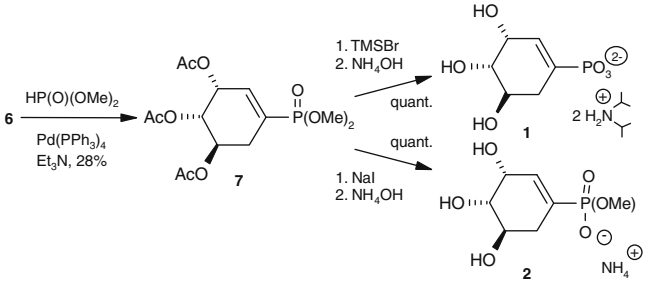


Figure 1. ORTEP-generated structure (CCDC 767943) of acetylated 'phospha'-shikimic acid dimethyl ester **7**.



Scheme 4. Synthesis of 'phospha'-shikimic acids.

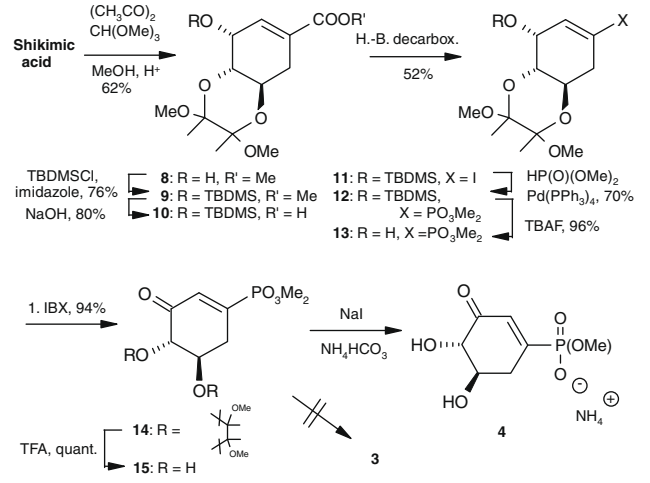
In our hands, a combination of the Barton procedure involving the intermediate generation of the acid chloride and subsequently the *O*-acyl hydroxypyridinethione, with 2,2,2-trifluoroethyl iodide[10] as iodine source and irradiation with an electric flood lamp gave the best results (Table 1).

As shown in entries 8–10, chloro- and bromodecarboxylation did not result in improved yields and neither did the use of a UV-source and the common iodine source diiodoethane. It is important to mention here that acetals and silyl ethers as protecting groups resulted in yields comparable to entry 1 (see below).

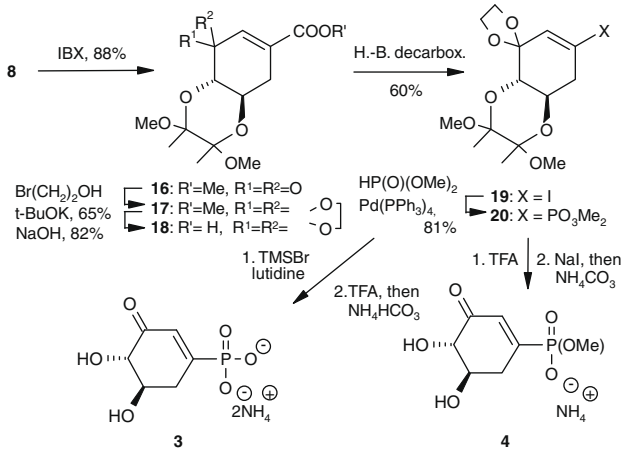
Palladium-mediated phosphonylation[13] of tris-acetoxy cyclohexenyl iodide **6** to furnish protected 'phospha'-shikimic acid dimethyl ester **7** proceeded in only poor yield. This is, however, due to the base labile acetyl groups as yields increased to >80% with acetal and silyl ether protecting groups (see below).

We were able to determine the crystal structure of **7** (Fig. 1) displaying the expected half-chair (cyclohexene-type) conformation with C-4 and C-5 below and above, respectively, the C-3/C-2/C-1/C-6 plane and the corresponding acetoxy groups in pseudo-axial positions.

Thus, we obtained our first targets 'phospha'-shikimic acid **1**[14] and the corresponding monomethyl ester **2** by either complete (TMSBr) or partial cleavage (NaI) of the methyl phosphonates and saponification of the acetates (Scheme 4). To allow for selective access to the 3-OH group of shikimic acid for subsequent oxidation to the dehydro derivative, we esterified and protected shikimic acid as the 4,5-*trans* diketal **8** in one step according to a



Scheme 5. Synthesis of 3-dehydro-'phospha'-shikimic acid monomethyl ester. H.-B. decarbox. = Hunsdiecker–Barton decarboxylation.



Scheme 6. Synthesis of 3-dehydro-'phospha'-shikimic acid via route **B**. H.-B. decarbox. = Hunsdiecker–Barton decarboxylation.

published procedure (Scheme 5).[15] Silylation of the 3-OH group to give **9** followed by saponification of the methyl ester afforded acid **10** which could be readily iododecarboxylated to furnish **11**. The yield of the following phosphonylation to give **12** roughly tripled compared to its acetyl-protected counterpart thus making this protecting group pattern the superior choice for the generation of **1** and **2** as well. Removal of the silyl group to give **13** and oxidation to the ketone **14** with IBX proceeded in high yields and thus protected 3-dehydro-'phospha'-shikimic acid **14** was obtained.

Following acid hydrolysis of the ketal to furnish **15** we successfully generated the monomethyl ester **4** by iodide-mediated *O*-alkyl cleavage followed by saponification (Scheme 5). TMSBr-mediated hydrolysis to the phosphonate **3** proved difficult however, resulting in only very low yields.

Finally, we adopted strategy (**B**) involving oxidation and protection of the ketone before halodecarboxylation and phosphonylation. We expected to gain information on further improvement of yields in the latter two steps and to allow for a more smooth deprotection towards target **3** (Scheme 6). IBX-oxidation of protected shikimic acid **8** yielded the ketone **16** which could be readily protected as its ethylene ketal to give **17**. Saponification of the methyl ester afforded acid **18** which was iododecarboxylated to form **19** in a yield comparable to those obtained before. The yield of the following phosphonylation to give **20** increased to 81% and finally, target **3** was readily obtained from **20** by TMSBr-mediated ester cleavage followed by removal of the ketal protecting group with TFA. In addition, this route provides an alternative access to monoester **4** as well.[16]

In conclusion, we have extended the scope of the Hunsdiecker–Barton decarboxylation to vinyl-, in particular trihydroxy- and dihydroxyketo-cyclohexenylcarboxylic acids carrying different protecting groups. In combination with phosphonylation and appropriate protecting groups, our approach represents a short and effective route to phospha-isosteres of various bioactive molecules such as shikimates or even neuraminidase inhibitors.[7] A set of 'phospha'-shikimic acids was synthesized in good yield and will be investigated for activity in a shikimate dehydrogenase assay in due course.

Acknowledgement

We thank Professor Jim Hanson, of our department, for helpful advice.

Supplementary data

Supplementary data (synthetic procedures, ^{1}H, ^{13}C and ^{31}P NMR and HR-ESI-MS data. Crystal data of cyclohexenephosphonate **7**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.03.044.

References and notes

1. Voet, D.; Voet, J. G.; Pratt, C. W. *Fundamentals of Biochemistry*, 2nd ed.; Wiley & Sons Inc.: New York, US, 2006.
2. Ernst, B.; Kolb, H. C.; Schwandt, O. In *The Organic Chemistry of Sugars*; Levy, D. E., Fügedi, P., Eds.; Taylor & Francis: Boca Raton, US, 2006; pp 803–861.
3. Wong, C.-H. *Carbohydrate-based Drug Discovery*; Wiley-VCH: Weinheim, Germany, 2003.
4. Sollogoub, M.; Sinay, P. In *The Organic Chemistry of Sugars*; Levy, D. E., Fügedi, P., Eds.; Taylor & Francis: Boca Raton, US, 2006; pp 349–381.
5. (a) Busse, H.; Streicher, H. *Bioorg. Med. Chem.* **2006**, *14*, 1047–1057; (b) Streicher, H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 361–364; (c) Streicher, H.; Bohner, C. *Tetrahedron* **2002**, *58*, 7573–7582.
6. Kim, C. U.; Lew, W.; Williams, M. A.; Liu, H.; Zhang, L.; Swaminathan, S.; Bischofberger, N.; Chen, M. S.; Mendel, D. B.; Tai, C. Y.; Laver, W. G.; Stevens, R. C. *J. Am. Chem. Soc.* **1997**, *119*, 681–690.
7. Parallel to this study, the methodology has been applied by us and others in the synthesis of phospha-isosteres of oseltamivir, see: (a) Carbain, B.; Collins, P. J.; Callum, L.; Martin, S. R.; Hay, A. J.; McCauley, J.; Streicher, H. *ChemMedChem* **2009**, *4*, 335–337; (b) Carbain, B.; Martin, S. R.; Collins, P. J.; Hitchcock, P. B.; Streicher, H. *Org. Biomol. Chem.* **2009**, *7*, 2570–2575; (c) Shie, J.-J.; Fang, J.-M.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2008**, *47*, 5788–5791.
8. (a) Hunsdiecker, H.; Hunsdiecker, C. *Ber. Dtsch. Chem. Ges.* **1942**, *75*, 291–297; (b) Johnson, R. G.; Ingham, R. K. *Chem. Rev.* **1956**, *56*, 219–269; (c) Kochi, J. K. *J. Org. Chem.* **1965**, *30*, 3265–3271.
9. Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron Lett.* **1983**, *24*, 4979–4982.
10. Kende, A. S.; Milbank, J. B. J.; Ebetino, F. H.; deLong, M. A. *Tetrahedron Lett.* **1999**, *40*, 8189–8192.
11. (a) Crich, D. In *Comprehensive Organic Synthesis*; Trost, B. M., Steven, V. L., Eds.; Pergamon: Oxford, UK, 1991; pp 717–734; (b) Kuang, C.; Yang, Q.; Senboku, H.; Tokuda, M. *Synthesis* **2005**, 1319–1325; (c) Katritzky, A. R.; Majumder, S.; Jain, R. *J. Indian Chem. Soc.* **2003**, *80*, 1073–1075; (d) Saraiva, M. F.; Couri, M. R. C.; Le Hyaric, M.; de Almeida, M. V. *Tetrahedron* **2009**, *65*, 3563–3572.
12. Schaub, C.; Mueller, B.; Schmidt, R. R. *Eur. J. Org. Chem.* **2000**, 1742–1758.
13. (a) Maffei, M. *Curr. Org. Synth.* **2004**, *1*, 355–375; (b) Attolini, M.; Iacazo, G.; Peiffer, G.; Maffei, M. *Tetrahedron: Asymmetry* **2003**, *14*, 3857–3860; (c) Hirao, T.; Masunaga, T.; Ohshiro, Y.; Agawa, T. *Tetrahedron Lett.* **1980**, *21*, 3595–3598.
14. For a synthesis of phospha-shikimic acid from D-lyxose, see: Mirza, S.; Harvey, J. *Tetrahedron Lett.* **1991**, *32*, 4111–4114.
15. (a) Liu, A.; Liu, Z. Z.; Zou, Z. M.; Chen, S. Z.; Xu, L. Z.; Yang, S. L. *Tetrahedron* **2004**, *60*, 3689–3694; (b) Armesto, N.; Ferrero, M.; Fernandez, S.; Gotor, V. *Tetrahedron Lett.* **2000**, *41*, 8759–8762.
16. Target compounds **3** and **4** could be isolated and purified without problems, but decomposed slowly when stored, see also Supplementary data.