REVIEW ARTICLE

Shikimic acid: a highly prospective molecule in pharmaceutical industry

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Shikimic acid (SA) is the key intermediate in the common pathway of aromatic amino acid biosynthesis (the shikimate pathway). The benzene ring, the basic unit of all aromatic compounds, is formed in plants and microorganisms through the shikimate pathway and the intermediate SA is an extremely essential compound in plants and microbes. The most important use of SA is as a substrate for the chemical synthesis of the drug oseltamivir, commercially known as Tamiflu®, an efficient inhibitor of the human influenza virus H1N1 of swine origin, seasonal influenza virus types A and B, and avian influenza virus H5N1. The fruits of the Chinese star anise (*Illicium verum*) contain SA to the extent of 17.14% on dry wt. basis and this is now the main source for commercial production of SA. The demand for Tamiflu® has increased tremendously and the pharmaceutical industry is unable to meet this demand due to shortage of SA. Therefore, significant attention needs to be paid towards the development of new technologies for the production of SA from available sources and to find alternative sources.

Keywords: Aromatic compounds, pharmaceutical industry, shikimic acid, star anise.

SHIKIMIC acid (SA, Figure 1 *a*) is a hydroaromatic intermediate in the common pathway of aromatic amino acid biosynthesis in plants, bacteria and fungi, but this pathway is absent in mammals. SA is being employed as a bulk chemical for various industrial and pharmaceutical uses. It is the precursor for the synthesis of the drug oseltamivir[1] (commercially called Tamiflu, Figure 1 *b*), an efficient inhibitor of the human influenza virus H1N1 of swine origin, seasonal influenza virus types A and B, and avian influenza virus H5N1. Currently, Roche produces majority of the world's supply of shikimic acid. Their method of extraction involves isolating the compound from Chinese star anise (Figure 1 *c*). In addition to being an inefficient extraction method, the harvest itself is labour-intensive and highly polluting. Furthermore, as demonstrated by the Tamiflu® shortages announced by Roche in 2005, a bad harvest will inevitably lead to mass shortages in drug supply. Currently most of the world's demand for shikimic acid is met only from fruits of Chinese star anise. Efforts need to be made to explore alternate sources of shikimic acid to meet the demands of the world market.

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Discovery and structure elucidation

Shikimic acid was first isolated in 1885 by Eykman[2] from the fruits of *Illicium religiosum* and derived its name from this Oriental plant which is called 'shikimi-no-ki' in Japanese. In the 1930s, Fischer[3–5], Freudenberg *et al.*[6], and Karrer and Link[7] determined the relative and absolute stereochemistry of (–)-shikimic acid (Figure 1 *a*). Subsequently Grewe and co-workers[8,9] carried out extensive work on the chemistry of SA. Bochkov *et al.*[10] have discussed thoroughly the physic-chemical properties and use of different analytical techniques for quantitative and qualitative analysis, including analysis of NMR data on SA.

The shikimate pathway

The shikimate pathway (Figure 2) includes key intermediate SA, which is the principal precursor for the synthesis of aromatic amino acids like phenylalanine, tyrosine and tryptophan, and other compounds such as alkaloids, phenolics and phenyl propanoids[11]. In plants and microorganisms, the benzene ring, the basic unit of all aromatic compounds, is formed through the shikimate pathway and the intermediate SA is an extremely essential compound in plants and microbes[10,12].

Production

The major drawback to meet the global requirements of SA is the expensive and inefficient extraction and

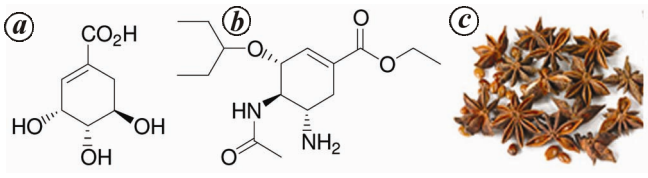


Figure 1. Structure of (***a***) shikimic acid; (***b***) oseltamivir; (***c***) Chinese star anise.

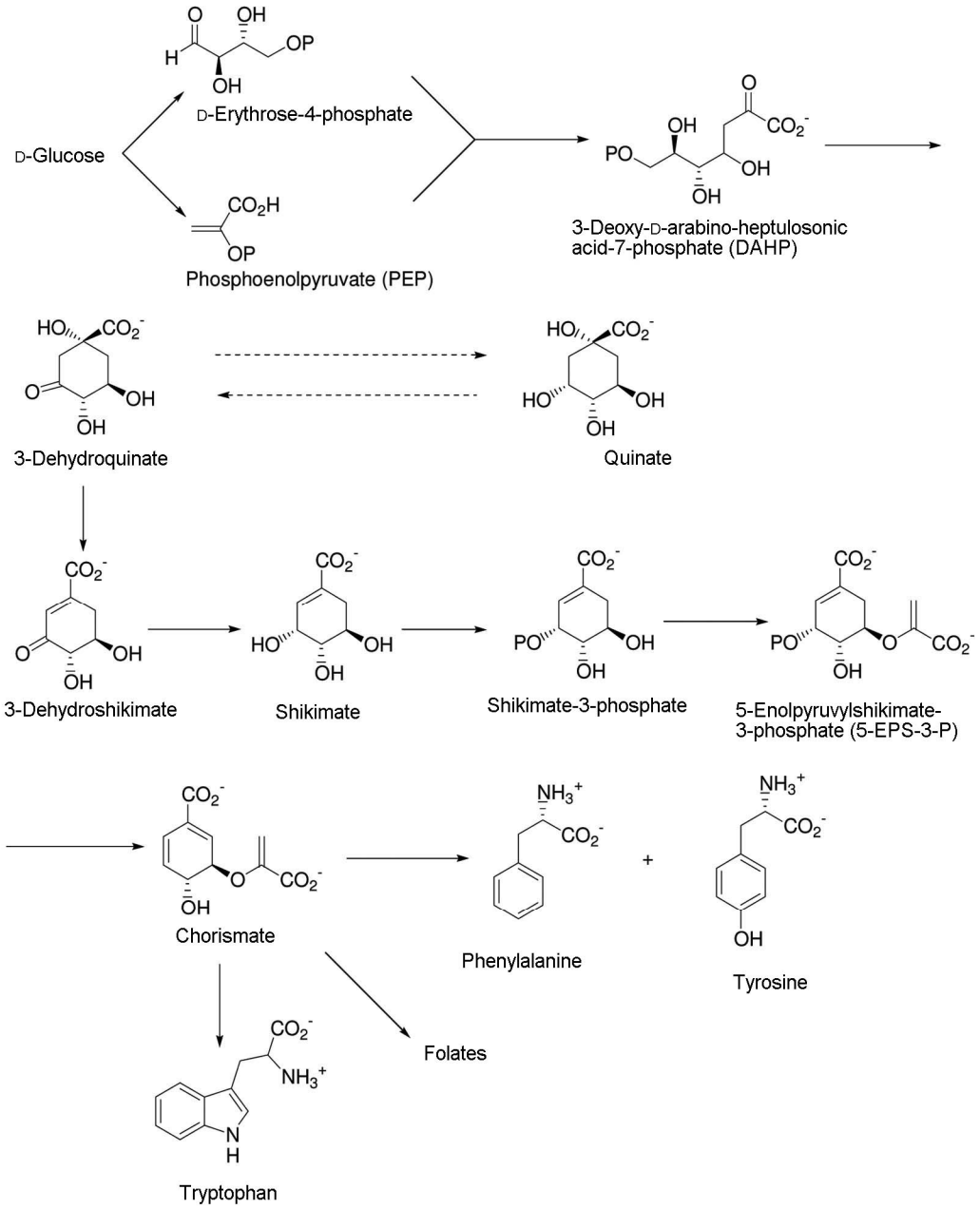
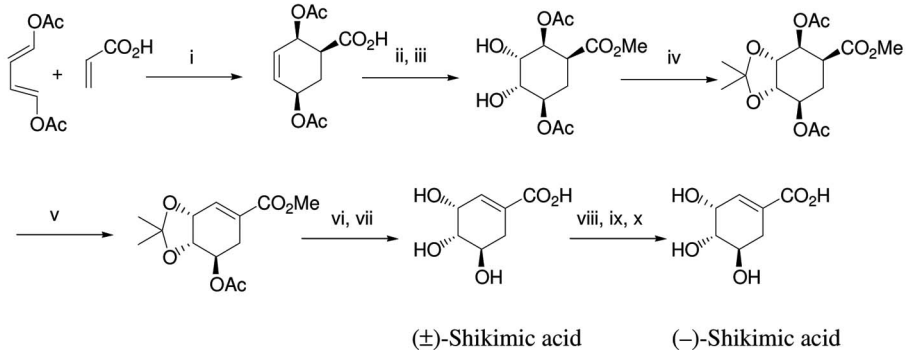


Figure 2. The shikimate pathway.

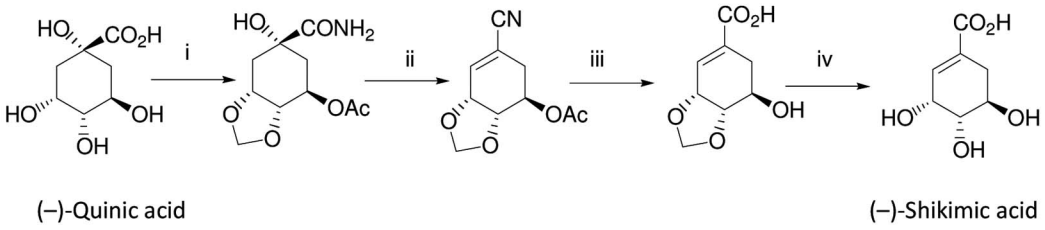
purification method. Star anise (*Illicium verum*), the primary source of SA, takes almost six years after plantation to bear fruits and the current commercial production method by Roche, a ten-stage process, is complex[13]. To overcome this problem different groups have developed several extraction methods with different plant materials. These include heat reflux extraction[14,15], maceration extraction[16] and homogenate extraction[17] using acidic water or different solvents such as methanol, ethanol, *n*-butanol and some mixtures of solvents[18]. However, production methods remain either too expensive or insufficiently developed. Therefore, research on the development of efficient techniques for the production of SA from known and novel sources as well as the search for new sources is highly imperative.

Extraction from plant

SA was first isolated from *I. religiosum* in 1885. In 1961, Plouvier[19] reported *Liquidambar styraciflua* as a potential source of SA. The content of SA in plant species varies and depends on the synthesis rate of aromatic amino acids. Sometimes SA accumulates in storage tissue of



Scheme 1. Reagents and conditions: (i) Hydroquinone, 85–90°C, 3 h; (ii) OsO_4, Et_2O, Py, 5 days; (iii) CH_2N_2; (iv) HCl, acetone, 16 h; (v) MgO, 290°C; (vi) H_2O–AcOH (1 : 4), 26 h; (vii) KOH, MeOH–H_2O (4 : 1), 16 h; (viii) Ac_2O, Py, 16 h; (ix) (–)-quinine, MeOH; (x) KOH, MeOH–H_2O (4 : 1).



Scheme 2. Reagents and conditions: (i) Protection (see Jiang and Singh[23]); (ii) *p*-TsCl, Py, 37°C, 7 days; (iii) Aq. NaOH, reflux, 2.5 h; (iv) aq. H_2SO_4.

seeds and fruits[20]. Recently, Bochkov *et al.*[10] reported different plant sources of SA. The content on dry weight basis ranged from 0.001% to 24.5%. Different species of the genus *Illicium* yielded maximum SA compared to other species. The highest content of 24.5% (dry basis content) SA has been reported from *I. religiosum*[21]. The fruits of the Chinese star anise (*I. verum*), which now constitute the main source for commercial production of SA, contain the same to the extent of 17.14% on dry weight basis. This is 16.86% in the fruits of *Illicium henryi*, followed by *Illicium pachyphyllum* (16.21%), *Terminalia arjuna* (15.64%), *Pistacia lentiscus* (13.28%), *Ribes aureum* (12.68%), *Symphytum officinalis* (12.53%), *Actaea pachypoda* (12.21%) and *Alangium salvifolium* (11.7%). In 2009, prospecting for alternate sources of shikimic acid from plants of the Western Ghats, a mega diversity hotspot in South India, was carried out. Analysis was performed on 210 plant species, out of which a total of 193 angiosperms belonged to 59 families and 17 gymnosperms belonged to five families. The highest level of shikimic acid (5.02%) was found in *Araucaria excelsa* R.Br. belonging to the family Araucariaceae. The same group reported higher and more widespread occurrence of shikimic acid in gymnosperms[22].

Chemical synthesis

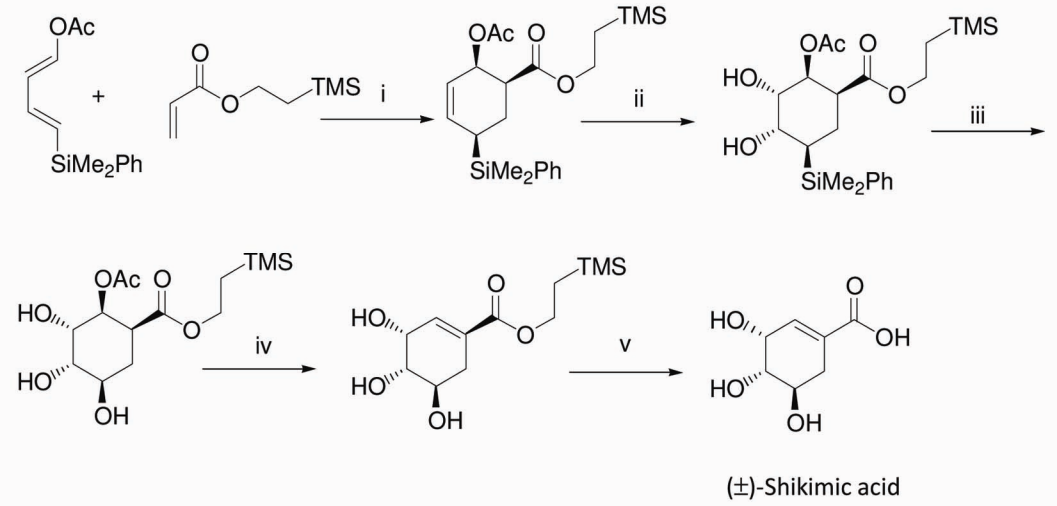
Out of several synthetic routes of SA, a few significant ones have been discussed below[23–25]. The first chemical synthesis of racemic SA was simultaneously reported by McCrindle *et al.*[26] and Smissman *et al.*[27] following an identical route based on Diels–Alder reaction with (1*E*, 3*E*)-1,4-diacetoxy-1,3-butadiene and acrylic acid as starting materials (Scheme 1) with 15% overall yield.

Dangschat and Fischer[28] synthesized SA from the readily available (–)-quinic acid found in *Cinchona* bark (Scheme 2).

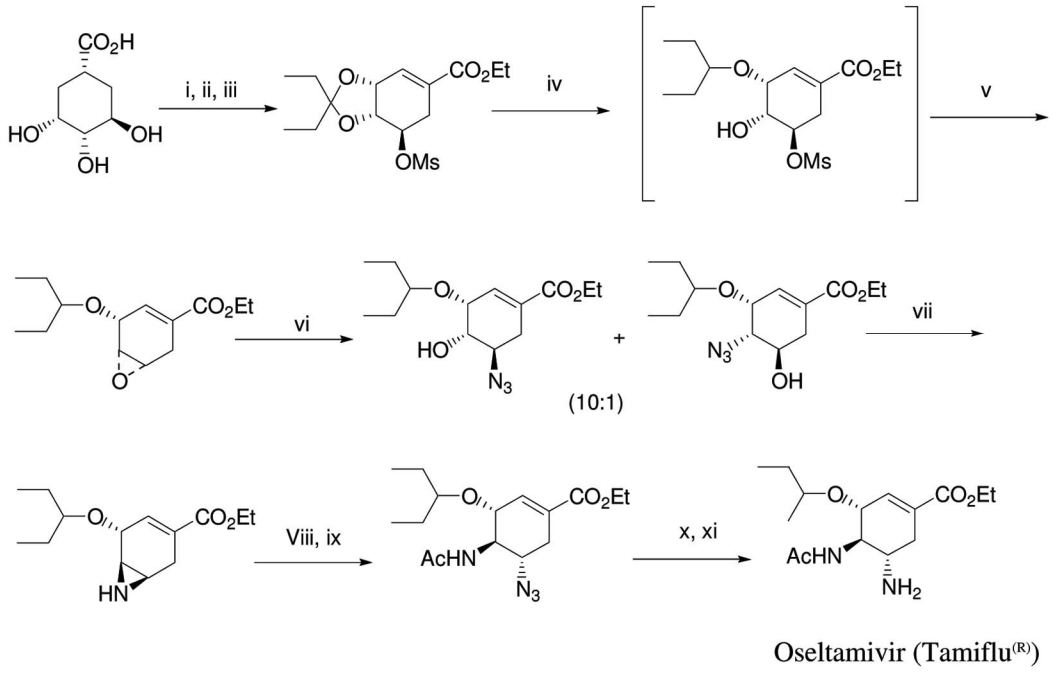
Grewe and Hinrichs[29] also reported a synthesis of SA, but achieved only 11% overall yield. Koreeda and Ciufolini[30] achieved a higher yield (29% overall yield). In 1990, Koreeda *et al.*[31] developed a highly efficient synthesis employing Fleming oxidation to achieve 55% overall yield (Scheme 3).

Microbial production

Although several efforts have been made to develop a commercially viable synthesis of SA, these methods remain expensive with other limitations. Therefore, significant attention has been paid towards alternative biotechnologically engineered bacterial strains. Although in 1954 Mitsuhashi and Davis[32] studied isolation of SA from microorganisms, it was Millican[33] who first obtained pure SA from *Escherichia coli*, where glucose was used as carbon source. Use of other microorganisms such as *Bacillus subtilis* enhanced the yield of SA, as the gene replicas responsible for the synthesis of a shikimate dehydrogenase enzyme proliferated and the genes responsible for



Scheme 3. Reagents and conditions: (i) Hydroquinone monomethyl ether, xylenes; (ii) OsO_4, NMO; (iii) KBr, AcOOH, AcOH, NaOAc; (iv) DBU, THF; (v) *n*-Bu_4NF.

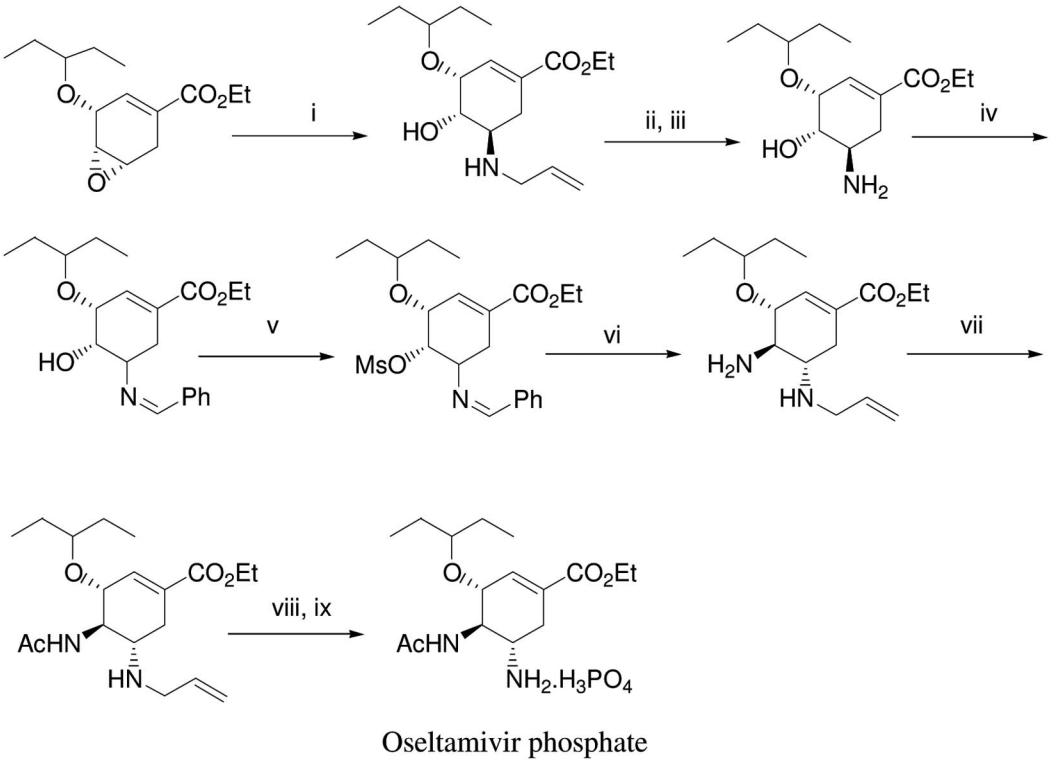


Scheme 4. Reagents and conditions: (i) EtO H, $SOCl_2$; (ii) 3-pentanone, TsOH; (iii) MsCl, Et_3N; (iv) TMSOTf, BH_3, Me_2S; (v) $KHCO_3$, aq. EtOH; (vi) NaN_3, NH_4Cl, aq. EtOH; (vii) Me_3P; (viii) NaN_3, NH_4Cl, DMF; (ix) Ac_2O; (x) Ra–Ni, H_2, EtOH; (xi) 85% H_3PO_4.

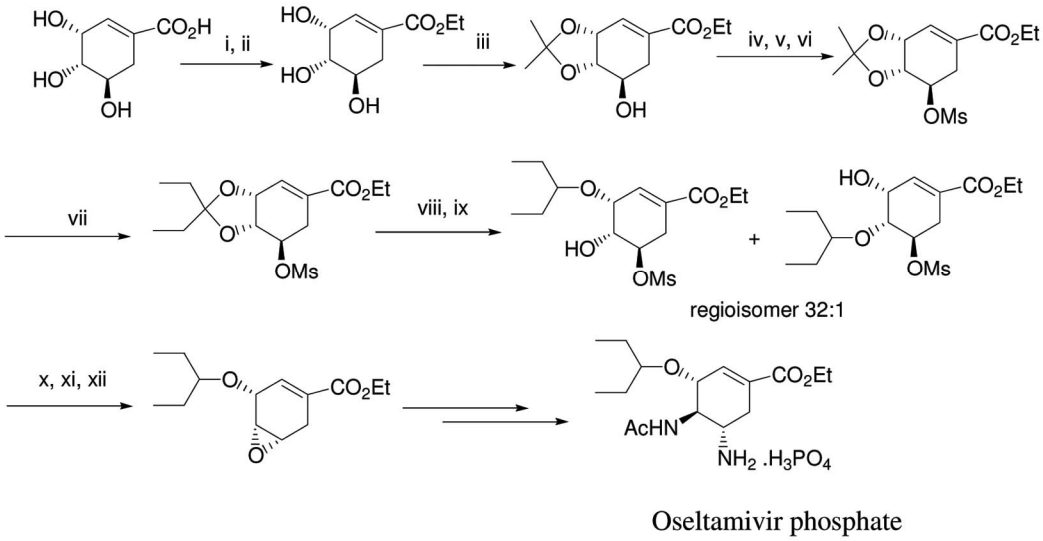
the synthesis of a shikimate kinase enzyme were inhibited. Several other methods for the microbial production of SA have been reported by different groups[10,24,34].

Significant role of SA in pharmaceutical industry

Forecast by WHO pandemic influenza preparedness and response guidance (2014) suggests that threats of influenza pandemics will continue to emerge. Tamiflu is the only orally administered approved drug for treatment of influenza[35]. Unfortunately, currently available Tamiflu is sufficient only for 2% of the world population[34]. SA has attracted worldwide attention as the precursor for the chemical synthesis of Tamiflu. The pilot-scale synthesis of Tamiflu from SA was developed by Gilead Sciences Inc. and F. Hoffmann-La Roche Ltd (Scheme 4)[36,37]. Karpf and Trussardi[38] developed an efficient azide-free synthesis with 35–38% overall yield (Scheme 5) and Federspiel *et al.*[39] reported 63–65% overall yield (Scheme 6).



Scheme 5. Reagents and conditions: (i) Allylamine, $MgBr_2.OEt_2$, *t*-BuOH–MeCN, 55°C, 16 h, $(NH_4)SO_4/H_2O$; (ii) Pd/C, EtOH, Ethanolamine, reflux, 3 h; (iii) H_2SO_4, H_2O; (iv) PhCHO, *t*-BuOMe; (v) MsCl, Et_3N; (vi) Allylamine, HCl/H_2O, 112°C, 15 h; (vii) Ac_2O, AcOH, MsOH, *t*-BuOMe, 20°C, 15 h; (viii) 10% Pd/C, EtOH, ethanolamine, reflux, 3 h; (ix) H_3PO_4, EtOH.



Scheme 6. Reagents and conditions: (i) EtOH, $SOCl_2$, reflux; (ii) Evaporation; (iii) $Me_2C(OMe)_2$, TsOH, EtOAc; (iv) MsCl; (v) Et_3N; (vi) Crystallization MeOH; (vii) Pentanone, CF_3SO_3H; (viii) Et_3SiH, $TiCl_4$, CH_2Cl_2, –34°C; (ix) Poured on H_2O, extraction $NaHCO_3$; (x) $NaHCO_3$, $EtOH/H_2O$, 60°C; (xi) Extraction *n*-hexane; (xii) Crystallization *n*-hexane.

SA as starting material for useful products

Zhang *et al.*[40] developed an enantioselective synthesis of (–)-zeylenone from (–)-shikimic acid. Zeylenone, which was isolated from *Uvaria grandiflora*, has shown promising antiviral, anticancer and antibiotic activities. SA is also used as a substrate for the synthesis of carbasuguars which are known to display a range of biological activities, particularly as glycosidase inhibitors. When used as a complex with platinum (II), SA acts as a potential antitumour agent[41] against L1210 and P388. Derivatives of SA exhibit anticoagulant and antithrombotic activities

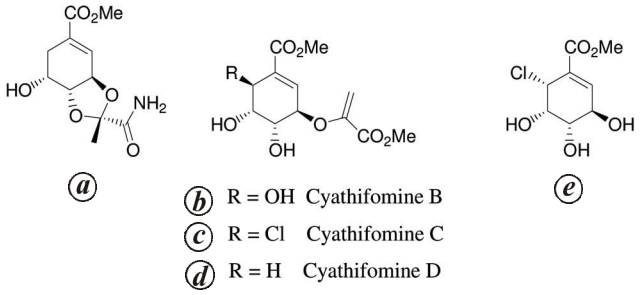
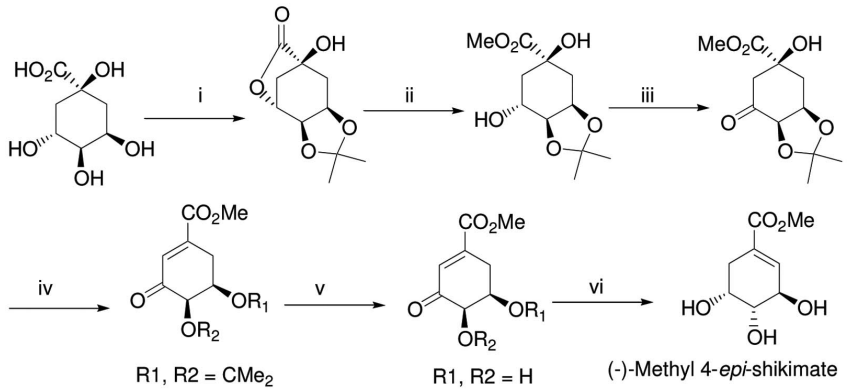
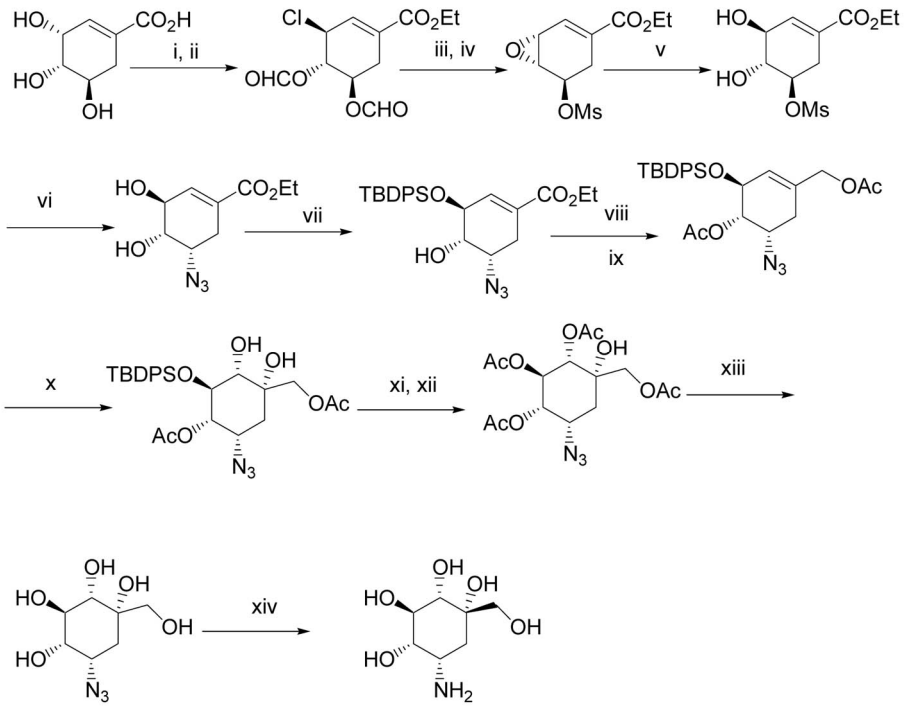


Figure 3. ***a***, Dioxolamycin; ***b***, Cyathifomine B, ***c***, Cyathifomine C; ***d***, Cyathifomine D; ***e***, Pericosine A.



Scheme 7. Reagents and conditions: (i) Na_2SO_4, H_2SO_4, acetone, reflux, 24 h; (ii) NaOMe, MeOH, 0°C to rt, 5 h; (iii) PCC, CH_2Cl_2, rt, 8 h; (iv) $POCl_3$, Py, 0°C to rt, 8 h; (v) CF_3CO_2H–H_2O (1 : 1), 0°C, 45 min; (vi) $NaBH(OAc)_3$, CH_2Cl_2, rt, 2 h.



Scheme 8. Reagents and conditions: (i) Quan et al.[44]; (ii) $SOCl_2$, DMF, 0°C to rt, 25 h; (iii) K_2CO_3, EtOH, rt, 20 h; (iv) MsCl, Et_3N, CH_2Cl_2, 0°C, 1 h; (v) CF_3CO_2H–H_2O (10 : 1), rt, 8 h; (vi) NaN_3, HOAc, DMSO, 85°C, 2 h; (vii) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, rt, 5 h; (viii) DIBAL-H, CH_2Cl_2, –10°C, 1 h; (ix) Ac_2O, Et_3N, DMAP, EtOAc, 0°C, 1 h; (x) $NaIO_4$, cat. $RuCl_3$, CH_3CN–H_2O (3 : 1), rt, 4 h; (xi) TBAF, THF, rt, 5 h; (xii) Ac_2O, Et_3N, DMAP, 0°C, 1 h; (xiii) CH_3OH–$NH_3.H_2O$ (5 : 1), reflux, 25 h; (xiv) Pd/C, H_2, CH_3OH–H_2O (1 : 1), rt, 24 h.

in rats[42]. Several antitumour compounds (Figure 3) such as dioxolamycin, pericosine A, and cythiaformines B, C and D are derivatives of 4-*epi*-SA (Scheme 7)[43]. Valiolamine, a potent α-glucosidase inhibitor against porcine intestinal sucrase, maltase and isomaltase originally isolated from *Streptomyces hygroscopicus* subsp. *limoneus*, is now synthesized from SA (Scheme 8)[44].

Conclusion

The shikimic acid is the key intermediate in the common pathway of aromatic amino acid biosynthesis. It is an economically important chiral compound used as a building block for the synthesis of different pharmaceutical and cosmetic products[24,45]. However, the most important use of (–)-shikimic acid is as substrate for industrial synthesis of Tamiflu. The demand for Tamiflu has increased tremendously and Roche is unable to meet this demand due to shortage of (–)-shikimic acid. The current availability of Tamiflu is not sufficient even for 2% of the world population. Hence, more attention needs to be paid for the development of efficient technologies for the production of SA as well as to find alternative sources of SA.

1. Widmer, N., Meylan, P., Ivanyuk, A., Aouri, M., Decosterd, L. A. and Buclin, T., Oseltamivir in seasonal, avian H5N1 and pandemic 2009 AH1N1 influenza: pharmacokinetic and pharmacodynamic characteristics. *Clin. Pharmacokinet.*, 2010, **49**, 741–765.
2. Eykman, J. F., Sur les principes constituants de *l'Illicium religiosum* (Sieb.) (Shikimi-no-ki en japonais). *Rec. Trav. Chim. Pays-Bas.*, 1885, **4**, 32–54.
3. Fischer, H. O. L. and Dangschat, G., *Bet. Deutsch. Chem. Ges.*, 1932, **65**, 1009.
4. Fischer, H. O. L. and Dangschat, G., *Helv. Chim. Acta*, 1934, **17**, 1196.
5. Fischer, H. O. L. and Dangschat, G., *Helv. Chim. Acta*, 1935, **18**, 1204.
6. Freudenberg, K., Meisenheimer, H., Lane, J. T. and Plankenhorn, E., Die Konfiguration des tertiären Kohlenstoffatoms. III. *Liebigs Ann. Chem.*, 1940, **543**, 162–171.
7. Karrer, P. and Link, K. P., Zur Kenntnis der Acylderivate der Chinasäure. *Helv. Chim. Acta*, 1927, **10**, 794–799.
8. Grewe, R. and Bllttner, H., Darstellung und Eigenschaften des Shikimialdehyds. *Chem. Ber.*, 1958, **91**, 2452–2458.
9. Grewe, R. and Haendler, H., Darstellung und Eigenschaften des Chinaaldehyds. *Liebigs Ann. Chem.*, 1962, **658**, 113–119.
10. Bochkov, D. V., Sysolyatin, S. V., Kalashnikov, A. I. and Surmacheva, I. A., Shikimic acid: review of its analytical, isolation, and purification techniques from plant and microbial sources. *J. Chem. Biol.*, 2012, **5**, 5–17.
11. Payne, R. and Edmonds, M., Isolation of shikimic acid from star aniseed. *J. Chem. Educ.*, 2005, **82**, 599–600.
12. Flores, N., Xiao, J., Berry, A., Bolivar, F. and Valle, F., Pathway engineering for the production of aromatic compounds in *Escherichia coli*. *Nature Biotechnol.*, 1996, **14**, 620–623.
13. Estévez, A. M. and Estévez, R. J., A short overview on the medicinal chemistry of (–)-shikimic acid. *Mini. Rev. Med. Chem.*, 2012, **12**, 1443–1454.
14. Ohira, H., Torii, N., Aida, T. M., Watanabe, M. and Smith Jr, R. L., Rapid separation of shikimic acid from Chinese star anise (*Illicium verum* Hook. f.) with hot water extraction. *Sep. Purif. Technol.*, 2009, **69**, 102–108.
15. Mueller, T. C., Massey, J. H., Hayes, R. M., Main, C. L. and Stewart Jr, C. N., Shikimate accumulates in both glyphosate-sensitive and glyphosate-resistant horseweed (*Conyza canadensis* L. Cronq.). *Food Chem.*, 2003, **51**, 680–684.
16. Zhou, B. and Xu, J., Production preparation process of high purity shikimic acid. CN Patent, 2009, 101391951.
17. Yang, L., Huang, J. and Liu, T., Extraction technology of shikimic acid homogenate from *Picea koraiensis* optimized by response surface methodology. *For. Eng.*, 2010, **26**, 9–13.
18. Chen, F., Hou, K., Li, S., Zu, Y. and Yang, L., Extraction and chromatographic determination of shikimic acid in Chinese conifer needles with 1-benzyl-3-methylimidazolium bromide ionic liquid aqueous solutions. *J. Anal. Meth. Chem.*, 2014, 1–12.
19. Plouvier, V., Sur la recherche des acides quinique et shikimique, de la bergenine et desheterosides chez quelques hamamelidacees. *CR Hebd. Seances Acad. Sci.*, 1961, **52**, 599.
20. Henshaw, G. G., Coult, D. A. and Boulter, D., Organic acids of the rhizome of *Iris pseudacorus* L. *Nature*, 1962, **194**, 579.
21. Adams, H. *et al.*, The shikimate pathway. Part 8. Synthesis of (–)-3(*R*)-amino-4(*R*),5(*R*)-dihydroxy-1-cyclohexene-1-carboxylic acid: the 3(*R*)-amino analogue of (–)-shikimic acid. *Tetrahedron*, 1996, **52**, 8565–8580.
22. Raghavendra, T. R. *et al.*, Prospecting for alternate sources of shikimic acid, a precursor of Tamiflu, a bird-flu drug. *Curr. Sci.*, 2009, **96**, 771–772.
23. Jiang, S. and Singh, G., Chemical synthesis of shikimic acid and its analogues. *Tetrahedron*, 1998, **54**, 4697–4753.
24. Ghosh, S., Chisti, Y. and Banerjee, U. C., Production of shikimic acid. *Biotechnol. Adv.*, 2012, **30**, 1425–1431.
25. Ambhaikar, 2005; https://www.scripps.edu/baran/images/grpmtgpdf/Ambhaikar_Jan_05.pdf
26. McCrindle, R., Overton, K. H. and Raphael, R. A., A stereospecific total synthesis of D-(–)-shikimic acid. *J. Chem. Soc.*, 1960, 1560–1565.
27. Smissman, E. E., Suh, J. T., Oxman, M. and Deniels, R., A stereospecific synthesis of dl-shikimic acid. *J. Am. Chem. Soc.*, 1959, **81**, 2909–2910.
28. Dangschat, G. and Fischer, H. O. L., *Biochim. Biophys. Acta*, 1950, **4**, 199.
29. Grewe, R. and Hinrichs, I., Eine neue synthese der Skikimisäure. *Chem. Ber.*, 1964, **97**, 443–448.
30. Koreeda, M. and Ciufolini, M. A., Natural product synthesis via allylsilanes. 1. Synthesis and reactions of (1E, 3E)-4-acetoxy-1-(trimethylsilyl)-1,3-butadiene and its use in the total synthesis of (±)-shikimic acid. *J. Am. Chem. Soc.*, 1982, **104**, 2308–2310.
31. Koreeda, M., Teng, K. and Murata, T., (1E, 3E)-4-Acetoxy-1-phenyldimethylsilyl-1,3-butadiene as a surrogate for (1E,3E)-1,4-diacetoxy-1,3-butadiene: a highly efficient synthesis of (±)-shikimic acid. *Tetrahedron Lett.*, 1990, **31**, 5997–6000.
32. Mitsuhashi, S. and Davis, B. D., Aromatic biosynthesis. XIII. Conversion of quinic acid to 5-dehydroquinic acid by quinic dehydrogenase. *Biochim. Biophys. Acta*, 1954, **15**, 268.
33. Millican, R. C., A thiobarbituric acid assay for shikimic acid. *Biochim. Biophys. Acta*, 1962, **57**, 407–409.
34. Quiroz, D. C. D., Carmona, S. B., Bolívar, F. and Adelfo Escalante, A., Current perspectives on applications of shikimic and aminoshikimic acids in pharmaceutical chemistry. *Res. Rep. Med. Chem.*, 2014, **4**, 35–46.
35. McKimm-Breschkin, J. L., Influenza neuraminidase inhibitors: antiviral action and mechanisms of resistance. *Influenza Respir. Viruses*, 2013, **7**, 25–36.
36. Kim, C. U. *et al.*, Influenza neuraminidase inhibitor possessing a novel hydrophobic interaction in the enzyme active site: design, synthesis, and structural analysis of carbocyclic sialic acid

analogues with potent anti-influenza activity. *J. Am. Chem. Soc*., 1997, **119**, 681–690.
37. Rohloff, J. C. *et al.*, Practical total synthesis of the anti-influenza drug GS-4104. *J. Org. Chem*., 1998, **63**, 4545–4550.
38. Karpf, M. and Trussardi, R., New, azide-free transformation of epoxides into 1,2-diamino compounds: synthesis of the anti-influenza neuraminidase inhibitor oseltamivir phosphate (Tamiflu). *J. Org. Chem*., 2001, **66**, 2044–2051.
39. Federspiel, M. *et al*., Industrial synthesis of the key precursor in the synthesis of the anti-influenza drug oseltamivir phosphate (Ro 64-0796/002, GS-4104-02): ethyl (3*R*,4*S*,5*S*)-4,5-epoxy-3-(1-ethyl-propoxy)-cyclohex-1-ene-1-carboxylate. *Org. Proc. Res. Dev.*, 1999, **3**, 266–274.
40. Zhang, Y., Liu, A., Ye, Z. G., Lin, J., Xu, L. Z. and Yang, S. L., New approach to the total synthesis of (–)-zeylenone from shikimic acid. *Chem. Pharm. Bull.* (*Tokyo*), 2006, **54**, 1459–1461.
41. Farrell, N., Roberts, J. D. and Hacker, M. P., Shikimic acid complexes of platinum. Preparation, reactivity, and antitumor activity of (R,R-1,2-diaminocyclohexane) bis(shikimate) platinum (II). Evidence for a novel rearrangement involving platinum-carbon bond formation. *J. Inorg. Biochem*., 1991, **42**, 237–246.
42. Huang, F., Xiu, Q., Sun, J. and Hong, E., Anti-platelet and anti-thrombotic effects of triacetylshikimic acid in rats. *J. Cardiovasc. Pharmacol*., 2002, **39**, 262–270.
43. Sanchez-Abella, L., Fernández, S., Armesto, N., Ferrero, M. and Gotor, V., Novel and efficient syntheses of (–)-methyl 4-epi-shikimate and 4,5-epoxyquinic and -shikimic acid derivatives as key precursors to prepare new analogues. *J. Org. Chem*., 2006, **71**, 5396–5399.
44. Quan, N., Nie, L. D., Zhu, R. H., Shi, X. X., Ding, W. and Lu, X., Total syntheses of (+)-valiolamine and (–)-1-epi-valiolamine from naturally abundant (–)-shikimic acid. *Eur. J. Org. Chem*., 2013, **78**, 6389–6396.
45. Rawat, G., Tripathi, P. and Saxena, R. K., Expanding horizons of shikimic acid. Recent progresses in production and its endless frontiers in application and market trends. *Appl. Microbiol. Biotechnol*., 2013, **97**, 4277–4287.

ACKNOWLEDGEMENTS. I thank the Director, IBSD, Imphal (an autonomous Institute of DBT, Government of India) for providing the necessary facilities and Prof. N. C. Talukdar, Director, IASST, Guwahati, Assam for valuable suggestions.

Received 28 April 2015; revised accepted 13 August 2015

doi: 10.18520/v109/i9/1672-1679