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Chemical Synthesis of Shikimic Acid and Its Analogues

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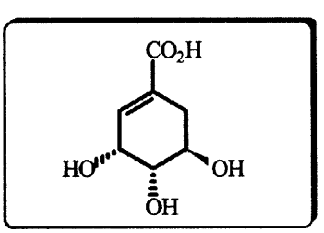
1. INTRODUCTION

(–)-Shikimic acid **1** was first isolated in 1885 by Eykman[1,2] from the fruit of *Illicium religiosum* Sieb. et Zucc.,[3] and derived its name from this oriental plant which is called *shikimi-no-ki* in Japanese. Later studies have shown that this acid exists widely in the leaves and fruit of many plants.[4]



(–)-shikimic acid **1**

In his early studies Eykman[5] described **1** as a trihydroxycyclohexene carboxylic acid, and also observed its ready aromatisation to *p*-hydroxybenzoic acid upon heating with an acid, but he was unable to define the relative and absolute stereochemistry of (–)-shikimic acid **1**, which was only realised in the 1930s by the

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works of Fischer,[6] Freudenberg[7] and Karrer.[8] Subsequently Grewe[9] carried out extensive work on the chemistry of (–)-shikimic acid 1. Since then, numerous publications on shikimic acid have appeared from different groups.[10]

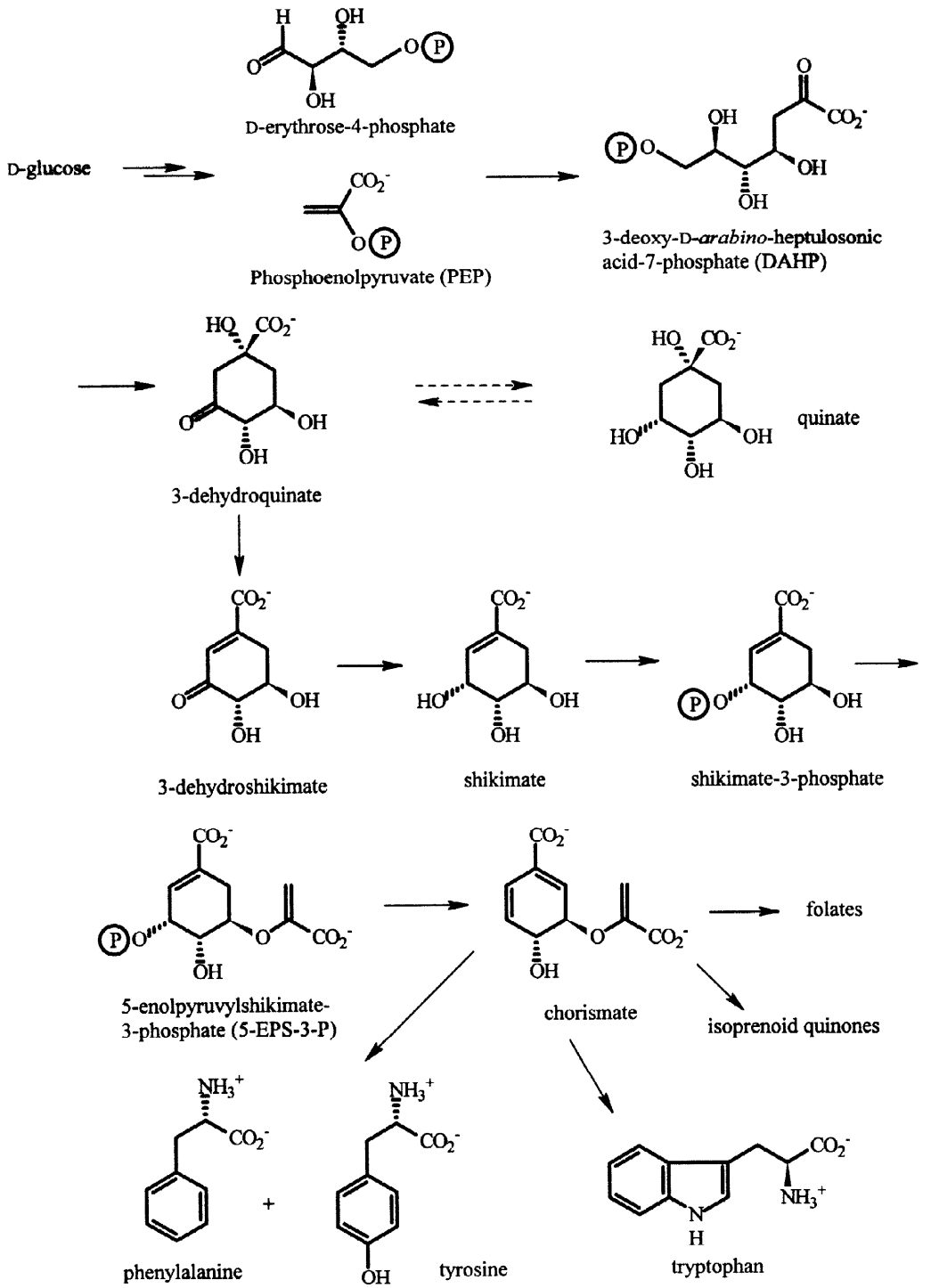


Fig. 1 The shikimate pathway

Note: The main stem of shikimate metabolism from glucose to chorismate is normally referred as the common pathway.

(–)-Shikimic acid **1** occupies an important position in the pathway of biosynthesis known as the shikimate pathway (Fig. 1), the discovery of which was largely attributed to the pioneering work of Davis,[11] Sprinson[12] and Gibson.[13]

The shikimate pathway is operative both in plants and microorganisms where the three aromatic amino acids (L-phenylalanine, L-tyrosine and L-tryptophan) are synthesised along this biosynthetic sequence. However, this pathway does not apply to mammals, which obtain these aromatic amino acids by dietary means. Thus there is great potential for the design and synthesis of enzyme inhibitors which may selectively block specific enzyme-catalysed transformations along this pathway.[14] This, in practice, has stimulated extensive search for herbicidal, antifungal or antibacterial agents of low environmental impact, an example of which is the commercial broad spectrum herbicide Roundup® which contains the active ingredient glyphosate (*N*-phosphonomethyl glycine) which specifically inhibits the enzyme 5-enolpyruvylshikimate-3-phosphate synthase in the pathway.[15]

The importance of the shikimate pathway has made itself the topic of several excellent reviews over the years covering some early literature.[16] However, it is not the intention of this review to engage in an exhaustive discussion on the progress in this field. Instead it brings together, from the perspective of synthetic organic chemistry, those methods available for the chemical synthesis of shikimic acid and its analogues from simple starting materials.

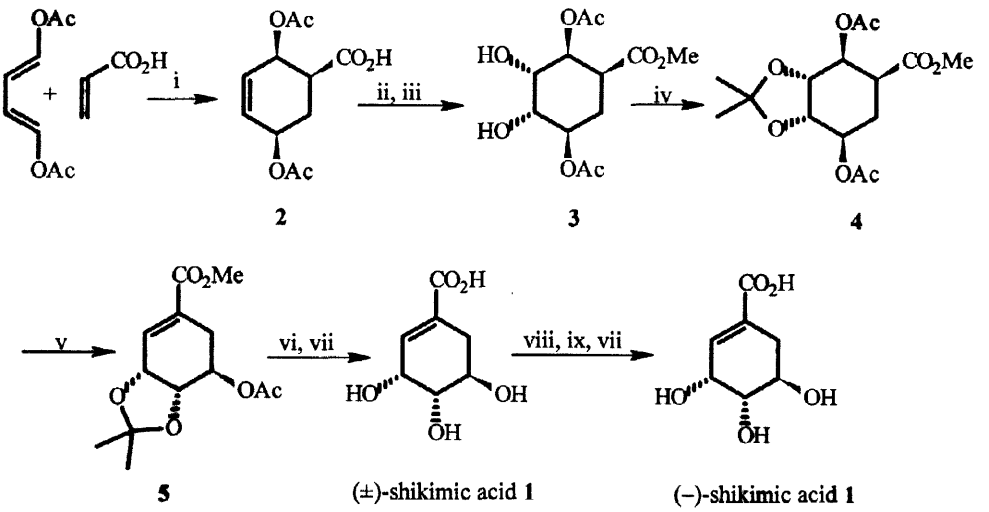
2. SYNTHETIC APPROACHES BASED ON THE DIELS–ALDER REACTION

2.1 Racemic syntheses

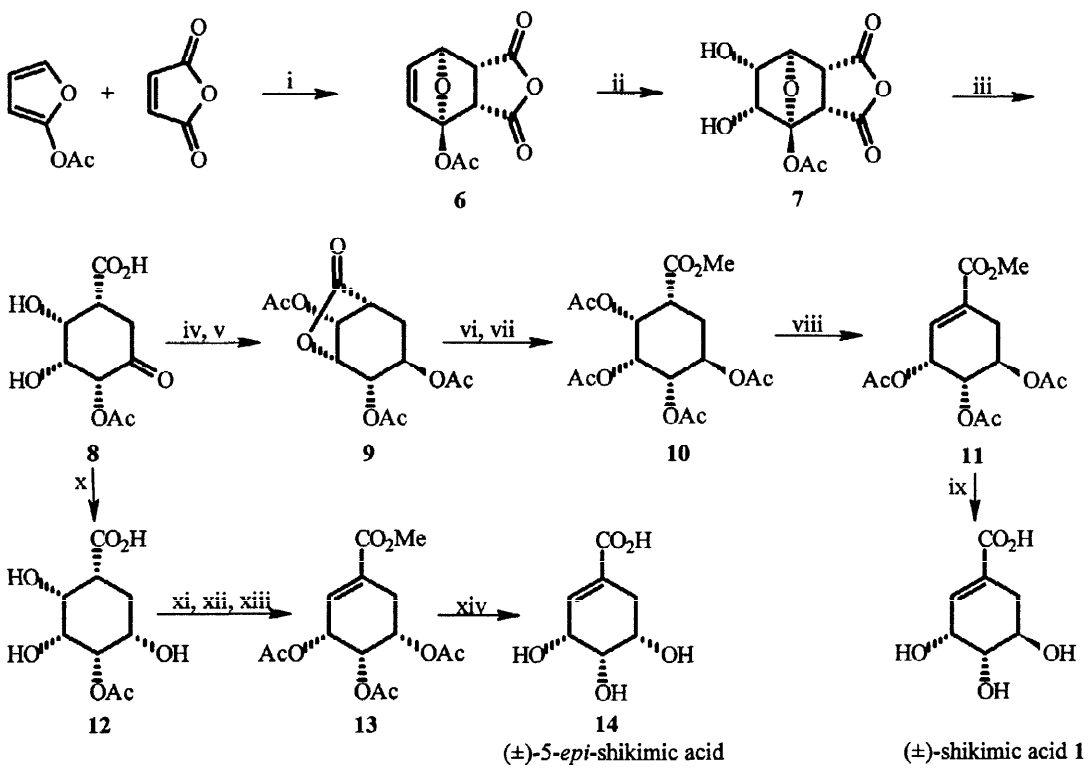
The first chemical synthesis of shikimic acid **1** in racemic form was reported simultaneously by the groups of Raphael[17] and Smissman[18] using, in their own words, 'an essentially identical route'. Raphael and co-workers (Scheme 1) employed the Diels–Alder reaction with (1*E*,3*E*)-1,4-diacetoxy-1,3-butadiene and acrylic acid as starting materials, while in Smissman's synthesis[18] methyl acrylate was used. The cycloadduct **2** was formed by *endo* addition which gave the correct stereochemistry for the subsequent base-catalysed 1,2-elimination. The assignment on the stereochemistry of adduct **2** by Raphael and co-workers was later supported by ^{1}H NMR measurements on **2**, **4** and their deuterated forms.[19] Although Smissman and co-workers originally reported that the cycloaddition of (1*E*,3*E*)-1,4-diacetoxy-1,3-butadiene and methyl acrylate proceeded in the *exo*-mode which was contrary to the result observed by Raphael and co-workers, they later retracted this claim and reassigned their adduct as also having *endo*-stereochemistry.[20]

In a recent report by Balasubramanian and Abell[21] on the synthesis of (6*R*)-[6-^{2}H]- and (6*S*)-[6-^{2}H]-5-enolpyruvylshikimate-3-phosphate the same strategy that Raphael and Smissman adopted was used for the synthesis of racemic [6-$^2H_\alpha$]- and [6-$^2H_\beta$]-shikimic acids, albeit with improved reaction conditions and reagents. Unaware of the revision on the stereochemistry of the cycloadduct by Smissman and Li,[20] Balasubramanian and Abell reinvestigated this Diels–Alder reaction[17,18] and found that the adduct was a mixture of diastereoisomers with an *exo*:*endo* ratio of approximately 1:4, irrespective of whether acrylic acid or methyl acrylate was used. This corroborates the earlier evidence for the predominance of the *endo*-adduct.

Shortly after the reports on the synthesis of racemic shikimic acid **1** by the groups of Raphael and Smissman, the latter also communicated an alternative synthesis of **1** (Scheme 2) in the form of a dissertation



Scheme 1 *Reagents and conditions:* i, hydroquinone, 85-90 °C, 3 h; ii, OsO_4, Et_2O, pyridine, 5 days; iii, CH_2N_2 (100%); 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, pyridine, 16 h; ix, (−)-quinine, MeOH



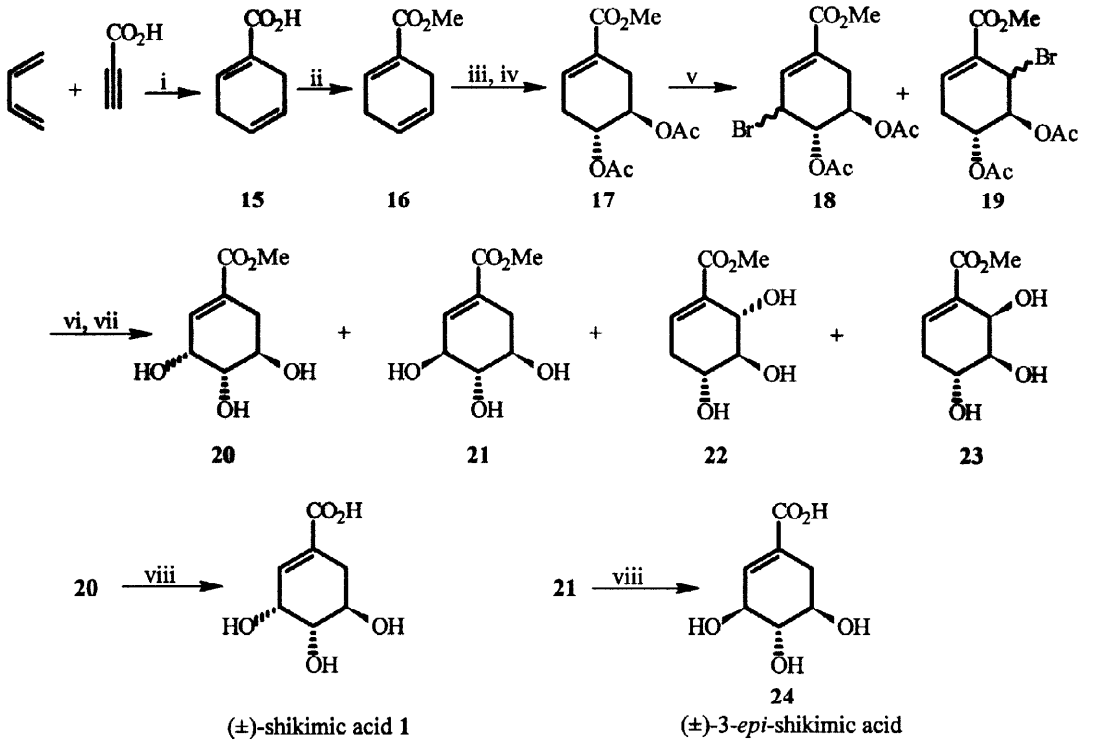
Scheme 2 *Reagents and conditions:* i, benzene, heat (67%); ii, OsO_4, H_2O_2 (30%), acetone, diethyl ether, 30 °C, 24 h (54%); iii, H_2O, rt, 3 days (66%); iv, $NaBH_4$; v, Ac_2O; vi, MeOH, HCl (cat.); vii, Ac_2O (57.5% two steps; 17% from **8**, see: ref. 25); viii, soft glass powder, sealed tube, vacuum, 256-258 °C, 20 min (92%); ix, saponification (75.5%); x, H_2, catalyst (33%); xi, CH_2N_2, xii, Ac_2O; xiii, sealed tube, vacuum, 256-258 °C, 30 min; xiv, hydrolysis

abstract and also an ACS meeting abstract.[22] This route started from the *exo*-adduct **6** which was prepared from the Diels–Alder reaction of 2-acetoxyfuran and maleic anhydride.[23] Dihydroxylation of **6** gave the diol **7**,[24] an aqueous solution of which was stirred at room temperature for three days to produce the keto acid **8**. It is interesting to note that although Raphael and co-workers[18] initially attempted to use this route to prepare shikimic acid, they were unable to cleave the hemiacetal acetate function in the acetonide of **7** without inducing aromatisation, which, in retrospect, may be attributed to the steric restriction imposed by the isopropylidene group. Sodium borohydride reduction of **8** and subsequent acetylation afforded the lactone **9** which was treated with methanolic hydrogen chloride and further acetylated to provide the methyl ester **10**. Pyrolysis of **10** in the presence of soft glass powder yielded the methyl triacetylshikimate **11**. Saponification gave the free (±)-shikimic acid **1** in an overall yield of 3% from 2-acetoxyfuran, which compares unfavourably with their previous synthesis (15% overall yield). It is important to mention that the authors also for the first time obtained what was believed to be 5-*epi*-shikimic aicd **14** *via* catalytic hydrogenation of the keto acid **8**.

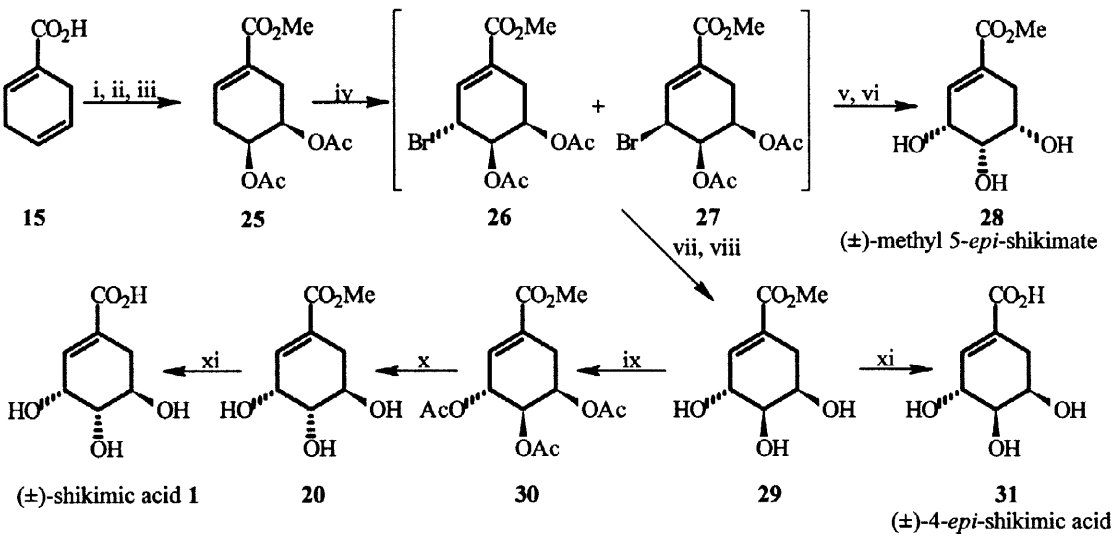
This approach has been successfully adopted by McCasland and co-workers[25] in their synthesis of pseudosugars[26] and also by Hanessian and co-workers[27] who prepared racemic methyl 5-methyl-5-*epi*-shikimate as an intermediate in natural product synthesis *via* the keto acid **8**.

Grewe and Hinrichs[28] prepared (±)-shikimic acid **1** and (±)-3-*epi*-shikimic acid **24**[29] (Scheme 3) from 2,5-dihydrobenzoic acid **15** which was obtained from butadiene and propiolic acid through a Diels–Alder reaction. Esterification of **15** followed by epoxidation, *in situ* epoxide ring opening and further acetylation gave the diacetate **17**. Lack of regio- and stereo-selectivity in the allylic bromination of **17** resulted in **18** and **19**, each as an epimeric mixture. Treatment of the mixture of **18** and **19** with silver acetate in moist acetic acid followed by deacetylation furnished the mixture of methyl esters **20**, **21**, **22** and **23**, which were separated. Separate saponification of esters **20** and **21** delivered (±)-shikimic acid **1** and (±)-3-*epi*-shikimic acid **24** in overall yields of 11% and 3% respectively from butadiene and propiolic acid.

A later synthesis of (±)-shikimic acid **1**, (±)-methyl 5-*epi*-shikimate **28** and (±)-4-*epi*-shikimic acid **32** (Scheme 4) by Grewe and Kersten[30] used a Woodward modification of the Prévost reaction to produce the *cis*-diacetate **25**. Regioselective bromination of **25** gave an epimeric mixture of **26** and **27** with the former as the major product. Treatment of this bromo mixture with silver acetate in moist acetic acid and subsequent deacetylation led to the isolation of (±)-methyl 5-*epi*-shikimate **28** as the major product. Use of potassium acetate in acetic acid for the substitution reaction with the bromo mixture resulted in (±)-methyl 4-*epi*-shikimate **29** as the major product. Both **28** and **29** were derived from **26**, and in the case of the latter the substitution reaction proceeded with retention of configuration. A noteworthy feature of this work was the transformation of triacetate **30** to methyl shikimate **20** which involved a process of epimerisation in the presence of liquid hydrogen fluoride to give **29** and **20** in a ratio of 1:5. The authors also demonstrated that this process would result in racemisation of optically active **30**, which was later confirmed by Snyder and Rapoport.[31] Saponification of the methyl ester **20** gave (±)-shikimic acid **1** which was resolved by fractional crystallisation of the diastereoisomeric salts of 3,4-*O*-cyclohexylideneshikimic acid with (−)-1-phenylethylamine and acidic hydrolysis. Saponification of methyl ester **29** afforded (±)-4-*epi*-shikimic acid **31**. This route starting from the cycloadduct **15** delivered (±)-shikimic acid **1**, (±)-methyl 5-*epi*-shikimate **28** and (±)-4-*epi*-shikimic acid **31** in overall yields of 41%, 19% and 52%, respectively.

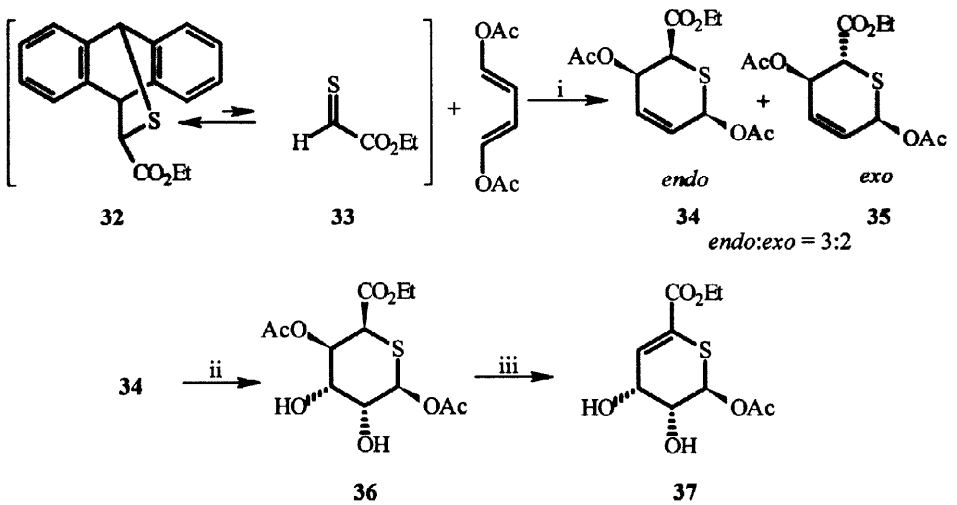


Scheme 3 *Reagents and conditions:* i, hydroquinone, toluene, 130-140 °C, 9 h (85%); ii, MeOH, conc. H_2SO_4 (cat.), 5 h (97%); iii, AcOH, H_2O_2 (30%), 40 °C, 4 h, then H_2O, 3 h (85%); iv, Ac_2O, pyridine (80%); v, *N*-bromosuccinimide, CCl_4, reflux; vi, AgOAc, AcOH, H_2O, rt, 14 h; vii, MeOH, HCl (cat.), reflux, 4 h (three steps, 20% for **20**, 5% for **21**, 1% for **22** and 7% for **23**); viii, KOH, MeOH, H_2O



Scheme 4 *Reagents and conditions:* i, AgOAc, I_2, AcOH, H_2O; ii, MeOH, HCl; iii, Ac_2O, pyridine (three steps, 94%); iv, *N*-bromosuccinimide, CCl_4, hv; v, AgOAc, AcOH, H_2O, rt, 24 h; vi, MeOH, HCl (cat.) (20% from **25**); vii, KOAc, AcOH, reflux; viii, MeOH, HCl (cat.) (55% from **25**); ix, Ac_2O, pyridine (100%); x, HF (80% for **20** and 16% for **29**); xi, MeOH, KOH (100%)

Raphael and Smissman's Diels–Alder strategy was applied again in a recent racemic synthesis of 6-thiashikimic acid derivative **37** (Scheme 5) by Kirby and co-workers.[32] In this case, the dienophile, ethyl thioxoacetate **33**, was generated *in situ* from **32**, the cycloadduct of anthracene and ethyl thioxoacetate **33**. The diastereoselectivity of the cycloaddition was poor, *endo*:*exo* = 3:2, although **34** was the major product as expected. With the presence of sulphur in the ring the base-catalysed 1,2-elimination of **36** proceeded in good yield without the need for an isopropylidene protecting group. However, Kirby and co-workers were unable to obtain the free (±)-6-thiashikimic acid because of the instability of the enethiol hemiacetal unit.

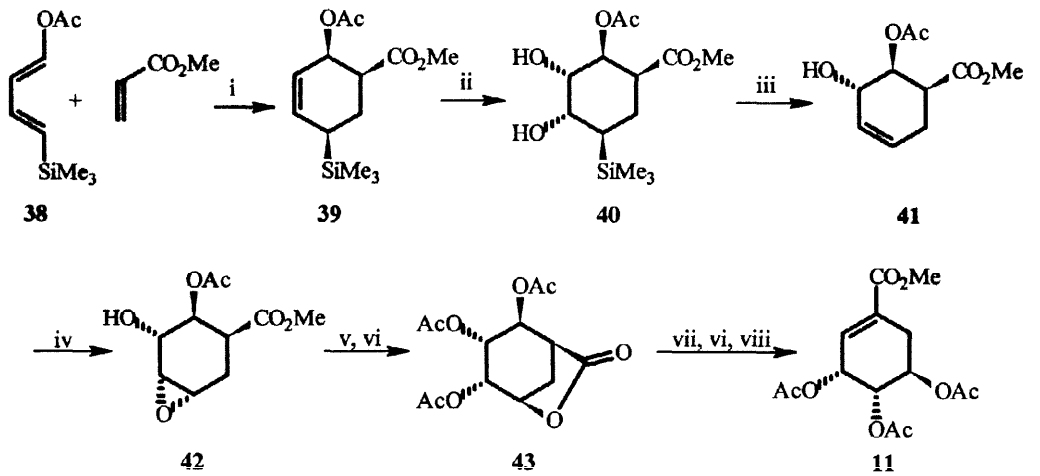


Scheme 5 *Reagents and conditions:* i, toluene, reflux, 6 h (59% for **34** and 35% for **35**); ii, OsO_4, pyridine, rt, 25 h (66%); iii, pyridine, reflux, 6 h (86%)

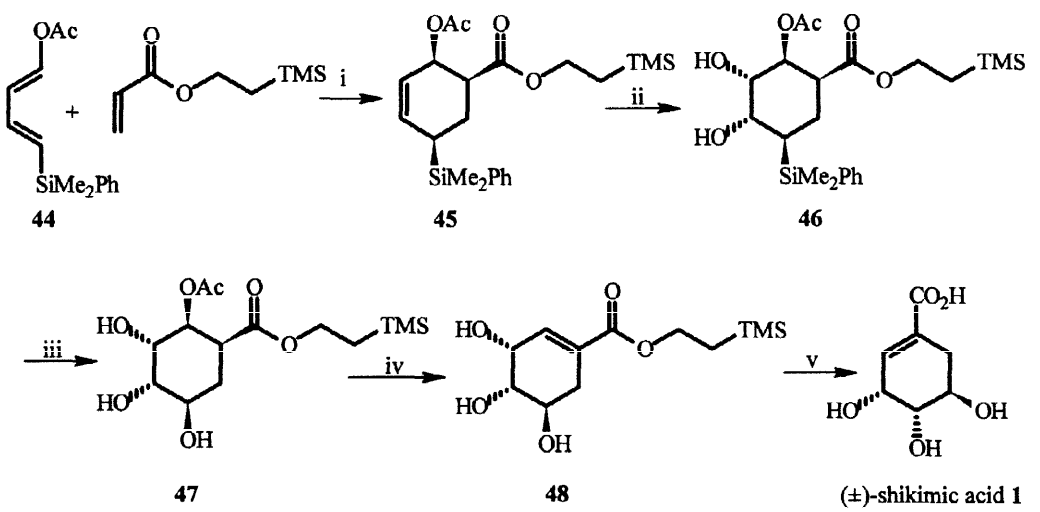
Koreeda and Ciufolini[33] used (1*E*,3*E*)-4-acetoxy-1-(trimethylsilyl)-1,3-butadiene **38** in their synthesis of (±)-methyl 3,4,5-triacetylshikimate **11** (Scheme 6). The cycloaddition of diene **38** with methyl acrylate gave the major *endo*-adduct **39** and the other *exo*-adduct in a ratio of 9:1. Osmylation of **39** using the Upjohn procedure[34] yielded the diol **40** which underwent elimination of the trimethylsilyl-hydroxy unit in the presence of a catalytic amount of *p*-TsOH to give the olefin **41**. Epoxidation of **41** with MCPBA, followed by treatment with lithium hydroxide and acetylation, led to the triacetate lactone **43**, which, after lactone ring opening and reacetylation, was treated with DBU to afford the (±)-methyl triacetylshikimate **11**. The overall yield of this synthesis from diene **38** was 29%.

Inspired by Fleming's work on the use of the phenyldimethylsilyl group as a latent hydroxyl group,[35] Koreeda and co-workers[36] later described another synthesis of (±)-shikimic acid **1** (Scheme 7) employing (1*E*,3*E*)-4-acetoxy-1-phenyldimethylsilyl-1,3-butadiene **44** as a surrogate for (1*E*,3*E*)-1,4-diacetoxy-1,3-butadiene. The authors claimed that they used 2-(trimethylsilyl)ethyl acrylate instead of methyl acrylate for the construction of the cyclohexene ring in order to avoid the final problematic hydrolysis of the acetate and methyl ester groups of methyl triacetylshikimate. The cycloaddition reaction gave the *endo*-adduct **45** as the major product (*endo*:*exo* = 11:1), the dihydroxylation of which delivered the diol **46**. The key to this synthesis is the transformation of **46** to **47** using Fleming's buffered, one-pot procedure[35b] to convert the

phenyldimethylsilyl group into the hydroxyl group with retention of configuration at the carbon atom. Treatment of **47** with DBU resulted in the elimination of acetic acid, and the product **48** was further deprotected to give (±)-shikimic acid **1**. The overall yield for this synthesis from **44** was 55%, which was twice the yield of their previous synthesis.

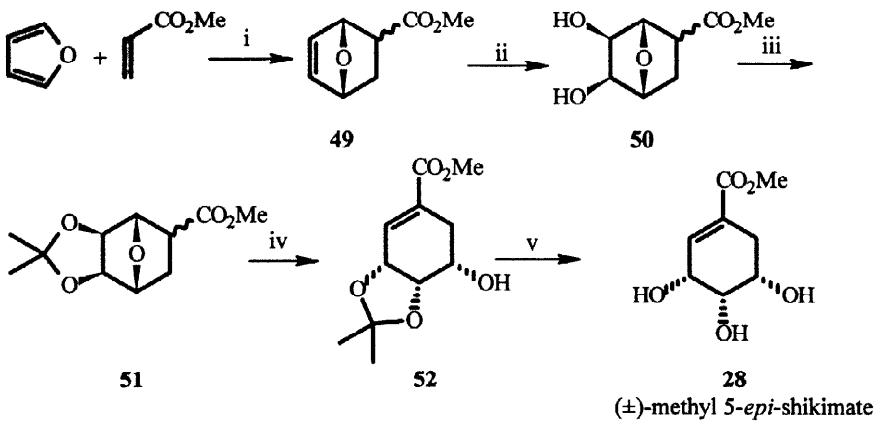


Scheme 6 *Reagents and conditions:* i, xylenes, reflux, 40 h (72% for **39** and 8% for the *exo*-isomer); ii, OsO_4 (cat.), *N*-methylmorpholine-*N*-oxide, *t*-BuOH-acetone-H_2O (30:6:5), rt, 10 h (96%); iii, *p*-TsOH (5 mole%), benzene, reflux, 20 min (98%); iv, MCPBA, CH_2Cl_2, rt, 20 h (91%); v, LiOH, THF-H_2O, rt, 6 h; vi, Ac_2O, pyridine, rt, 20 h (65% from **42** to **43**); vii, HCl, MeOH, rt, 3 h; viii, DBU, THF, rt, 6 h (71% from **43**)



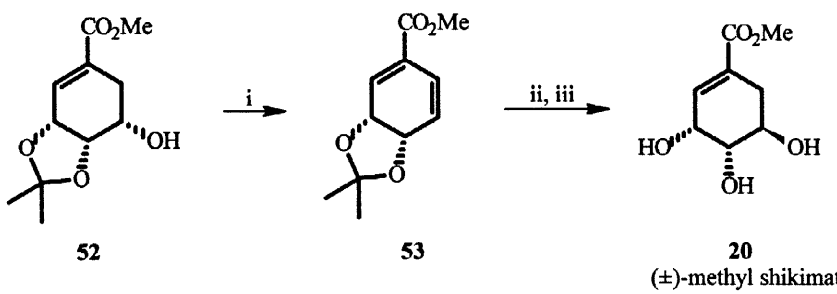
Scheme 7 *Reagents and conditions:* i, hydroquinone monomethyl ether (cat.), xylenes, reflux, 40 h (77%); ii, OsO_4 (cat.), *N*-methylmorpholine-*N*-oxide (1.2 equiv.), THF-H_2O (1:1), rt, 8 h (96%); iii, KBr (1.33 equiv.), AcOOH (15%, 30 equiv.) in AcOH, NaOAc (15 equiv.), rt, 18 h (81%); iv, DBU (1.35 equiv.), THF, rt, 4 h (94%); v, *n*-Bu_4NF (2.71 equiv.), THF, rt, 12 h (98%)

The synthesis of (±)-methyl shikimate **20** and (±)-methyl 5-*epi*-shikimate **28** (Schemes 8, 9 and 10) by Campbell, Sainsbury and co-workers[37] was based on the Diels–Alder reaction of furan and methyl acrylate. An important element of their approach that was previously developed by Brion[38] is the base-mediated opening of the oxabicyclo unit of the cycloadduct with lithium hexamethyldisilazide, which provides a rapid entry into the cyclohexene system. The cycloadduct **49** (a 1:2 mixture of the *endo*- and *exo*-adducts[38]) was treated with osmium tetroxide to yield the *exo*-diols **50**, isopropylidenation of which then gave the acetonide **51**. Ring opening of **51** was effected by lithium hexamethyldisilazide, and subsequent deprotection of **52** afforded the (±)-methyl 5-*epi*-shikimate **28** (Scheme 8). The overall yield for **28** was 17% from furan and methyl acrylate.



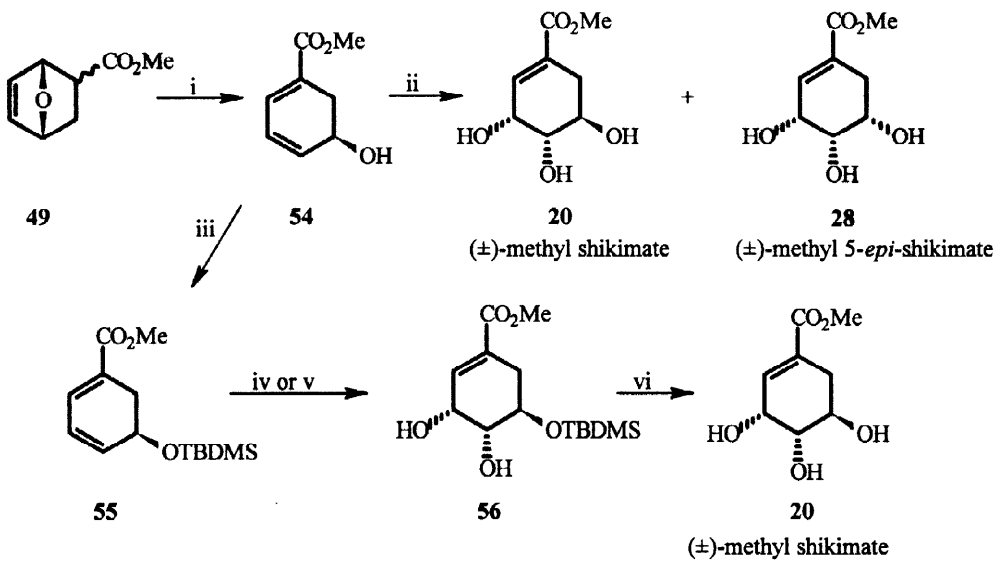
Scheme 8 *Reagents and conditions:* i, ZnI_2, 40 °C, 48 h (55%); ii, OsO_4, H_2O_2, Et_2O, acetone (71%); iii, $(MeO)_2CMe_2$, *p*-TsOH, acetone (94%); iv, *n*-BuLi, HMDS, THF, –78 °C (49%); v, aq. AcOH, 55 °C, 3 h (96%)

In order to synthesise the racemic methyl shikimate, these authors attempted to invert the stereochemistry at C-5 of **52** under Mitsunobu[39] conditions. However, they obtained a low yield of the diene **53**, a product of dehydration. Hydroboration-oxidation of **53** and further deprotection then gave the (±)-methyl shikimate **20** (Scheme 9). This sequence of manipulation produced **20** in an overall yield of 2.7% from furan and methyl acrylate.



Scheme 9 *Reagents and conditions:* i, DEAD, Ph_3P, THF (39%); ii, B_2H_6, THF, followed by NaOH, H_2O_2 (45%); iii, Dowex W X-8 (H^+), MeOH (85%)

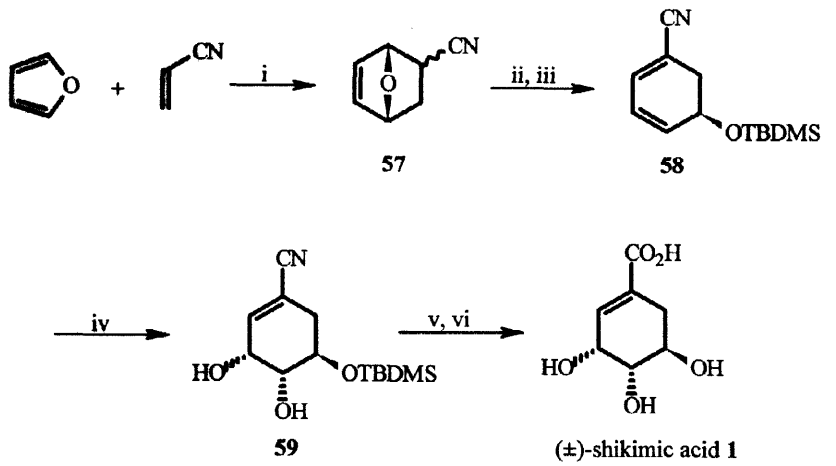
For a more direct route to (±)-methyl shikimate **20**, these authors reversed the order of dihydroxylation and ring-opening of cycloadduct **49** (Scheme 10). The dihydroxylation of diene **54** gave a 5:1 mixture of (±)-methyl shikimate **20** and (±)-methyl 5-*epi*-shikimate **28**, which were separated by column chromatography. Complete selectivity for the methyl shikimate **20** was achieved by using a bulky *t*-butyldimethylsilyl protecting group in **55** followed by dihydroxylation and deprotection. The dihydroxylation was achieved using either osmium tetroxide or the Woodward modification of the Prévost reaction. The overall yield for (±)-methyl shikimate **20** (either direct dihydroxylation of **54** or *via* the silyl ether **55**) was 27% from furan and methyl acrylate. By extending the methodology, Campbell, Sainsbury and co-workers also prepared (±)-methyl 6α-fluoroshikimate and (±)-homoshikimic acid.[40]



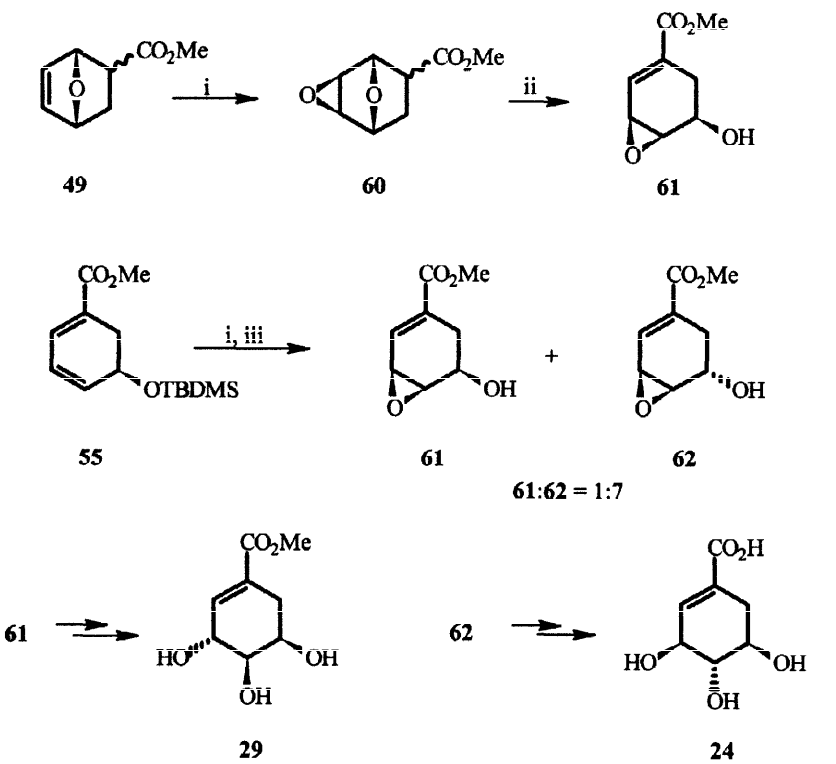
Scheme 10 *Reagents and conditions:* i, *n*-BuLi, HMDS, THF, −78 °C (80%); ii, OsO_4, H_2O_2, Et_2O, acetone (74%, **20**:**28** = 5:1) iii, TBDMSOTf, 2,6-lutidine, CH_2Cl_2 (95%); iv, OsO_4, H_2O_2, Et_2O, acetone (78%); v, (a) AgOAc, I_2, AcOH, H_2O, 70 °C (80%); (b) aq. NH_3, MeOH, 2 h (100%); vi, Bu_4NF, THF, 0 °C (86%)

A contemporaneous synthesis of (±)-shikimic acid **1** (Scheme 11) and (±)-5-*epi*-shikimic acid **14** by Rodrigo and co-workers[41] bears a close relationship to that of Campbell, Sainsbury and co-workers. The (±)-5-*epi*-shikimic acid **14** was synthesised in 21% overall yield from furan and methyl acrylate in virtually identical fashion, using lithium diisopropylamide (LDA) in place of lithium hexamethyldisilazide for the key ring opening of **51**. The (±)-shikimic acid **1** was obtained in 31% overall yield from furan and acrylonitrile *via* a similar sequence of reactions.

Rodrigo and co-workers also attempted to make analogues of shikimic acid *via* epoxidation of **49** and **55**[42] (Scheme 12). The epoxide **61** has been previously transformed to (±)-methyl 4-*epi*-shikimate **29** (Scheme 16) by McGowan and Berchtold.[43] The dextrorotatory epoxide **62**,[10d] a natural product isolated from the culture medium of *Chalara microspora* Hughes,[44] has recently been converted to (−)-3-*epi*-shikimic acid **24** *via* aqueous trifluoroacetic acid ring opening and subsequent saponification by Haslam and co-workers.[10p]



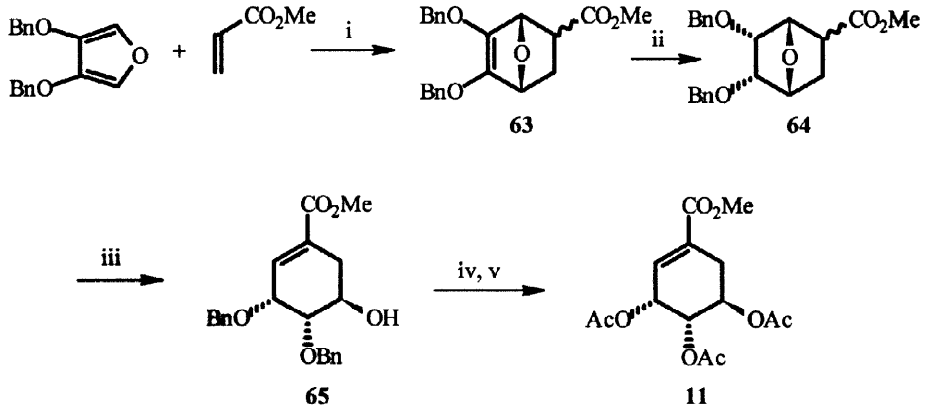
Scheme 11 *Reagents and conditions:* i, ZnI_2, 40 °C, 48 h (100%, 1:1 mixture of *endo*- and *exo*-adducts, see: ref. 38); ii, LDA, THF, −78 °C; iii, standard protection; iv, OsO_4, pyridine; v, Bu_4NF, THF; vi, H_2O, OH^-



Scheme 12 *Reagents and conditions:* i, MCPBA, CH_2Cl_2; ii, LDA, THF, −78 °C (43%); iii, Bu_4NF, THF

Koreeda and co-workers[45] some years later published another procedure (Scheme 13) for the synthesis of (±)-methyl 3,4,5-triacetylshikimate **11**, which was similar to Campbell, Sainsbury and Rodrigo's work. They used 3,4-dibenzyloxyfuran as an enophile for the Diels–Alder reaction to give the cycloadduct **63** with an *endo*:*exo* ratio of 15.3:1. The introduction of the benzyloxy groups in the starting material eliminated the need for further dihydroxylation which was the case in previous examples. Catalytic hydrogenation of **63** led

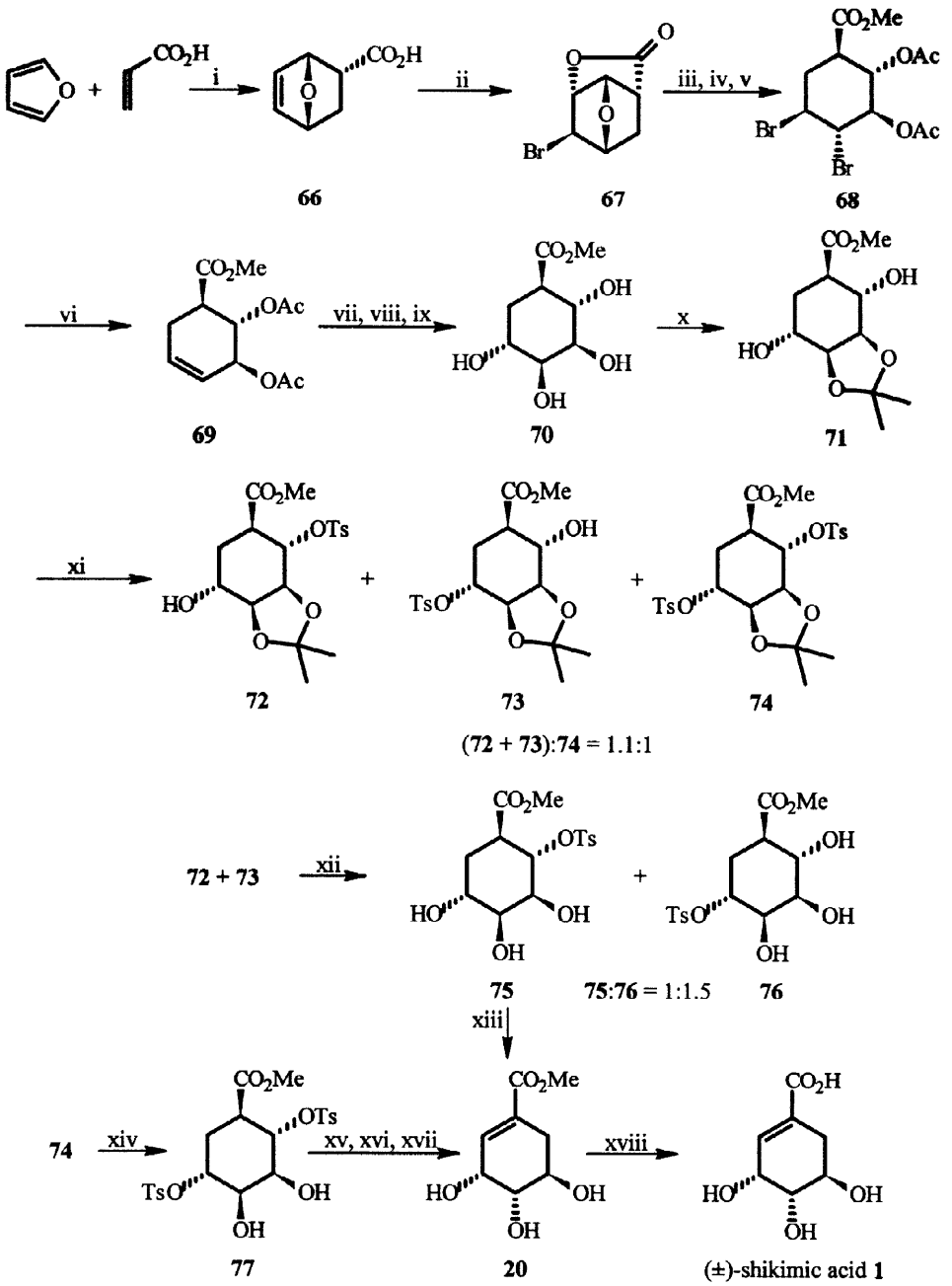
to exclusively the *endo*-product **64**. The ring opening of **64** with lithium hexamethyldisilazide followed by debenzylation and acetylation furnished the (±)-methyl 3,4,5-triacetylshikimate **11** in an overall yield of 63.9% from 3,4-dibenzyloxyfuran.



Scheme 13 *Reagents and conditions:* i, ZnI_2 (0.1 equiv.), neat, rt, 1 h (98%); ii, H_2, PtO_2, EtOAc, rt, 1 h (93%); iii, *n*-BuLi, HMDS, THF, −42 °C, 9 h (78%); iv, $BF_3{\cdot}Et_2O$, EtSH, CH_2Cl_2, 0 °C, 12 h; v, Ac_2O, pyridine, rt, 24 h (90% for two steps)

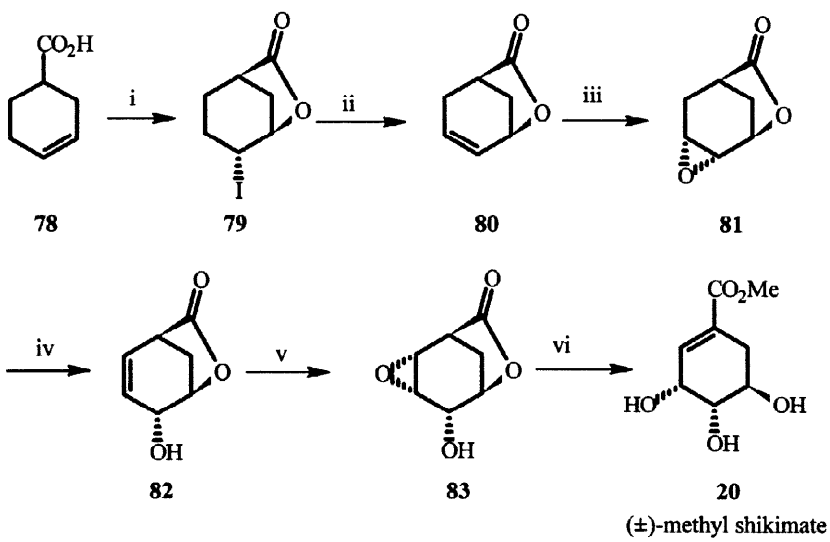
Ogawa and co-workers[46,47] reported the synthesis of (±)-shikimic acid **1** from the *endo*-cycloadduct of furan and acrylic acid (Scheme 14). Instead of using the reverse-Michael ring opening of the cycloadduct to generate the cyclohexene system as in previous examples, they employed a mixture of acetic anhydride, acetic acid and sulphuric acid or hydrogen bromide in acetic acid to effect the ring opening to furnish a cyclohexane system which was more suitable for further elaboration to pseudosugars[26] than to shikimic acid analogues. Mainly for this reason, this synthesis of (±)-shikimic acid **1** was quite protracted, and the overall yield from furan and acrylic was *ca.* 2%.

The *endo*-cycloadduct **66** was obtained through crystallisation from the cycloaddition of furan and acrylic acid and was treated with bromine in water to produce the bromo lactone **67**. Lactone and ether ring cleavages in **67** were effected with hydrogen bromide in acetic acid. Esterification of the resulting acid followed by acetylation afforded the dibromo ester **68**. Debromination of **68** was accomplished using excess of zinc dust in acetic acid to give the olefin **69**. Treatment of **69** with hydrogen peroxide and formic acid followed by further acetylation and deacetylation gave the tetrol **70**. Isopropylidenation of **70**, followed by treatment with tosyl chloride, afforded a mixture of monotosylates **72**, **73** and ditosylate **74**. The inseparable mixture of monotosylate **72** and **73** was deprotected by acidic hydrolysis and the resulting triols **75** and **76** were separated by chromatography. Triol **75** was converted to (±)-methyl shikimate **20** *via* the base-catalysed elimination of the tosylate unit. The ditosylate **74** was deprotected to give the diol **77** which was then treated consecutively with sodium acetate in aqueous 2-methoxyethanol, acetic anhydride in pyridine and methanolic sodium methoxide to afford the (±)-methyl shikimate **20**, which was then hydrolysed to (±)-shikimic acid **1**. It is interesting to note that the base-catalysed elimination of tosylate group from **75** and **77** adopted a *syn* pathway, which was different from Raphael and Kirby's observations.[17,32]

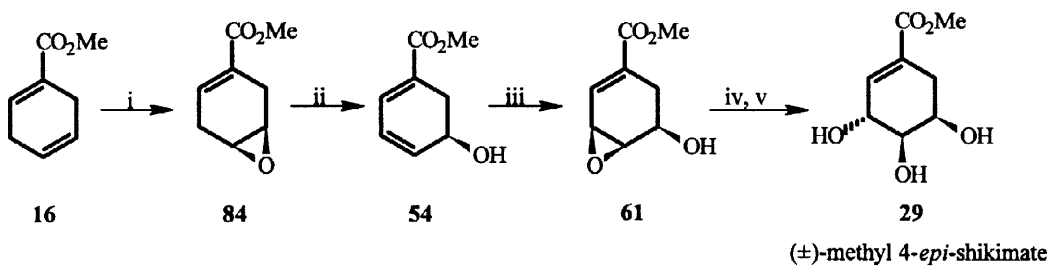


Scheme 14 *Reagents and conditions:* i, hydroquinone, 75 days (45%); ii, Br_2, H_2O, rt; iii, HBr, AcOH, sealed tube, 80 °C, 2 days (61%); iv, MeOH, AcCl (cat.), reflux, 2 h; v, Ac_2O, pyridine (two steps, 96%); vi, Zn, AcOH, 70 °C, 1 h (84%); vii, aq. HCO_2H (90%), H_2O_2 (35%), 60 °C, 1 h; viii, Ac_2O, pyridine (100% two steps); ix, NaOMe, MeOH (58%); x, $(MeO)_2CMe_2$, DMF, *p*-TsOH, 60 °C, 3 h (92%); xi, TsCl, pyridine, rt, 4 days (49% for **72** and **73**; 45% for **74**) xii, aq. AcOH (80%), 70 °C, 2 h (33% for **75**; 50% for **76**); xiii, NaOMe, MeOH, rt, 5 min; xiv, aq. AcOH (80%), 70 °C, 8 h (87%); xv, NaOAc, aq. 2-methoxyethanol (90%), reflux, 1.5 h; xvi, Ac_2O, pyridine; xvii, NaOMe, MeOH (29% three steps); xviii, KOH, MeOH-H_2O (4:1), rt, 12 h (76%)

Bartlett and McQuaid's report[48] on the synthesis of (±)-methyl shikimate **20** (Scheme 15) started with 3-cyclohexene-1-carboxylic acid **78**, the Diels–Alder adduct of butadiene and acrylic acid. Iodolactonisation of **78** with iodine, potassium iodide in aqueous sodium hydrogen carbonate gave **79** which underwent DBU-induced elimination to provide the olefinic lactone **80**.[49] The formation of epoxide **81** (*exo*-isomer) was accomplished with high stereoselectivity (*endo*:*exo* = 1:13.5) using 3,5-dinitroperoxybenzoic acid. Triphenylphosphine-catalysed epoxide opening with trimethylsilyl bromide, followed by DBU-induced elimination, provided the allylic alcohol **82**. Epoxidation of **82** led to the epoxy lactone **83** which was treated with potassium carbonate in methanol to afford the (±)-methyl shikimate **20** (50% overall yield from **78**).



Scheme 15 *Reagents and conditions:* i, I_2, KI, $NaHCO_3$, H_2O, 21 °C, 21 h (94%); ii, DBU, THF, reflux, 16 h (89%); iii, 3,5-dinitroperoxybenzoic acid, 2,6-di-*t*-butyl-4-methylphenol (cat.), CH_2Cl_2, reflux, 11 h (81%); iv, Ph_3P, TMSBr, MeCN, 0 °C to 25 °C, 1 h, then DBU, reflux, 21 h (85%); v, 3,5-dinitroperoxybenzoic acid, 2,6-di-*t*-butyl-4-methylphenol (cat.), CH_2Cl_2, reflux, 9 h, then 25 °C, 10 h (89%); vi, K_2CO_3, MeOH, 30 min (98%)



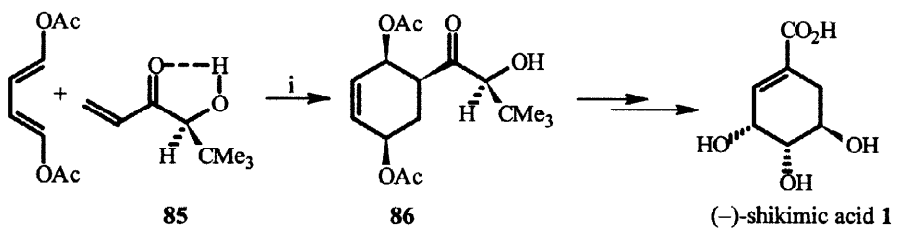
Scheme 16 *Reagents and conditions:* i, NaOAc, AcO_2H, $CHCl_3$, rt, 17 h (80%); ii, DBN, Et_2O, reflux, 25 h (80%); iii, MCPBA, CH_2Cl_2 (65%); iv, AcOH, reflux, 1.25 h; v, NaOMe, MeOH, rt, 1.5 h (47% for two steps)

McGowan and Berchtold's synthesis of (±)-methyl 4-*epi*-shikimate **29**[43] (Scheme 16), an important intermediate for the synthesis of (±)-chorismic acid, is an interesting one, as the synthesis of intermediate **54** also constitutes a formal synthesis of (±)-methyl shikimate **20** (Scheme 10). The diene **16**,[28] prepared from the

esterification of the cycloadduct of butadiene and propiolic acid, was treated with peracetic acid to give epoxide **84** which was isomerised to **54** in the presence of DBN. Epoxidation of **54** with MCPBA afforded **61** and its corresponding *trans*-isomer **62** in a ratio of 19:1. Solvolysis of epoxide **61** in acetic acid and subsequent deacetylation furnished (±)-methyl 4-*epi*-shikimate **29** with an overall yield of 20% from diene **16**.

2.2 Chiral Syntheses

An enantiospecific synthesis of (−)-shikimic acid **1** (Scheme 17), based on the asymmetric Diels–Alder reaction, was first reported by Masamune and co-workers,[50] who used the chiral ketol **85** as a dienophile. The high diastereofacial selectivity of ketol **85** is largely attributed to the strong hydrogen bonding between the hydroxyl and ketonic functions. The formation of a five-membered chelate effectively freezes rotation along the C(=O)-C (asym) axis, thus making the two diastereotopic faces of the enone system highly distinguishable. With the aid of a catalyst ($BF_3{\cdot}Et_2O$), the *endo*-adduct **86** was obtained as an exclusive diastereoisomer from the cycloaddition reaction. The adduct **86** was converted to (−)-shikimic acid **1** *via* a sequence of transformations similar to those used by Raphael[17] and Smissman.[18]

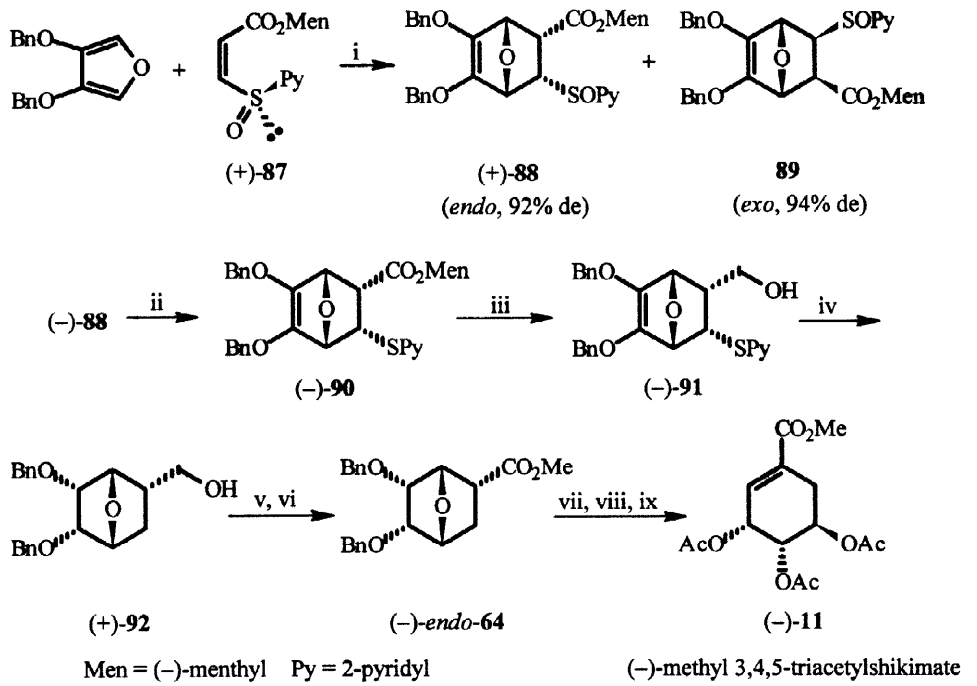


85 **86** (−)-shikimic acid **1**

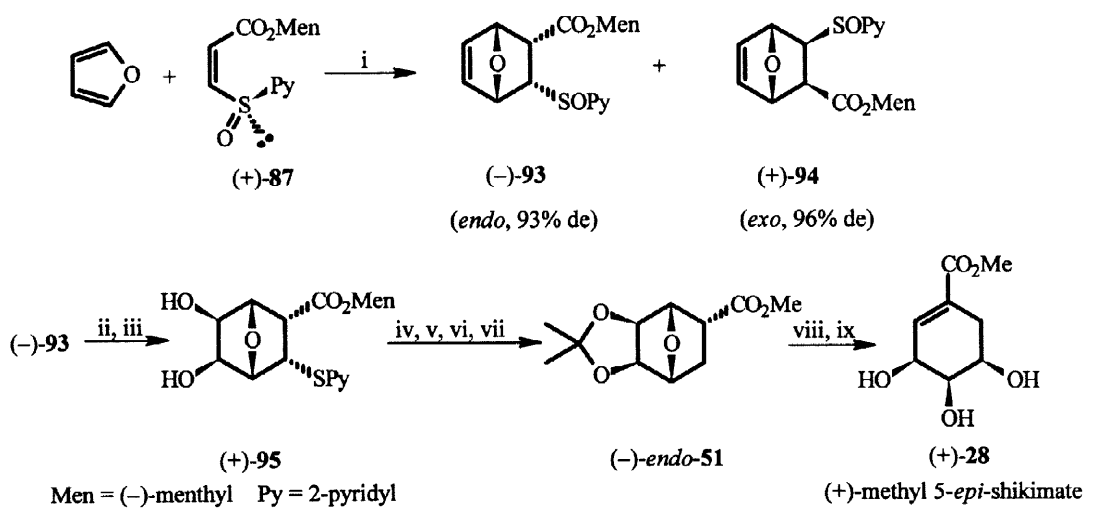
Scheme 17 *Reagents and conditions:* i, $BF_3{\cdot}Et_2O$ (0.5 equiv.), CH_2Cl_2, −40 °C, 12 h (72%, > 98% de)

Another application of an asymmetric Diels–Alder reaction to the enantioselective synthesis of (−)-methyl 3,4,5-*O*-triacetylshikimate **11** (Scheme 18) was reported by Koizumi and co-workers.[51] They employed (+)-**87**,[52] $(S)_s$-menthyl 3-(2-pyridylsulphinyl)acrylate, as a chiral dienophile. The cycloaddition reaction of (+)-**87** and 3,4-dibenzyloxyfuran gave a mixture of four diastereoisomers, the major two of which, *endo*-**88** and *exo*-**89**, were obtained in isolated yields of 50% and 29%, respectively. The *endo*-adduct **88** was reduced with phosphorus tribromide to give the sulphide (−)-**90** which was treated with lithium aluminium hydride to remove the chiral auxilary. Hydrogenation of (−)-**91** led to (+)-**92** which was oxidised with Jones reagent and treated with diazomethane. The resulting ester (−)-*endo*-**64** was transformed to (−)-methyl 3,4,5-*O*-triacetylshikimate **11** in a fashion similar to Koreeda's synthesis.[45] The overall yield of (−)-**11** from (+)-**87** was 3.5%. It should be noted that although Koizumi and co-workers indicated the possibility of transforming *exo*-**89** to the unnatural (+)-shikimic acid **1**, no report on that has been forthcoming.

By the same methodology, Koizumi and co-workers[53] also prepared (+)-methyl 5-*epi*-shikimate **28** in an overall yield of 10.6% from (+)-**87** (Scheme 19). The *endo*-adduct **93**, a major cycloadduct of (+)-**87** and furan, was subjected to a series of transformations analogous to those of previous syntheses and also those by Campbell, Sainsbury and co-workers[37] to afford (+)-methyl 5-*epi*-shikimate **28**.

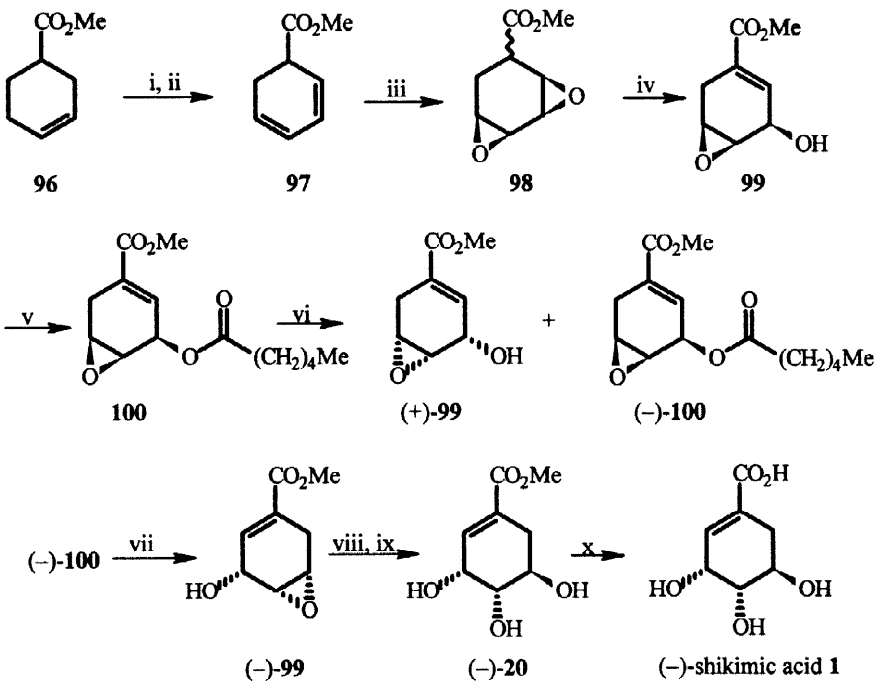


Scheme 18 *Reagents and conditions:* i, Et_2AlCl, CH_2Cl_2, −20 °C, 5 days (50% for *endo*-**88**, and 29% for *exo*-**89**); ii, PBr_3, DMF, 0 °C (84%); iii, $LiAlH_4$, Et_2O, rt (95%); iv, Raney Ni (W-2), EtOH, rt (45%); v, Jones reagent, acetone, rt; vi, CH_2N_2, MeOH, Et_2O (67% for two steps); vii, *n*-BuLi, HMDS, THF, −78 °C (56%); viii, TMSCl, NaI, MeCN, rt; ix, Ac_2O, pyridine, rt (53% for two steps)



Scheme 19 *Reagents and conditions:* i, Et_2AlCl (1.1 equiv.), CH_2Cl_2, rt, 7 days (44% for *endo*-**93**, and 25% for *exo*-**94**); ii, $TiCl_3$, EtOH, rt, 10 min (84%); iii, OsO_4 (cat.), trimethylamine-*N*-oxide, acetone, rt, 12 h; iv, $(MeO)_2CMe_2$, acetone, *p*-TsOH, 65 °C, 6 h (92% for two steps); v, $LiAlH_4$, Et_2O, rt, 2 h (79%); vi, Raney Ni (W-4), EtOH, rt, 24 h (92%); vii, (a) Jones reagent, acetone, rt, 2.5 h; (b) CH_2N_2, MeOH, Et_2O (80% two steps); viii, *n*-BuLi, HMDS, THF, −78 °C, 0.5 h (56%); ix, aq. AcOH, 55 °C, 3 h (96%)

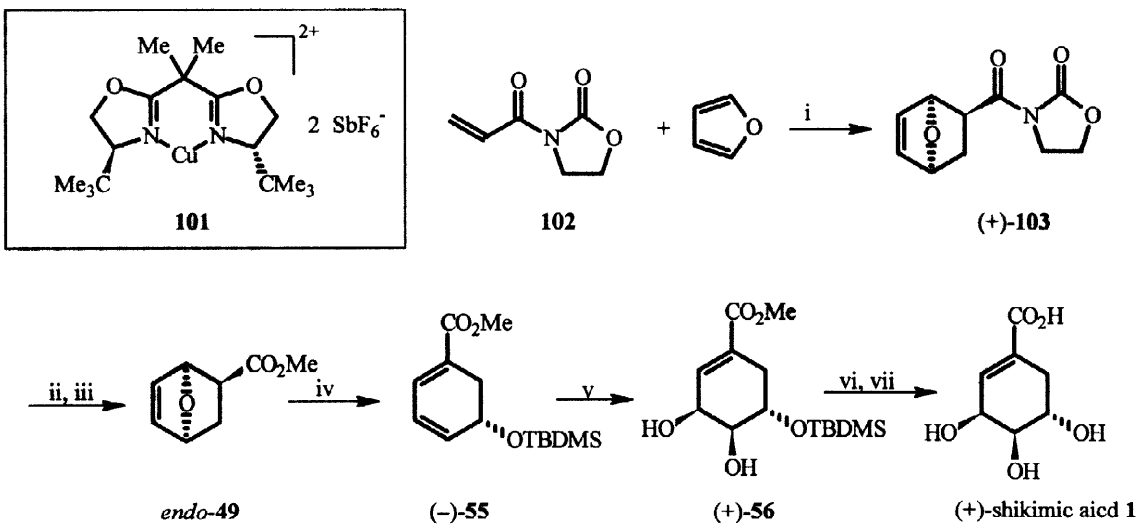
Pawlak and Berchtold[54] have detailed a preparation of (−)-shikimic acid **1** (Scheme 20) from racemic starting material *via* an enzyme-catalysed kinetic resolution that provided enantiomerically pure intermediate. Methyl 3-cyclohexene-1-carboxylate **96**, a Diels–Alder adduct of butadiene and methyl acrylate, was treated with *N*-bromosuccinimide to give a mixture of epimeric dibromides which were then debrominated with either tri-*n*-butyltin hydride in benzene or sodium iodide in acetone to furnish the diene **97**.[55] Rose Bengal-sensitised photo-oxidation of **97** led to the *endo*-peroxide which underwent rearrangement in the presence of $RuCl_2(PPh_3)_3$ to give the epoxide **98**. Base-catalysed isomerisation of **98**, followed by treatment with *n*-hexanoyl chloride, gave the *n*-hexanoate ester **100**. Enantioselective hydrolysis of racemic **100** with cholesterol esterase led to (+)-**99** and unhydrolysed (−)-**100**. The latter was subjected to base-catalysed ester interchange to give (−)-**99**. Epoxide ring opening of (−)-**99** in aqueous acetic acid and subsequent deacetylation afforded (−)-methyl shikimate **20** which was hydrolysed to give (−)-shikimic acid **1** (11.5% overall yield from **96**).



Scheme 20 *Reagents and conditions:* i, *N*-bromosuccinimide, AIBN, CCl_4, reflux, 40 min; ii, Bu_3SnH, AIBN, benzene, reflux, 3 h (75%) or NaI, acetone (57%); iii, (a) O_2, Rose Bengal, acetone, −10 °C, hν, 10 h; (b) $RuCl_2(PPh_3)_3$, CH_2Cl_2, rt; iv, NaOMe, MeOH (34% overall yield form **96**); v, hexanoyl chloride, DMAP, Et_3N, CH_2Cl_2 (100%); vi, cholesterol esterase, H_2O, pH 7.8, 0-5 °C (total 54% conversion); vii, NaOMe, MeOH, 0-5 °C, 1 h (85%) (36% from racemic **100**); viii, aq. AcOH (80%), heat; ix, NaOMe, MeOH (97% for two steps); xi, NaOH, THF, H_2O, then Amberlite IR-120 (plus) ion-exchange resin (97%)

A recent synthesis of unnatural (+)-shikimic acid **1** by Evans and Barnes[56] made use of the chiral bis(4-*t*-butyloxazoline)-$Cu(SbF_6)_2$ complex **101** as a Lewis acid catalyst in the enantioselective Diels–Alder reaction of furan and acrylimide **102** (Scheme 21). This Diels–Alder reaction was performed at -78 °C to give a kinetic

mixture of products with the *endo*:*exo* isomeric ratio as 4:1. The *endo*-isomer was obtained in 97% ee and recrystallisation delivered enantiomerically pure (+)-**103** in 67% yield. The cycloadduct (+)-**103** was converted to enantiomerically pure *endo*-**49** which was further elaborated to (+)-shikimic acid **1** in a fashion almost identical to that of the racemic **49** (a mixture of *endo*- and *exo*-adducts) (Scheme 10). The overall yield for (+)-shikimic acid **1** was 37% from acrylimide **102**.

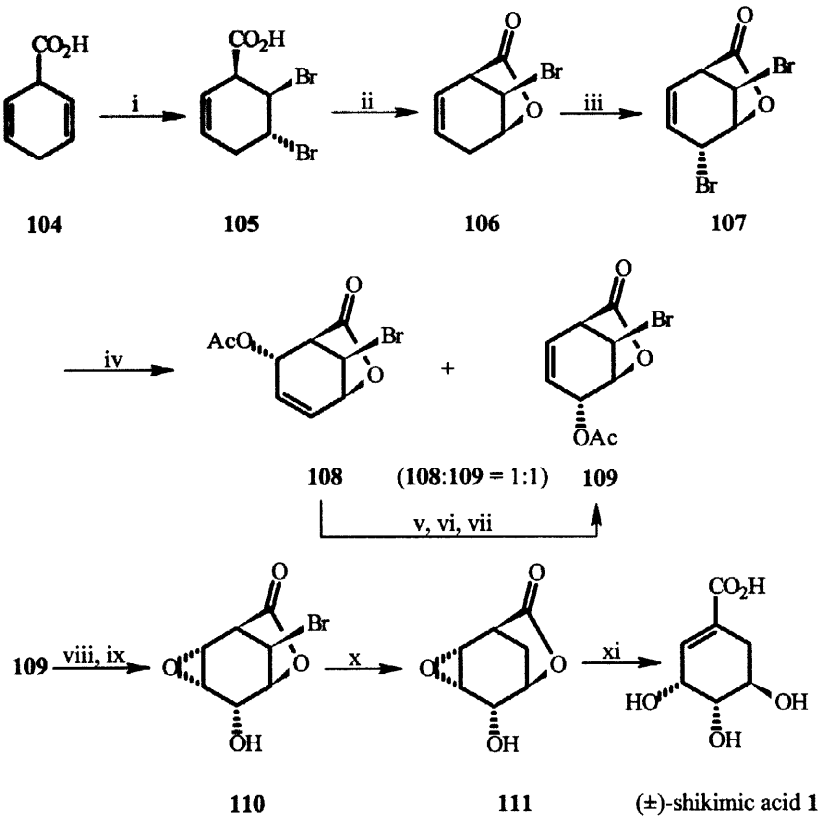


Scheme 21 *Reagents and conditions:* i, **101** (5 mol%), CH_2Cl_2, −78 °C, 42 h (67%); ii, LiSEt, THF, −20 °C; iii, Cs_2CO_3, MeOH, 0 °C (93% for two steps); iv, *n*-BuLi, HMDS, THF, −78 to 0 °C, then TBDMSOTf, 2,6-lutidine, −78 °C (90%); v, OsO_4, *N*-methylmorpholine-*N*-oxide, THF, H_2O, 0 °C (76%); vi, Bu_4NF, THF (97%); vii, TMSOK, THF, then IR-120, H_2O, (90%)

3. SYNTHESES FROM BENZENE AND ITS DERIVATIVES

3.1 Racemic syntheses

Ganem and co-workers[57] described a synthesis of (±)-shikimic acid **1** (Scheme 22) from 1,4-dihydrobenzoic acid **104**[58] prepared from benzoic acid by Birch reduction. Bromination of **104** gave a mixture of dibromo acids from which the major isomer **105** was crystallised. Cyclisation of **105** in aqueous sodium hydrogen carbonate afforded lactone **106** which was treated with *N*-bromosuccinimide to generate stereospecifically the dibromide **107**. Treatment of **107** with sodium acetate in hexamethylphosphoramide gave a 1:1 mixture of allylic acetates **108** and **109** which were readily separated by column chromatography. The former was converted to the latter in three steps (deacetylation, mesylation and substitution with lithium acetate) in 68% overall yield. Acidic hydrolysis of **109** followed by stereospecific epoxidation with trifluoroperoxyacetic acid furnished the epoxide **110** which was reduced with tributyltin hydride to deliver epoxide **111**. Saponification of **111** led to (±)-shikimic acid **1** (overall yield of 9.5% from 1,4-dihydrobenzoic acid **104**, including the recycling of **108** to **109**).[57c] It is worthy to note that debromination of lactones **109** and **110** with tributyltin deuteride to introduce the deuterium label resulted in complete retention of configuration at C-6 of the monodeuterio lactones which were then converted to 6β-deuterioshikimic acid.



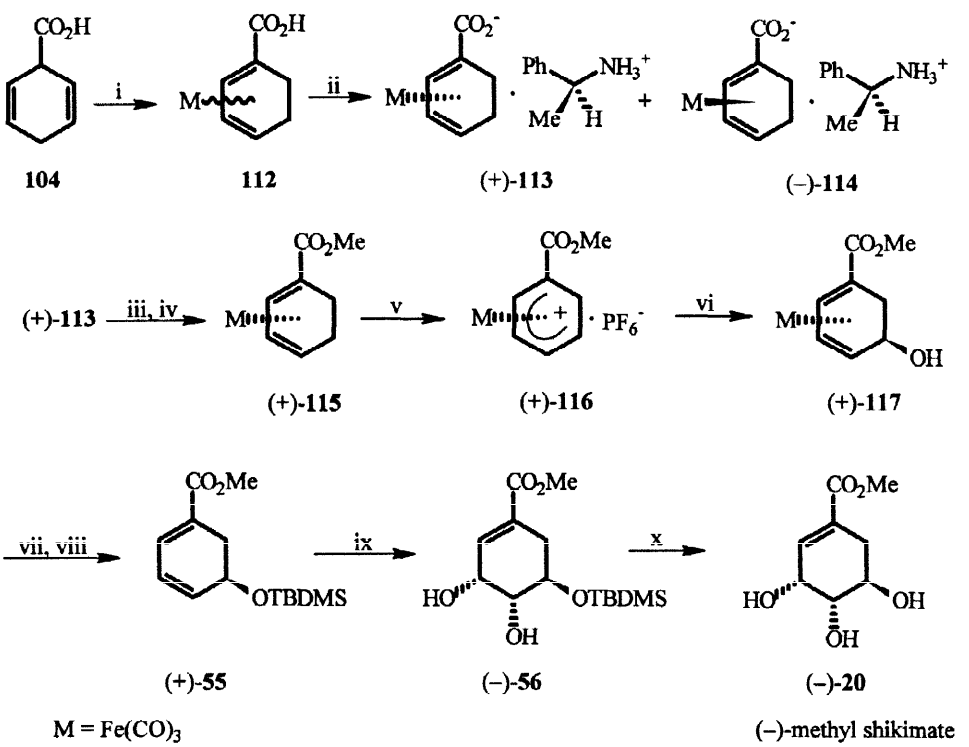
Scheme 22 *Reagents and conditions:* i, Br_2, CH_2Cl_2 (62%); ii, aq. $NaHCO_3$ (65%); iii, *N*-bromosuccinimide, CCl_4, $(PhCO_2)_2$ (70%); iv, NaOAc, HMPA (43% for **108** and 43% for **109**); v, aq. H_2SO_4, THF, reflux (80%); vi, MsCl, pyridine, 0 °C (85%); vii, LiOAc, HMPA (100%); viii, aq. H_2SO_4 (86%); ix, CF_3CO_3H, 1,2-dichloroethane, reflux, 23 h (84%); x, Bu_3SnH, AIBN, toluene, reflux, 2 h (72%); xi, KOH (1.25 equiv.), MeOH-H_2O (4:1), 24 h (90%)

3.2 Chiral syntheses

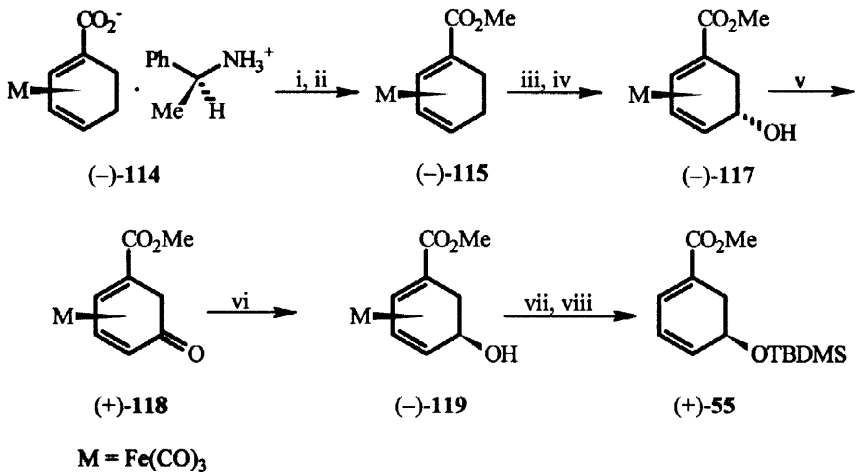
An elegant synthesis of (−)-methyl shikimate **20** by Birch and co-workers[59] utilised tricarbonyliron as a lateral control group for installing enantiospecifically the 5-OH group in the shikimate ring (Schemes 23 and 24). They complexed iron pentacarbonyl with a non-chiral, unsymmetrical olefin to produce chirality in the resulting complex in which the tricarbonyliron group exercised lateral control on the formation of new asymmetric centres. The 1,4-dihydrobenzoic acid **104** was converted to its methyl ester which then reacted with iron pentacarbonyl to form a mixture of tricarbonyl(2-methoxycarbonylcyclohexa-1,3-diene)iron and tricarbonyl(5-methoxycarbonylcyclohexa-1,3-diene)iron. These two isomeric complexes underwent isomerisation in methanol containing sulphuric acid to afford the tricarbonyl(1-methoxycarbonylcyclohexa-1,3-diene)iron which was hydrolysed in aqueous sulphuric acid to give the racemic complex **112**. Resolution of **112** by conventional method with (−)-1-phenylethylamine gave (+)-**113** and (−)-**114**.[60] The phenylethylammonium salt (+)-**113** was reconverted to the carboxylic acid by treatment with aqueous hydrochloric acid in ethanol, and subsequent methylation afforded the ester (+)-**115**. Hydride abstraction by the triphenylmethyl cation on (+)-**115** proceeded from the face opposite the iron at C-5 (5-*exo*) to deliver the cation salt (+)-**116**. Reaction of (+)-**116** with aqueous sodium hydrogen carbonate in acetonitrile at the 5-*exo*

position led to the alcohol complex (+)-**117**. Silylation of (+)-**117** followed by decomplexation with trimethylamine *N*-oxide yielded the silyl ether (+)-**55**, whose racemic form was the precursor in the synthesis of (±)-methyl shikimate **20** by Campbell, Sainsbury and co-workers,[37] and enantiomer the precursor in the synthesis of (+)-shikimic acid **1** by Evans and Barnes.[56]

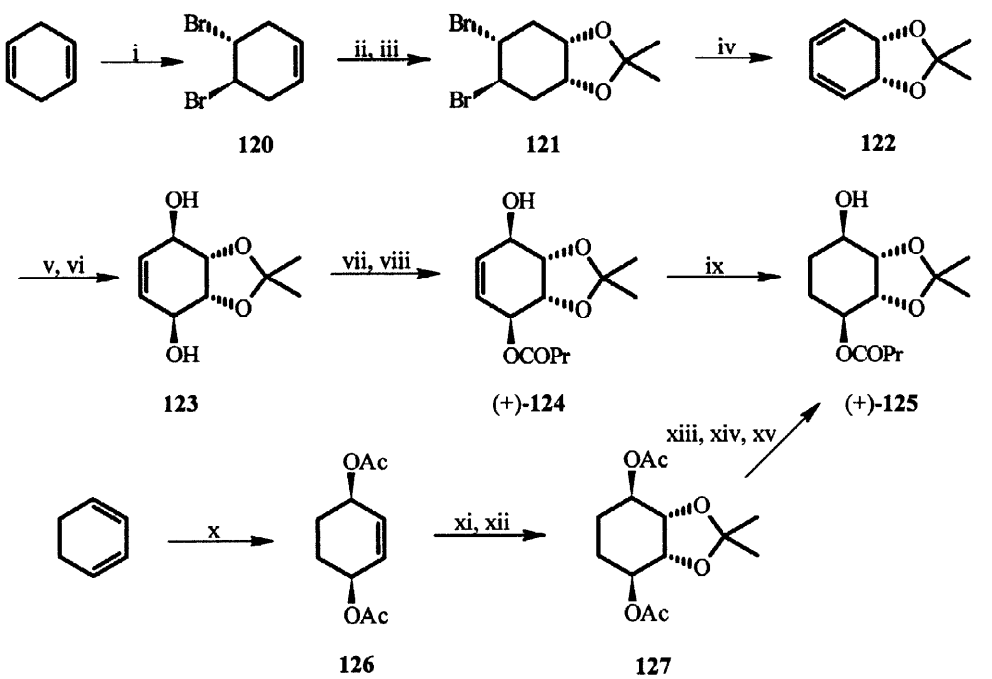
The phenylethylammonium salt (−)-**114** could be converted not only to (+)-methyl shikimate **20** by a set of reactions identical to those of (+)-**113**, but also to (−)-methyl shikimate **20** *via* inversion of the stereochemistry at C-5 of (−)-**117** (Scheme 24). Collins oxidation of (−)-**117** gave the ketone (+)-**118** in which the molecular asymmetry due to complexation was still retained. Stereospecific reduction of the carbonyl group in (+)-**118** was accomplished with sodium borohydride-zinc chloride to afford, after silylation with *t*-butyldimethylsilyl trifluoromethanesulphonate and removal of the tricarbonyliron group with trimethylamine *N*-oxide, the silyl ether (+)-**55** which was further manipulated to (−)-methyl shikimate **20** (*vide supra*). It is worth noting that treatment of tricarbonyl(2-methoxycarbonylcyclohexa-1,3-diene)iron and tricarbonyl(5-methoxycarbonylcyclohexa-1,3-diene)iron with $^2H_2SO_4$-Me^{2}H gave the 6-*endo*-monodeuterio complex which on resolution and further transformations led to (6R)- and (6S)-methyl 6-deuterioshikimates, respectively.



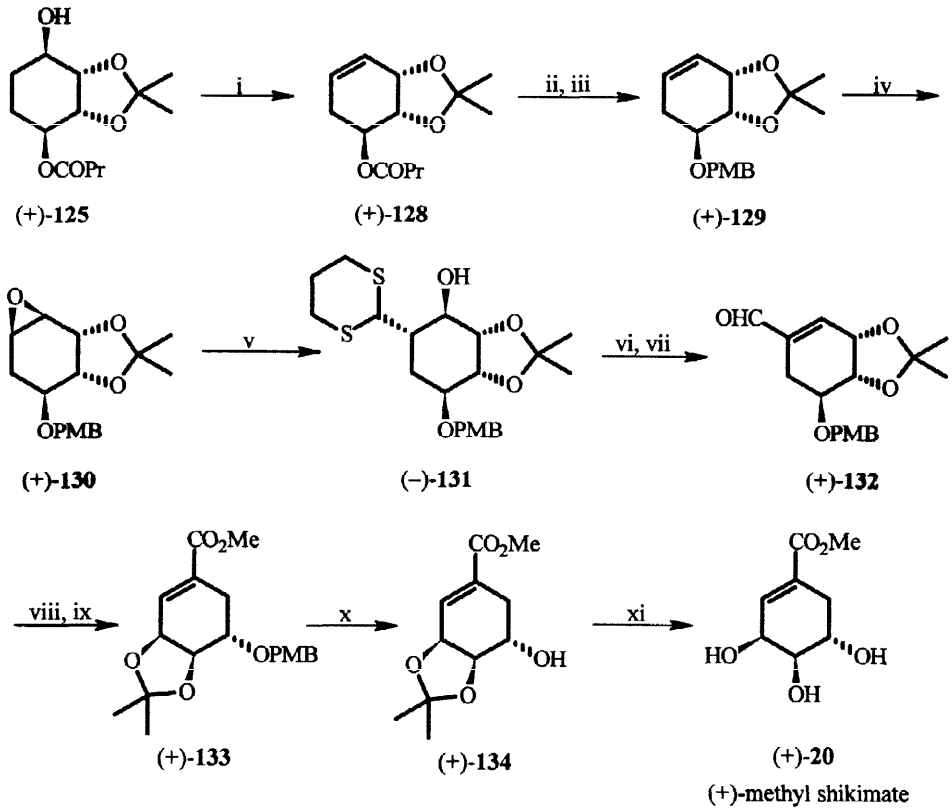
Scheme 23 *Reagents and conditions:* i, (a) $(CH_3O)_2SO_2$, MeOH, KOH, reflux, 5 h; (b) $Fe(CO)_5$, di-*n*-butyl ether, reflux; (c) conc. H_2SO_4, MeOH, reflux, 24 h, then H_2O, reflux 30 h; ii, (−)-1-phenylethylamine, $CHCl_3$-acetone (3:1), then repeated recrystallisation from $CHCl_3$; iii, aq. HCl, EtOH (100%); iv, CH_2N_2, Et_2O (100%); v, trityl hexafluorophosphate, hexane, CH_2Cl_2, 3 h (73%); vi, $NaHCO_3$, H_2O, MeCN, 30 min (95%); vii, TBDMSCl, (*i*-Pr)$_2$NEt, DMF (98%); viii, Me_3NO, benzene (84%); ix, OsO_4, acetone (67%); x, Bu_4NF, THF (85%)



Scheme 24 *Reagents and conditions:* i, aq. HCl, EtOH (100%); ii, CH_2N_2, Et_2O (100%); iii, trityl hexafluorophosphate, hexane, CH_2Cl_2, 3 h; iv, $NaHCO_3$, H_2O, MeCN; v, CrO_3, pyridine, CH_2Cl_2 (85%); vi, $NaBH_4$, $ZnCl_2$, Et_2O (98%); vii, TBDMSOTf, $(i\text{-Pr})_2NEt$, DMF (83%); viii, Me_3NO, benzene (82%)



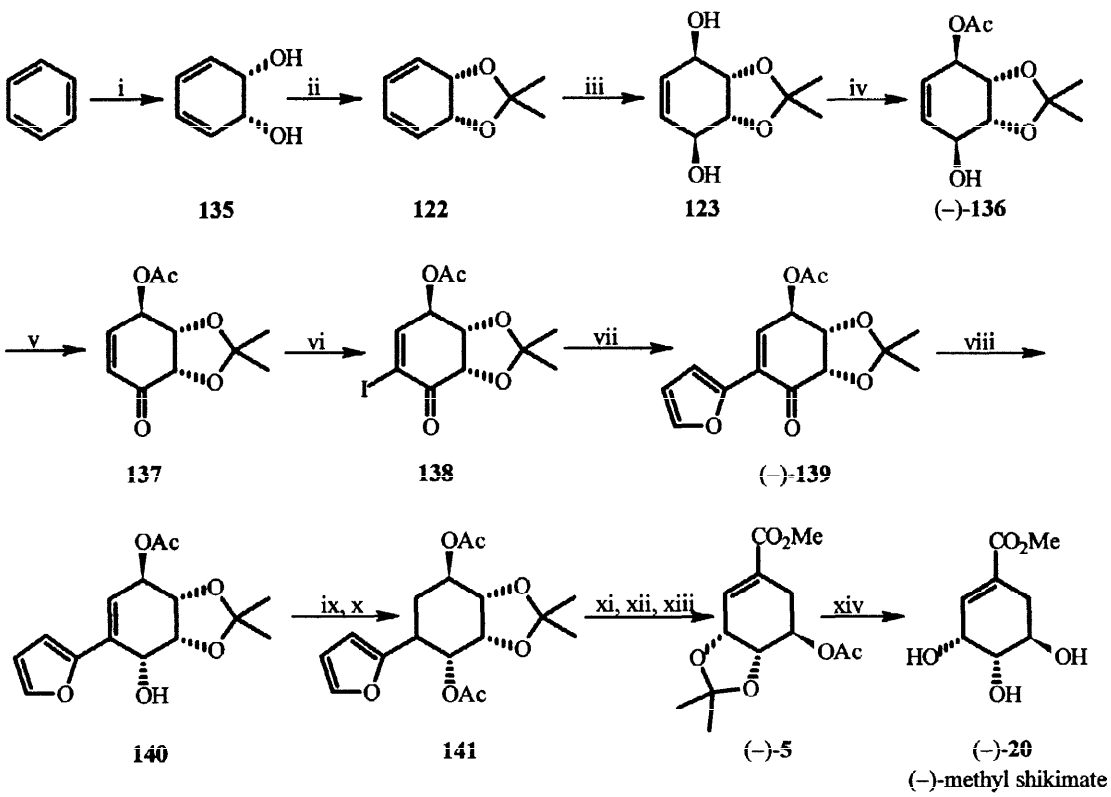
Scheme 25 *Reagents and conditions:* i, Br_2, $CHCl_3$, −78 °C (90%); ii, $KMnO_4$, $MgSO_4$, EtOH, H_2O, −20 °C (45%); iii, $Me_2C(OMe)_2$, H_2SO_4 (cat.), CH_2Cl_2, rt; iv, DBU, benzene, reflux, 6 h; v, O_2, tetraphenylporphine, CCl_4, rt, hv (95%); vi, thiourea, MeOH, rt (80%); vii, *n*-PrCOCl, Et_3N, DMAP, CH_2Cl_2, rt, 4 h (100%); viii, PGL, pH 7, 35 °C, NaOH (83%); ix, Rh/Al_2O_3 (5%), H_2 (1 atm), EtOAc (95%); x, $Pd(OAc)_2$ (5 mol%), LiCl (cat.), LiOAc, *p*-benzoquinone, MnO_2, AcOH, pentane, 22 h (79%); xi, OsO_4, $KClO_3$, THF, H_2O, rt, 18 h (78%); xii, acetone, *p*-TsOH, rt, 5 h (85%)



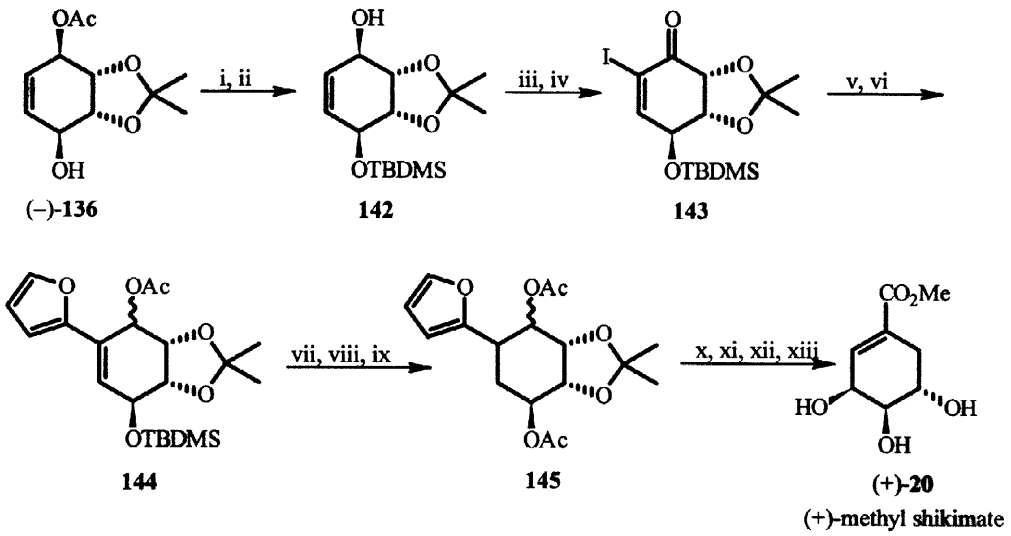
Scheme 26 *Reagents and conditions:* i, DEAD, Ph_3P, THF, reflux, 16 h (89%); ii, K_2CO_3, MeOH, rt, 3 h (85%); iii, *p*-(MeO)$PhCH_2Br$, *t*-BuOK, THF, rt, 5 h (84%); iv, MCPBA, CH_2Cl_2, THF, rt, 48 h (74%); v, 1,3-dithiane, *n*-BuLi, HMPA, THF, −20 °C (97%); vi, HgO, $BF_3{\cdot}Et_2O$, THF-H_2O (5:1), 40 °C, 21 h; vii, MsCl, Et_3N, CH_2Cl_2, rt, 1 h (39% two steps); viii, $NaClO_2$, 2-methyl-2-butene, aq. NaH_2PO_4 (pH 3), *t*-BuOH, rt, 16 h; ix, CH_2N_2, Et_2O, 0 °C (90% two steps); x, DDQ, CH_2Cl_2, H_2O, rt, 2 h (92%); xi, *p*-TsOH, MeOH, 50 °C, 3 h (84%)

Vandewalle and co-workers[61] obtained the unnatural (+)-methyl shikimate **20** (Schemes 25 and 26) by means of an enzymatic asymmetrisation to convert a *meso*-substrate into an enantiopure intermediate which was then subjected to further elaboration. The advantage of this enzymatic transformation is that all the starting material can be utilised, while in the case of conventional resolution or enzyme-catalysed kinetic resolution of a racemate only half of the starting material will be suitable for further conversion. The *meso*-diene **122**,[62] prepared from 1,4-cyclohexadiene, the product of Birch reduction of benzene, *via* bromination, dihydroxylation, isopropylidenation and base-catalysed elimination, was photo-oxidised to give the *endo*-peroxide which was reduced with thiourea. The resulting *meso*-**123**[63] was converted to its dibutyrate which was hydrolysed by PGL, a recombinant *Fusarium solani pisi* cutinase, to afford the enantiomerically pure (+)-**124**, the hydrogenation of which then gave (+)-**125**.[64] Alternatively, the alcohol (+)-**125** could be prepared from 1,3-cyclohexadiene. The palladium-catalysed 1,4-diacetoxylation of 1,3-cyclohexadiene produced exclusively the *cis*-diacetate **126**,[65] which, after dihydroxylation and isopropylidenation, gave the *meso*-acetonide **127**. Conversion of **127** to its dibutyrate, followed by PGL-catalysed hydrolysis, afforded the enantiomerically pure (+)-**125**. Elimination of the hydroxy unit in (+)-**125** occured under Mitsunobu[39]

conditions. The resulting olefin (+)-**128** was converted to its *p*-methoxybenzyl ether (+)-**129**, which was oxidised with MCPBA to give exclusively the epoxide (+)-**130**. Reaction of (+)-**130** with lithiodithiane introduced the required one-carbon unit to give (−)-**131**. Unmasking of the carbonyl fuction in (−)-**131** was accomplished using mercuric oxide and boron trifluoride in water and THF to give, after further mesylation and simultaneous elimination, the α,β-unsaturated aldehyde (+)-**132**. Oxidation of (+)-**132** with sodium chlorite, followed by esterification, delivered the shikimate derivative (+)-**133**, which was further deprotected to give (+)-methyl shikimate **20**. It is worth pointing out that the enantiomerically pure product of the enzyme-catalysed hydrolysis of *meso*-dibutyrate can be converted *via* judicious functional group interconversions to the derivatives of its enantiomer, which, in turn, can be elaborated to (−)-methyl shikimate **20**. However, the lengthy manipulation from either 1,4-cyclohexadiene or 1,3-cyclohexadiene highlights the major drawback of an otherwise elegant synthesis. The overall yield of (+)-methyl shikimate **12** was 12% from the intermediate (+)-**125**, and between 3% and 4% from either 1,4-cyclohexadiene or 1,3-cyclohexadiene.



Scheme 27 *Reagents and conditions:* i, *Pseudomonas putida* 39D; ii, $(MeO)_2CMe_2$, CH_2Cl_2, *p*-TsOH (82%); iii, O_2, tetraphenylporphine, CH_2Cl_2, MeOH, 0 °C, hν, 4-6 h, then thiourea, 12 h (65%); iv, *Pseudomonas cepacia* (Amano P-30) lipase, isopropenyl acetate, 55 °C, 2 days (90%); v, PCC, CH_2Cl_2, molecular sieves; vi, I_2, pyridine, CCl_4 (80%); vii, 2-tributylstannylfuran, $Pd(PhCN)_2Cl_2$, CuI, Ph_3As, *N*-methylpyrrolidone (100%); viii, $NaBH_4$, $CeCl_3$, MeOH, −78 °C (75%); ix, H_2 (1 atm), Pd/C, EtOH (83%); x, Ac_2O, DMAP, Et_3N, CH_2Cl_2 (88%); xi, RuO_2, $NaIO_4$, CCl_4, H_2O, MeCN; xii, CH_2N_2, Et_2O; xiii, DBU, CH_2Cl_2, 20 °C, 12 h (69% for three steps); xiv, *p*-TsOH, MeOH, reflux (89%)

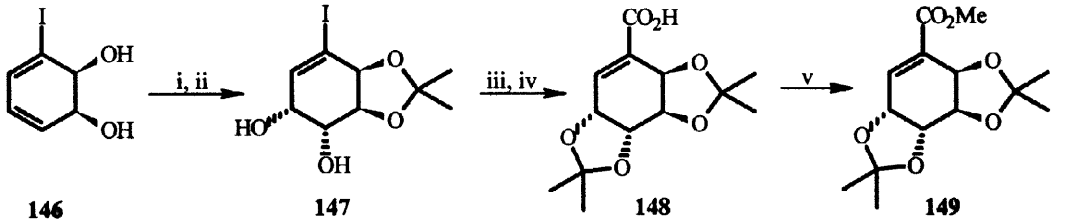


Scheme 28 *Reagents and conditions:* i, TBDMSCl, imidazole, DMF; ii, K_2CO_3, MeOH; iii, PCC, CH_2Cl_2, molecular sieves; iv, I_2, pyridine, CCl_4; v, 2-tributylstannylfuran, $Pd(PhCN)_2Cl_2$, CuI, Ph_3As, *N*-methylpyrrolidone (93%); vi, $NaBH_4$, $CeCl_3$, MeOH, –78 °C (75%); vii, Bu_4NF, THF, 25 °C, 24 h; viii, Ac_2O, DMAP, Et_3N, CH_2Cl_2 (85% for two steps); ix, H_2 (1 atm), Pd/C, EtOH (97%); x, RuO_2, $NaIO_4$, CCl_4, H_2O, MeCN; xi, CH_2N_2, Et_2O; xii, DBU, CH_2Cl_2, 20 °C (88% for three steps); xiii, *p*-TsOH, MeOH, reflux

Johnson and co-workers[66] made use of the *meso*-cyclohexa-3,5-diene-1,2-diol **135**,[67,68] available from microbial oxidation of benzene by mutants of the microorganism *Pseudomonas putida*, in their synthesis of (+)- and (–)-methyl shikimate **20** (Schemes 27 and 28). Apart from this, their approach was analogous to that of Vandewalle and co-workers in that they both used enzymetic asymmetrisation to convert a similar *meso*-intermediate into an enantiomerically pure form. Isopropylidenation of the diol **135** gave the acetonide **122**,[62] which was also prepared alternatively from 1,4-cyclohexadiene with an improved overall yield of 87%. The acetonide **122** was converted to *meso*-**123**[63] by addition of singlet oxygen followed by reduction with thiourea. Lipase-mediated acetylation of *meso*-**123** in isopropenyl acetate delivered the enantiopure monoacetate (–)-**136**, which was oxidised with PCC. Conversion of the enone **137** to the vinyl iodide **138**, followed by coupling with 2-tributylstannylfuran, gave the enone (–)-**139**. Reduction of (–)-**139** under Luche conditions afforded the allylic alcohol **140** and its corresponding epimer in a ratio of 6:1. Hydrogenation of **140** produced a single diastereoisomer whose relative stereochemistry was not assigned. Further acetylation gave the diacetate **141**. Oxidation of the furan ring in **141** to carboxylic acid, followed by esterification, base-induced elimination and deprotection, yielded the (–)-methyl shikimate **20**. The overall yield from *meso*-**135** was approximately 12%. By interconverting the functional groups, enantiomerically pure (–)-**136** was also elaborated in a similar manner to the unnatural (+)-methyl shikimate **20** (Scheme 28).

The chiral microbial metabolite, 1-iodo-1,3-cyclohexadiene-5,6-diol **146**,[69] obtained by whole cell fermentation of iodobenzene with *Pseudamonas Putida* 39D, has been used by Entwistle and Hudlicky[70] for the synthesis of optically active pseudosugars.[26] Enantiomerically pure **148** and **149**, derivatives of 6β-hydroxyshikimic acid, were produced as key intermediates (Scheme 29). The diol **146** was converted to the acetonide which was then dihydroxylated stereoselectively to give the diol **147**. Isopropylidenation of **147**

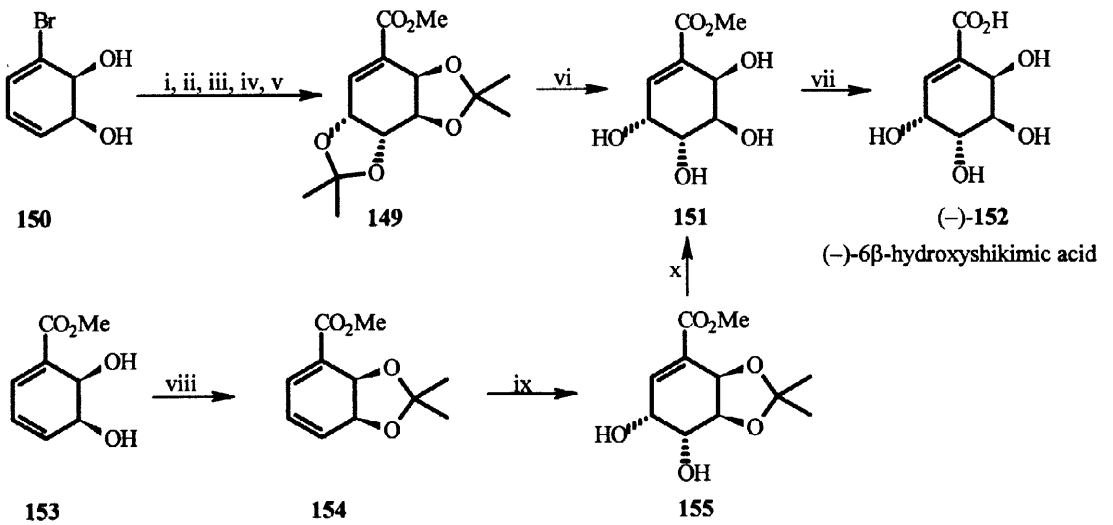
gave the diacetonide which was treated with *t*-butyllithium and subsequently quenched with carbon dioxide. Esterification of the resulting acid **148** with potassium carbonate and methyl iodide furnished the ester **149** in an overall yield of 67% from diol **146**.



146 **147** **148** **149**

Scheme 29 *Reagents and conditions:* i, $Me_2C(OMe)_2$, *p*-TsOH; ii, OsO_4, *N*-methylmorpholine-*N*-oxide, *t*-BuOH, H_2O; iii, $Me_2C(OMe)_2$, *p*-TsOH (75% for three steps); iv, *t*-BuLi, Et_2O, −78 °C, then CO_2; v, MeI, K_2CO_3, acetone (90% for two steps)

Shortly after that publication, Sutherland and co-workers[71] disclosed a similar synthesis of (−)-6β-hydroxyshikimic acid **152** and its derivatives from similar microbial metabolites (Schemes 30 and 31).



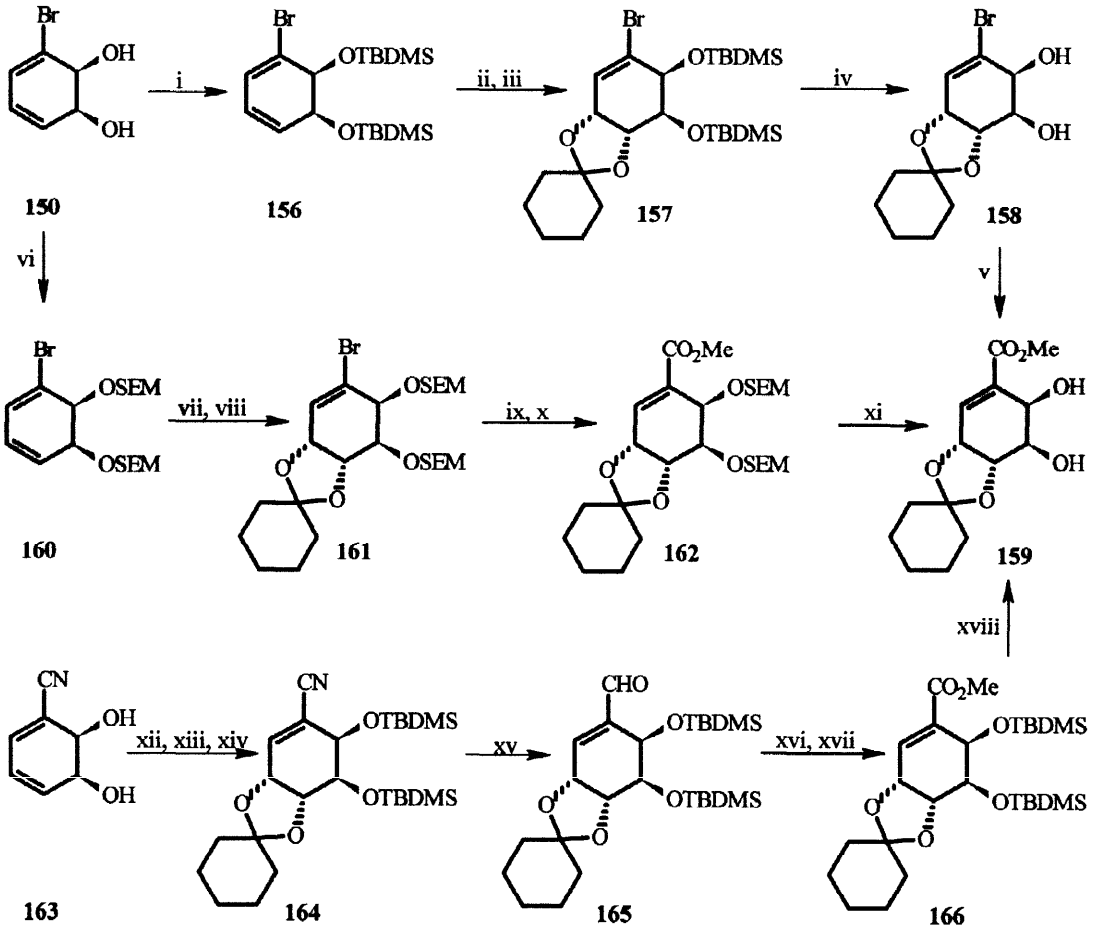
150 **149** **151** **(−)-152**

153 **154** **155**

Scheme 30 *Reagents and conditions:* i, $Me_2C(OMe)_2$, *p*-TsOH, acetone; ii, OsO_4, *N*-methylmorpholine-*N*-oxide, *t*-BuOH, H_2O; iii, $Me_2C(OMe)_2$, *p*-TsOH, CH_2Cl_2, 1 h (95%); iv, *t*-BuLi, Et_2O, −109 °C, 15 min, then CO_2; v, MeI, CsF, DMF, 16 h (80%); vi, aq. TFA, THF (90%); vii, aq. HCl, 60 °C, 4 h (60%); viii, $Me_2C(OMe)_2$, CSA, CH_2Cl_2, 1 h (48%); ix, OsO_4, *N*-methylmorpholine-*N*-oxide, *t*-BuOH, H_2O (27%); x, aq. TFA, THF

One of their reported routes to (−)-6β-hydroxyshikimic acid **152** was almost identical to that of Entwistle and Hudlicky, although they used bromo dienediol **150** instead of the iodo dienediol **146** as the starting material and added extra steps to remove the protecting groups in **149** to give the free acid (−)-**152**. They also prepared (5*S*, 6*S*)-methyl 5,6-dihydroxycyclohexa-1,3-diene-1-carboxylate **153** by microbial oxidation of methyl benzoate with an aqueous culture of *Pseudomonas putida* UV4, and confirmed its

absolute stereochemistry by its conversion into methyl 6β-hydroxyshkimate **151**. However, the dihydroxylation of acetonide **154** using the Upjohn procedure[34] gave low yield of **155** with poor regioselectivity.

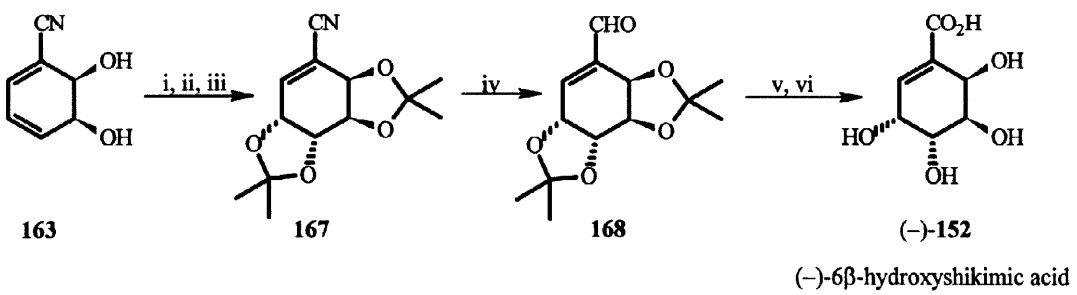


Scheme 31 *Reagents and conditions:* i, TBDMSOTf, imidazole, DMF, 2 h (90%); ii, OsO_4, *N*-methylmorpholine-*N*-oxide, *t*-BuOH, H_2O (66%); iii, 1,1-diethoxycyclohexane, CSA, CH_2Cl_2, 3 h (90%); iv, Bu_4NF, CH_2Cl_2, 3.5 h (75%); v, $Ni(CO)_2(Ph_3P)_2$, Et_3N, MeOH, THF, 60 °C, in sealed tube (70%); vi, SEMCl, *i*-Pr_2NEt, DMAP, CH_2Cl_2 (48%); vii, OsO_4, *N*-methylmorpholine-*N*-oxide, *t*-BuOH, H_2O (67%); viii, 1,1-diethoxycyclohexane, CSA, CH_2Cl_2, 10 min (72%); ix, *t*-BuLi, hexane, −78 °C, 25 min, then CO_2; x, MeI, CsF, DMF (78%); xi, $MgBr_2$, BuSH (in excess), Et_2O, 1.5 h (75%); xii, TBDMSOTf, imidazole, DMF, 3 h (85%); xiii, OsO_4, *N*-methylmorpholine-*N*-oxide, *t*-BuOH, H_2O (85%); xiv, 1,1-diethoxycyclohexane, CSA, CH_2Cl_2, 3 h (90%); xv, DIBAL-H, hexane, −78 °C (70%); xvi, $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O; xvii, MeI, K_2CO_3, acetone, 2 h (80% for two steps); xviii, pyridine-HF, THF (90%)

These authors were interested in further transformation of the protected 6β-hydroxyshikimic acid to 6-fluoroshikimic acid, which required the differentiation of the diol systems and also that of the 5- and 6-hydroxy groups during the synthesis of **159**. For that, they used *t*-butyldimethylsilyl and 2-(trimethylsilyl)ethoxymethyl groups for the protection of diol **150**, and the cyclohexylidene group for the

protection of the diol after dihydroxylation. With the bulky *t*-butyldimethylsilyl group in **157**, no halogen lithium exchange occurred when it was treated with *t*-butyllithium. However, methoxycarbonylation of **158** was effected with $Ni(CO)_2(Ph_3P)_2$-Et_3N-MeOH to give **159**. Selective silylation of **159** at the 5-position was accomplished using excess of *t*-butyldimethylsilyl chloride. The authors also converted (5*S*, 6*S*)-5,6-dihydroxycyclohexa-1,3-diene-1-carbonitrile **163** obtained by the oxidation of benzonitrile with *Pseudomonas putida* UV4 to **159**. As the nitrile **164** could not be converted to a carboxylic acid by base-cataysed hydrolysis, it was reduced with DIBAL-H to the α,β-unsaturated aldehyde **165** which was then oxidised with sodium chlorite to give, after esterification, the methyl ester **166**.

Two independent syntheses of (−)-6β-hydroxyshikimic acid **152** from (5*S*, 6*S*)-5,6-dihydroxycyclohexa-1,3-diene-1-carbonitrile **163** were reported simultaneously by the groups of Carless[72] and Crout,[73] both used an identical route and obtained the same overall yield of 18% (Scheme 32). Isopropylidenation of **163** followed by catalytic osmylation gave the diol which was converted to the diacetonide **167**. Reduction of **167** with DIBAL-H afforded the unsaturated aldehyde **168**, oxidation of which with sodium chlorite gave the corresponding carboxylic acid. Deprotection then afforded the (−)-6β-hydroxyshikimic acid **152**. It is interesting to note that Sutherland and co-workers[71] had previously prepared the diacetonide **167** from the nitrile **163** and because of the difficulties in the base-catalysed hydrolysis of **167** they did not proceed with further elaboration.



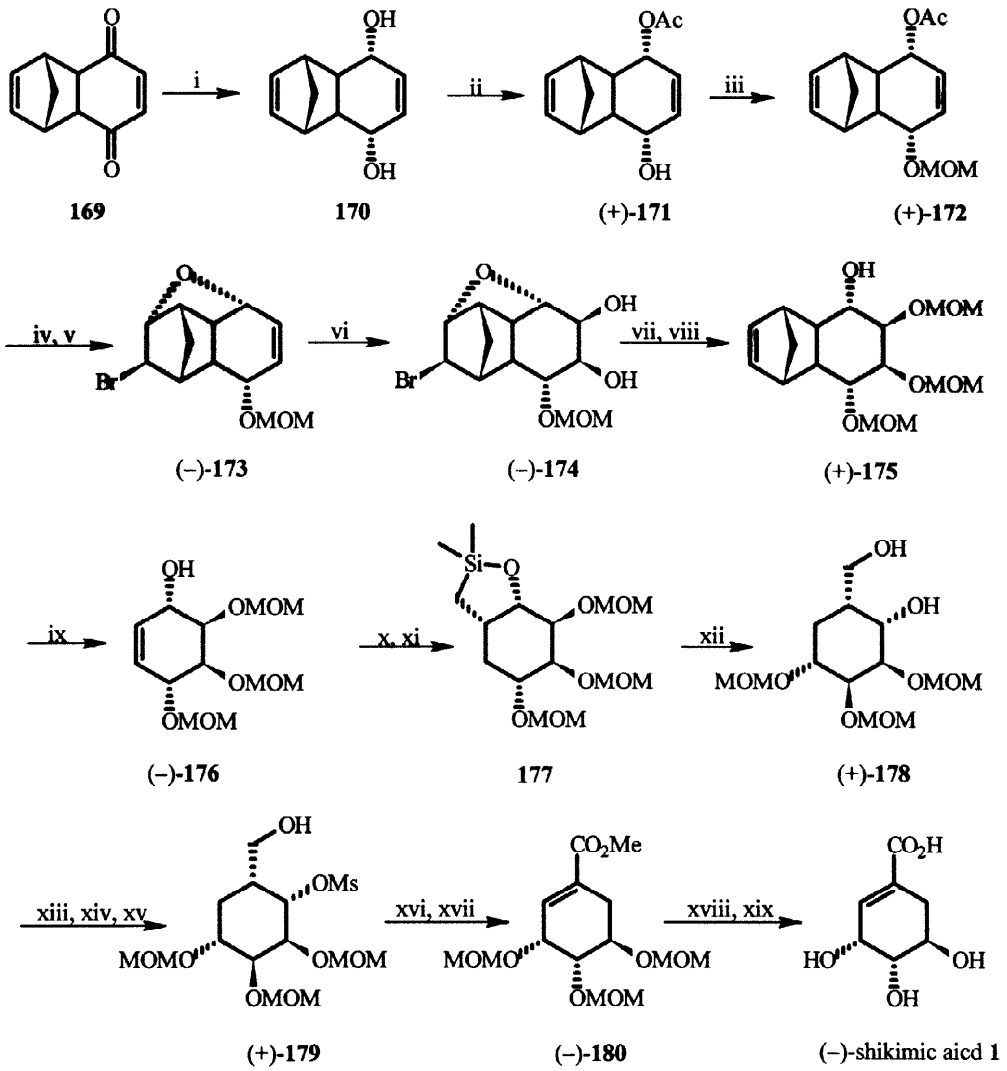
163 **167** **168** **(−)-152**

(−)-6β-hydroxyshikimic acid

Scheme 32 *Reagents and conditions:* i, $Me_2C(OMe)_2$, *p*-TsOH, DMF, 20 h (94%); ii, OsO_4, *N*-methylmorpholine-*N*-oxide, *t*-BuOH, H_2O (72%); iii, $Me_2C(OMe)_2$, *p*-TsOH, DMF, 20 h (94%); iv, DIBAL-H, THF, 0 °C (38.7%); v, $NaClO_2$, NaH_2PO_4, H_2O_2, MeCN, H_2O (72%); vi, aq. HCl, THF, 3 days (100%)

Kamikubo and Ogasawara[74] recently completed a synthesis of (−)-shikimic acid **1** (Scheme 33) *via* the chiral synthon (+)-**171**.[75] The cycloadduct **169**[76] of cyclopentadiene and *p*-benzoquinone was reduced with either DIBAL-H or sodium borohydride-ceric chloride to give the *meso*-diol **170**.[77] Lipase-mediated asymmetric esterification of **170** provided the optically pure monoacetate (+)-**171** which was methoxymethylated to give (+)-**172**. Deacetylation of (+)-**172**, followed by treatment with *N*-bromosuccinimide, afforded the bromo ether (−)-**173**. Dihydroxylation of (−)-**173** gave the diol (−)-**174** which, after methoxymethylation, was treated with activated zinc in the presence of a catalytic amount of acetic acid to regenerate the olefinic functionality. Subsequent retro Diels–Alder reaction of (+)-**175** gave the allylic alcohol (−)-**176**. Treatment of (−)-**176** with bromomethyldimethylsilyl chloride, followed by reaction with tributyltin hydride in the presence of AIBN, furnished the cyclic silyl ether **177**, which was subsequently oxidised to the diol (+)-**178**. Selective silylation, followed by mesylation and desilylation, afforded (+)-**179**.

Oxidation of (+)-**179** occurred with concomitant elimination to give α,β-unsaturated aldehyde which was further oxidised to afford, after esterification, (−)-methyl 3,4,5-*O*-tri(methoxymethyl)shikimate **180**. Further deprotection then delivered (−)-shikimic acid **1** in 11% overall yield from cycloadduct **169**.



169 **170** (+)-**171** (+)-**172**

(−)-**173** (−)-**174** (+)-**175**

(−)-**176** **177** (+)-**178**

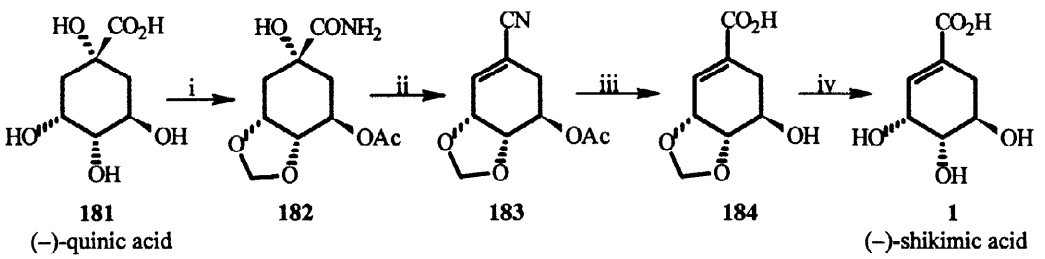
(+)-**179** (−)-**180** (−)-shikimic aicd **1**

Scheme 33 *Reagents and conditions:* i, $NaBH_4$, $CeCl_3$, MeOH, 0 °C (82%) or DIBAL-H, benzene (92%); ii, lipase PS, MeCN, 30 °C, 2 weeks (87%); iii, CH_3OCH_2Cl, *i*-Pr_2NEt, CH_2Cl_2 (88%); iv, K_2CO_3, MeOH, rt; v, *N*-bromosuccinimide, CH_2Cl_2 (76% for two steps); vi, OsO_4, *N*-methylmorpholine-*N*-oxide, THF, H_2O (85%); vii, CH_3OCH_2Cl, *i*-Pr_2NEt, CH_2Cl_2 (97%); viii, Zn, AcOH (cat.), EtOH, reflux (79%); ix, diphenyl ether, $NaHCO_3$, 30 min (86%); x, $ClSi(Me)_2CH_2Br$, Et_3N, DMAP, CH_2Cl_2, 0 °C; xi, Bu_3SnH, AIBN, benzene, 80 °C; xii, aq. H_2O_2 (30%), $KHCO_3$, THF-MeOH (1:1), reflux (89% for two steps); xiii, TBDMSCl, imidazole, DMF (100%); xiv, MsCl, *i*-Pr_2NEt, DMAP, CH_2Cl_2; xv, Bu_4NF, THF (65% for two steps); xvi, SO_3·pyridine, DMSO, Et_3N; xvii, (a) $NaClO_2$, $NaH_2PO_4·H_2O$, 2-methyl-2-butene, *t*-BuOH-H_2O (4:1); (b) CH_2N_2, CH_2Cl_2, (77% overall from **178**); xviii, AcCl (cat.), MeOH (98%); xix, NaOH, THF, H_2O (96%)

4. CHIRAL SYNTHESES FROM (–)-QUINIC ACID

Another chiral approach to the synthesis of shikimic acid and its analogues is based on the utilisation of (–)-quinic acid **181** as starting material. (–)-Quinic acid **181** as a natural product was first isolated from cinchona bark. It is widely found, often alongside (–)-shikimic acid **1**, in the plant kingdom. Although (–)-quinic acid **181** is not an intermediate on the main stem of shikimate pathway, its structural resemblance to shikimic acid has stimulated much interest in their chemical interconversions. A lot of early studies of the chemistry of (–)-quinic acid **181** and (–)-shikimic acid **1** were actually intertwined

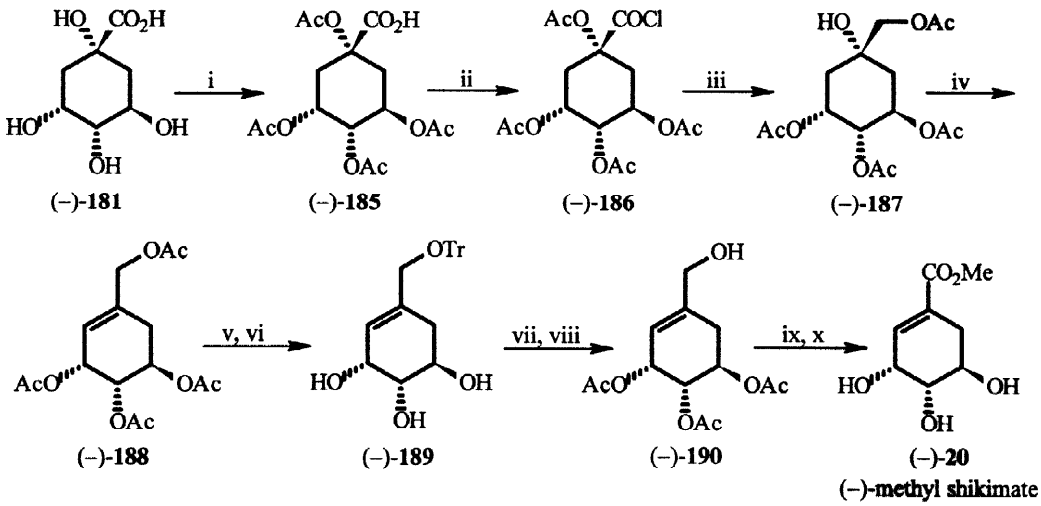
The first conversion of (–)-quinic acid **181** to (–)-shikimic acid **1** was reported by Dangschat and Fischer[78] in 1938 (Scheme 34). (–)-Quinic acid **181** was converted to 5-*O*-acetyl-3,4-*O*-methylenequinamide **182**[79] which was treated with *p*-toluenesulphonyl chloride in pyridine to induce the dehydration of the amide function and also the elimination of the newly formed *p*-toluenesulphonate ester unit. The resulting α,β-unsaturated nitrile **183** was hydrolysed to give the 3,4-*O*-methyleneshikimic acid **184** which was deprotected to afford the (–)-shikimic acid **1**.



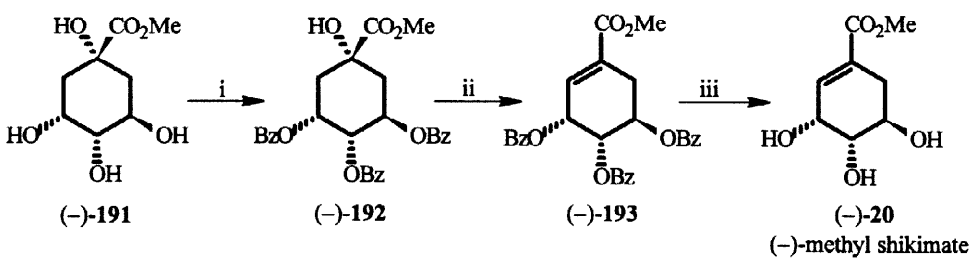
Scheme 34 *Reagents and conditions:* i, see: ref. 79; ii, *p*-TsCl, pyridine, 37 °C, 7 days; iii, aq. NaOH, reflux, 2.5 h; iv, aq. H_2SO_4, reflux

Grewe and co-workers[80] published a detailed conversion of (–)-quinic acid **181** to (–)-methyl shikimate **20** in 1957 (Scheme 35). Acetylation of (–)-quinic acid **181**, followed by treatment with thionyl chloride, gave the acid chloride (–)-**186**.[9e] Reduction of (–)-**186** was accomplished using sodium trimethoxyborohydride with concomitant acetyl group migration to give the tetraacetate (–)-**187**. Treatment of (–)-**187** with phosphorus oxychloride in pyridine afforded the olefin (–)-**188**. Deacetylation of (–)-**188** gave the tetrol which was selectively protected using trityl chloride. The resulting trityl ether (–)-**189** was acetylated and detritylated to give the alcohol (–)-**190**.[9c] Oxidation of (–)-**190** with chromium trioxide in acetic acid furnished the acetylated shikimic acid which was treated with mathanolic hydrogen chloride to yield the (–)-methyl shikimate **20**.

Gero and co-workers[81] have converted (–)-methyl quinate **191** to (–)-methyl shikimate **20** (Scheme 36) *via* dehydration of (–)-methyl 3,4,5-*O*-tribenzoylquinate **192** with either sulphuryl chloride or phosphorus oxychloride in pyridine. (–)-Methyl quinate **191**[31] was treated with excess of benzoyl chloride in pyridine to give the tribenzoate (–)-**192**.[82] These authors claimed that the dehydration of (–)-**192** proceeded regiospecifically to give (–)-**193** as the only isolated product, which was later proved by Snyder and Rapoport[31] to be incorrect (*vide infra*). Treatment of (–)-**193** with sodium methoxide in methanol gave the (–)-methyl shikimate **20**.



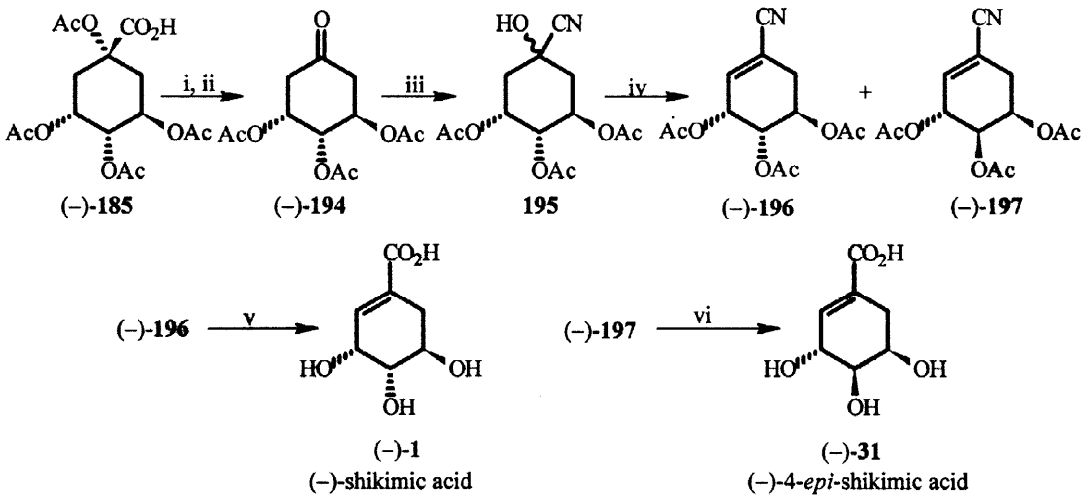
Scheme 35 *Reagents and conditions:* i, Ac_2O, pyridine, 18 h; ii, $SOCl_2$, benzene, 70 °C, 2 h; iii, $NaBH(OMe)_3$ (72%); iv, $POCl_3$, pyridine (94%); v, aq. NaOH; vi, Ph_3CCl, pyridine (80%); vii, Ac_2O, pyridine (81%); viii, aq. AcOH, reflux (80%); ix, CrO_3, AcOH; x, MeOH, HCl



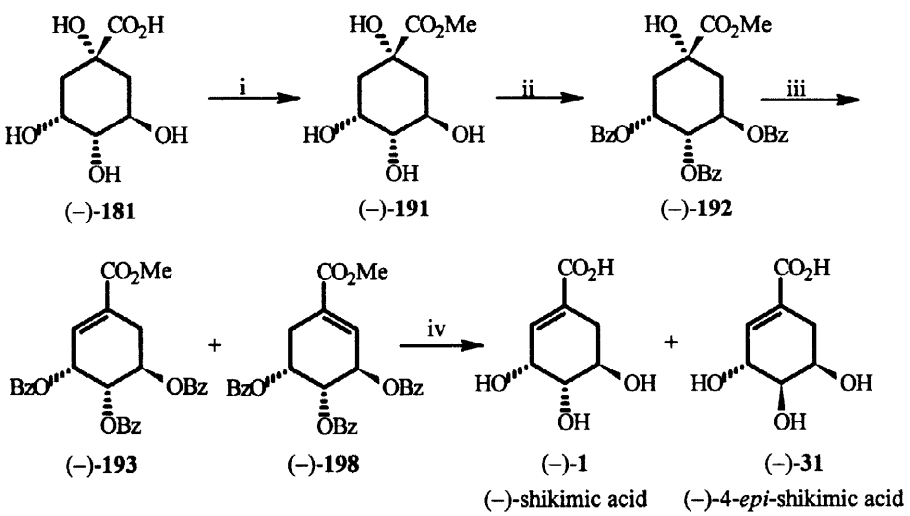
Scheme 36 *Reagents and conditions:* i, BzCl (excess), pyridine, –20 to 30 °C (85%); ii, SO_2Cl_2, pyridine, $CHCl_3$, –70 °C, 2 h, then –10 °C, 1 h (78%) or $POCl_3$, pyridine, 4 h (75%); iii, NaOMe, MeOH

Snyder and Rapoport[31] carried out a detailed study on the stereochemistry of quinate-shikimate conversion and obtained (–)-shikimic acid **1** as well as (–)-4-*epi*-shikimic acid **31** (Schemes 37 and 38). They repeated some of the early work by Grewe and Vangermain,[83] and prepared cyclohexanone (–)-**194** from the acid (–)-**185** under improved conditions and with good yield. They found that the cyanohydrin **195** that was obtained from hydrogen cyanide addition to (–)-**194** and previously thought to be a single isomer was actually a mixture of epimers, which was characterised, after acetylation, as a separable mixture of tetraacetates in a ratio of 2:3 in favour of the *epi*-quinate isomer. Contrary to previous observations that dehydration of the cyanohydrin was regiospecific,[83,84,85] The authors found that dehydration of **195** gave a mixture of nitriles (–)-**196** and (–)-**197** in approximately equal amounts. This explains the lower yield of nitrile (–)-**196** in previous dehydration cases. The fact that nitrile (–)-**196** could be crystallised while (–)-**197** remained as an oil may help to explain the previous omission of (–)-**197** from the reaction work-up. The nitriles (–)-**196** and (–)-**197** were separated and each was hydrolysed to give (–)-shikimic acid **1** and (–)-4-*epi*-shikimic acid **31**, respectively.

With these findings, Snyder and Rapoport also investigated the dehydration of tribenzoate (–)-**192** (Scheme 38) which was previously studied by Gero and co-workers.[81] Under the same conditions they obtained, after hydrolysis, a mixture of (–)-shikimic acid **1** and (–)-4-*epi*-shikimic acid **31** in a ratio of *ca.* 4:1, while the latter had not been previously identified. They also found that substituting the benzoyl groups of (–)-**192** with acetyl groups did not significantly change the ratio of the isomers from dehydration.

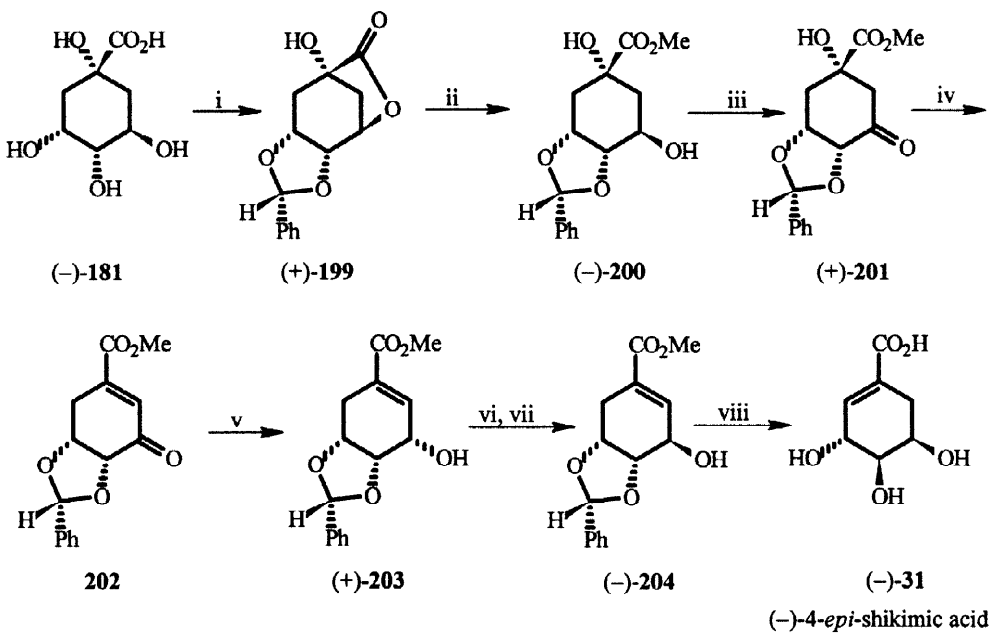


Scheme 37 *Reagents and conditions:* i, Ag_2O, acetone; ii, AgOAc, CCl_4, Br_2 (77%); iii, H_2SO_3, KCN (87%); iv, $POCl_3$, pyridine (83%, **196**:**197** = 47:53) or SO_2Cl_2, pyridine, $CHCl_3$, –78 °C to –10 °C (85%, **196**:**197** = 47:53); v, KOH, H_2O, reflux, 3 h, then Dowex AG 50W-X1 (H^+) (62%); vi, KOH, H_2O, reflux, 3 h, then Dowex AG 50W-X1 (H^+), then cyclohexylamine, H_2O, then H^+ resin (50%)



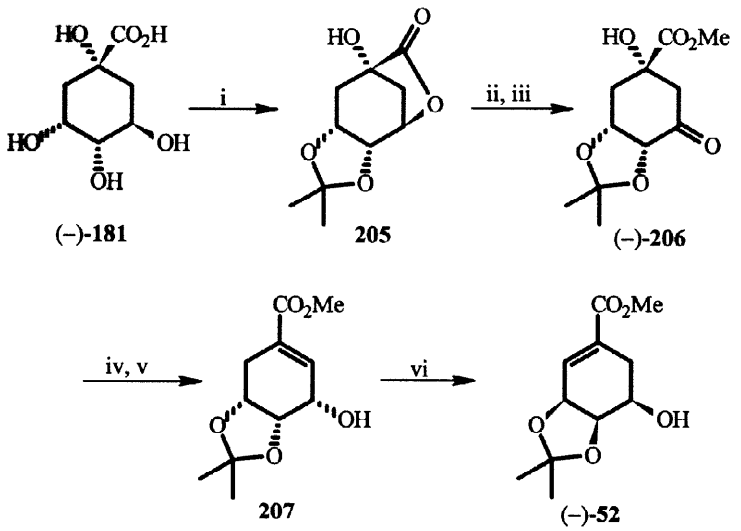
Scheme 38 *Reagents and conditions:* i, CH_2N_2, MeOH, 0 °C; ii, BzCl, pyridine, –30 °C to –10 °C (65%); iii, $POCl_3$, pyridine (72%) or SO_2Cl_2, pyridine, $CHCl_3$, –78 °C to –10 °C (95%); iv, dioxane, KOH, 24 h, then HCl, H^+ resin, then cellulose column for separation (**1**:**31** = 84:16 for $POCl_3$ dehydration and 82:18 for SO_2Cl_2 dehydration)

Lesuisse and Berchtold[86] reported a synthesis of (−)-4-*epi*-shikimic acid **31** *via* (+)-methyl 4,5-*O*-benzylidene-5-*epi*-shikimate **203** from (−)-quinic acid **181** (Scheme 39). Benzylidenation of (−)-quinic acid **181** gave a *ca.* 3:1 mixture of diastereoisomers because of the newly created chiral centre at the acetal carbon. The major diastereoisomer (+)-**199** crystallised from the mixture and was assigned *S* configuration at the new chiral centre on the basis of steric arguments. Opening of the lactone functionality of (+)-**199** with sodium methoxide in methanol afforded the methyl ester (−)-**200**. Swern[87] oxidation of (−)-**200** followed by dehydration with phosphorus oxychloride in pyridine gave enone **202** which was reduced with sodium borohydride to provide the 5-*epi*-shikimate derivative (+)-**203**. Inversion of stereochemistry at C-3 of (+)-**203** was effected under Mitsunobu[39] conditions. Subsequent deprotections gave (−)-4-*epi*-shikimic acid **31**. The overall yield for (−)-**31** was 18% from (−)-quinic acid **181** including the use of both diastereoisomers of the bezylidenation reaction. This route provided an alternative to Snyder and Rapoport's synthesis of (−)-4-*epi*-shikimic acid **31** from (−)-quinic acid **181** with the advantage being that the dehydration of enone (+)-**201** was regiospecific.



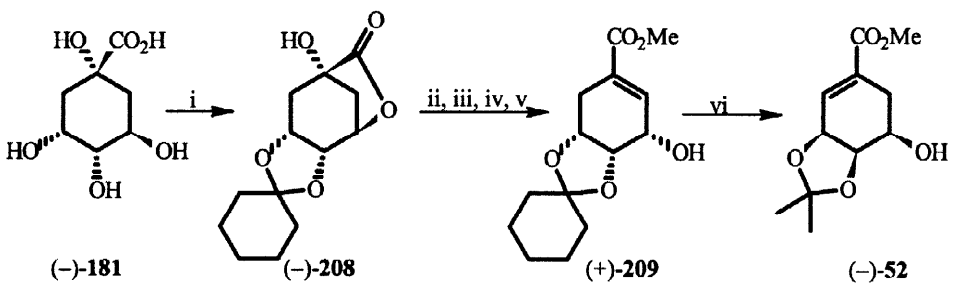
Scheme 39 *Reagents and conditions:* i, benzaldehyde, *p*-TsOH, benzene, reflux, 12 h (75% total); ii, NaOMe, MeOH, rt, 1 h (97%); iii, DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, then Et_3N (45%); iv, $POCl_3$, pyridine, rt, 2 h; v, $NaBH_4$, MeOH (68% two steps); vi, Ph_3P, DIAD, $PhCO_2H$, THF, rt, 3 h (91%); vii, NaOMe, MeOH, rt, 1 h (92%); viii, KOH, H_2O, THF, rt, 1 h, then AcOH (80%), rt, 12 h, then MeOH, Et_2NH, then Amberlite IR-120 (H^+) (96%)

Following Lesuisse and Berchtold's protocol, Hanessian and co-workers[27] converted (−)-quinic acid **181** to (−)-methyl 3,4-*O*-isopropylidene-5-*epi*-shikimate **52** (Scheme 40) which was a key intermediate in their synthetic approach to avermectins and milbemycins. It is interesting to note that thermodynamically controlled isopropylidenation of **207** afforded the more stable (−)-methyl 3,4-*O*-isopropylidene-5-*epi*-shikimate **52**. The overall yield of (−)-**52** from (−)-quinic acid **181** was 51%.



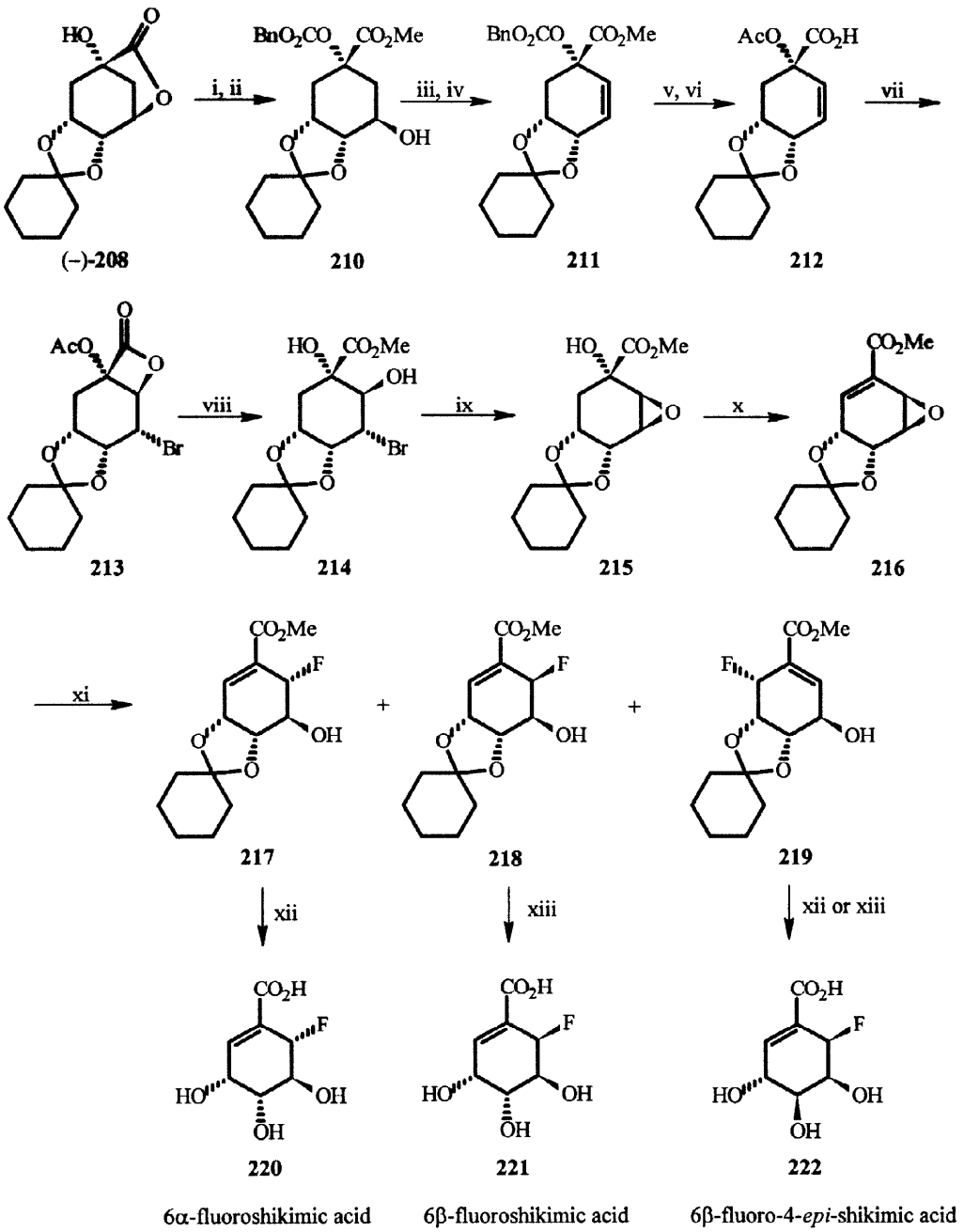
Scheme 40 *Reagents and conditions:* i, *p*-TsOH, acetone; ii, MeOH, NaOMe; iii, PCC (60% three steps); iv, $POCl_3$, pyridine; v, $NaBH_4$; vi, *p*-TsOH, acetone (85% for three steps)

For their synthesis of pseudosugars,[26] Shing and Tang[88] also prepared (–)-methyl 3,4-*O*-isopropylidene-5-*epi*-shikimate **52** (Scheme 41) in 42% overall yield from (–)-quinic acid **181** in a precedure that was almost identical to that of Hanessian and co-workers. The only difference was that they used cyclohexylidene instead of isopropylidene as the initial protecting group.



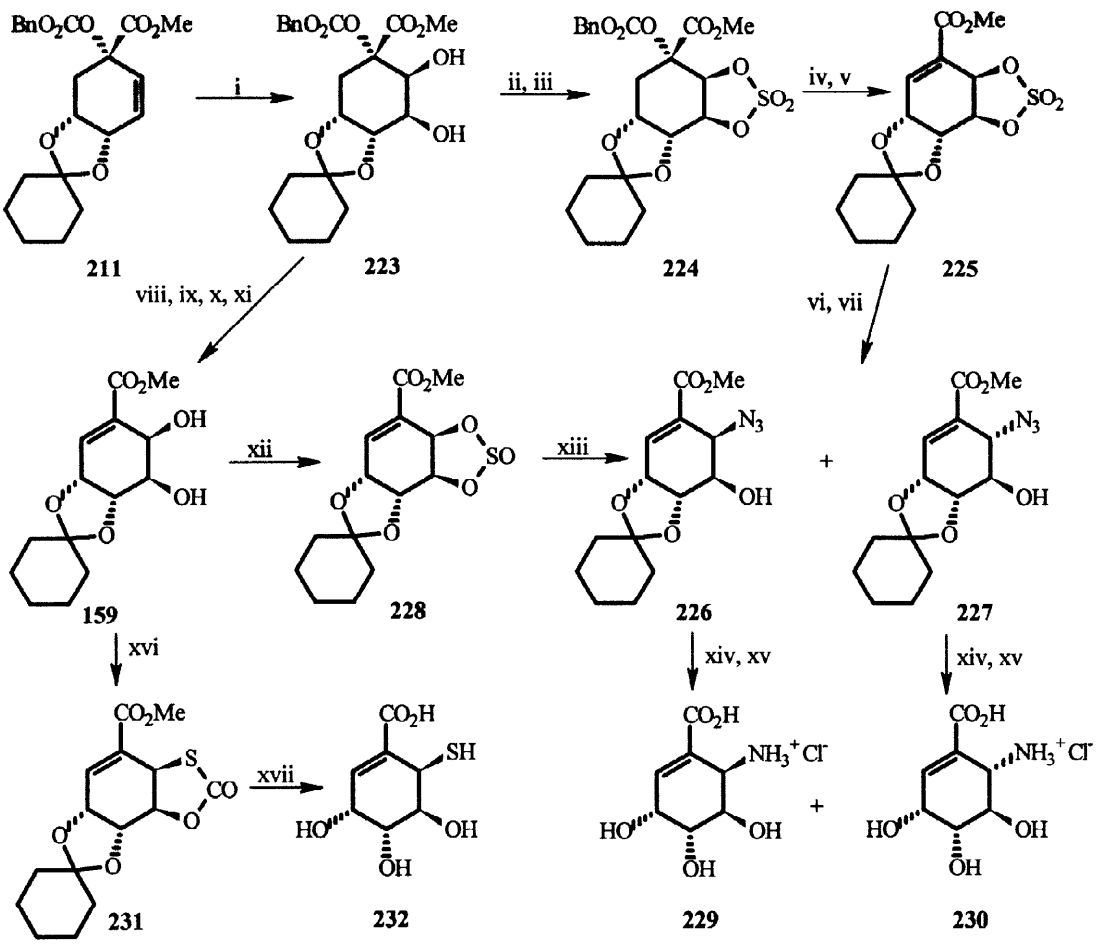
Scheme 41 *Reagents and conditions:* i, cyclohexanone, benzene, DMF, Dowex 50WX8 resin (H^+), reflux (79%); ii, NaOMe, MeOH, 0 °C (96%); iii, DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2; iv, $POCl_3$, pyridine, rt, (76% two steps); v, $NaBH_4$, MeOH, 0 °C (82%); vi, acetone, *p*-TsOH (88%)

Sutherland and co-workers[89,90] utilised (–)-quinic acid **181** to prepare a series of 6-substituted shikimic acids (Schemes 42, 43, 44 and 45; Note: no optical rotation values were given in the original reports, all the structures depicted in the schemes show absolute stereochemistry). The lactone (–)-**208** was treated with benzyl chloroformate followed by cleavage of the lactone ring with methanolic sodium methoxide to give the ester **210**. Treatment of **210** with trifluoromethanesulphonic anhydride gave the triflate which underwent elimination in the presence of DBU to provide the olefin **211**. Hydrolysis of **211** and subsequent acetylation gave the acid **212**, bromolactonisation of which afforded the lactone **213**. Ring opening of the lactone **213**



Scheme 42 *Reagents and conditions:* i, NaH, BnOCOCl, Bu_4NI, CH_2Cl_2 (92%); ii, NaOMe, MeOH (81%); iii, $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2 (96%); iv, DBU, $CHCl_3$; v, KOH, H_2O, dioxane; vi, Ac_2O, pyridine; vii, $C_5H_6NBr_3$, $NaHCO_3$, H_2O, THF, (68% for four steps); viii, NaOMe, MeOH (75%); ix, Bu_4NOAc, Me_2NCHO (82%); x, $[PhC(CF_3)_2O]_2SPh_2$ (87%); xi, HF, pyridine (54% total, 35% for **217**); xii, TFA, CH_2Cl_2, then 6 M HCl (59%); xiii, LiOH, H_2O, dioxane, then TFA, CH_2Cl_2 (40%)

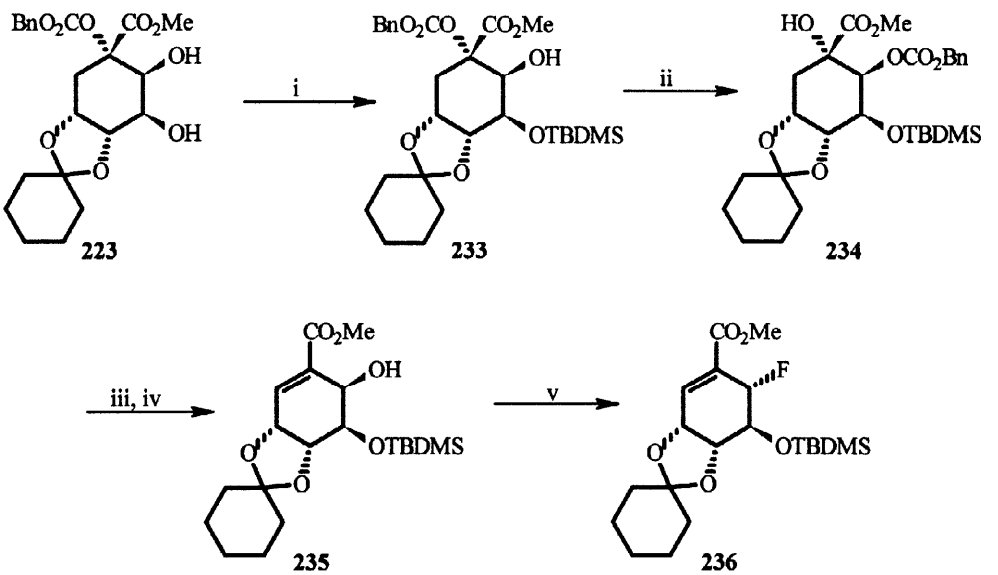
with sodium methoxide in methanol gave the ester **214** which was treated with butylammonium acetate in DMF to form the epoxide **215**. Dehydration of **215** was accomplished with Martin's reagent,[91] and the resulting epoxide **216** was treated with HF-pyridine. This epoxide ring opening was non-stereospecific, and three products **217**, **218** and **219** resulted from this reaction with **217** as the predominant one. With **217** being partially purified by silica gel chromatography, the remaining mixture of **218** and **219** was separated by liquid chromatography. Subsequent removal of protecting groups produced fluoroshikimic acids **220**, **221** and **222**, respectively (Scheme 42). The overall yield of 6α-fluoroshikimic acid **220** was 4% from (−)-quinic acid **181**. As for the 6β-fluoroshikimic acid **221** and 6β-fluoro-4-*epi*-shikimic acid **222** their overall yields from (−)-quinic acid **181** were *ca.* 0.4% each.



Scheme 43 *Reagents and conditions:* i, OsO_4, *N*-methylmorpholine-*N*-oxide, *t*-BuOH (89%); ii, $SOCl_2$; iii, $RuCl_3$, $NaIO_4$ (90% two steps); iv, H_2; v, Et_2NSF_3 (46% two steps); vi, NaN_3, DMF; vii, hydrolysis (71% two steps for **226** and 25% two steps for **227**); viii, TMSCl, Et_3N, CH_2Cl_2; ix, H_2; x, $[PhC(CF_3)_2]_2SPh_2$; xi, desilylation (70% four steps); xii, $SOCl_2$ (72%); xiii, NaN_3, DMF, 20 °C (90% total); xiv, Ph_3P, THF, then H_2O; xv, MeOH, HCl, then aq. HCl (39% two steps for **229** and 28% two steps for **230**); xvi, thiocarbonyldiimidazole, toluene (74%); xvii, hydrolysis

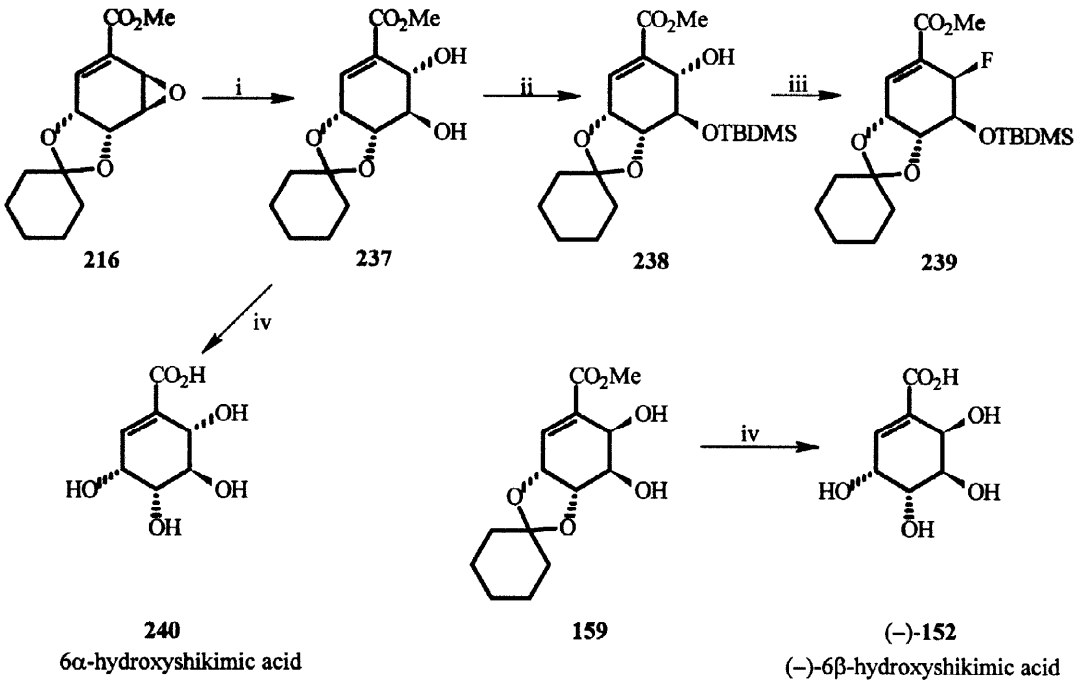
Dihydroxylation of olefin **211** gave the diol **223** which was treated with thionyl chloride and followed by oxidation of the resulting sulphite with rhodium chloride and sodium periodate to afford the sulphate **224**. Removal of the carbobenzoxy group of **224** by hydrogenolysis and dehydration of the resulting alcohol with DAST gave the olefin **225**. Treatment of **225** with sodium azide gave, after hydrolysis, a readily separable mixture of azides **226** and **227** in a ratio of 3:1. Alternatively, silylation of diol **223** followed by hydrogenolysis, dehydration and desilylation provided the diol **159** which was converted to the sulphite **228** and then treated with sodium azide to give a 7:2 mixture of azides **226** and **227**. The azides were separated, reduced with triphenylphosphine and further hydrolysed to give the hydrochlorides of 6β- and 6α-aminoshikimic acids **229** and **230** (Scheme 43). The 6β-mercaptoshikimic acid **232** was also prepared from the diol **159** by formation of the S-thiocarbonate **231** and subsequent hydrolysis.

The diol **223** was selectively silylated to give the silyl ether **233** which underwent *trans*-transesterification in the presence of sodium hydride to provide **234**. Dehydration of **234** and subsequent hydrogenolysis produced the allylic alcohol **235** which was treated with DAST to give the 6α-fluoroshikimic acid derivative **236** (Scheme 44). The overall yield of **236** from (−)-quinic acid **181** was approximately 18%.



Scheme 44 *Reagents and conditions:* i, TBDMSOTf (64%); ii, NaH, CH_2Cl_2 (91%); iii, $[PhC(CF_3)_2]_2SPh_2$; iv, H_2 (78% two steps); v, Et_2NSF_3 (72%)

Ring opening of the epoxide **216** in aqueous trifluoroacetic acid yielded the diol **237** which was selectively silylated and treated with DAST to give the 6β-fluoroshikimic aicd derivative **239** (Scheme 45) in 7% overall yield from (−)-quinic acid **181**. Deprotection of **237** gave 6α-hydroxyshikimic acid **240** in an overall yield of 9% from (−)-quinic acid **181**. (−)-6β-Hydroxyshikimic acid **152** was obtained from deprotection of **159** in an overall yield between 20% and 30% from (−)-quinic acid **181** depending on the yield of the final hydrolysis.

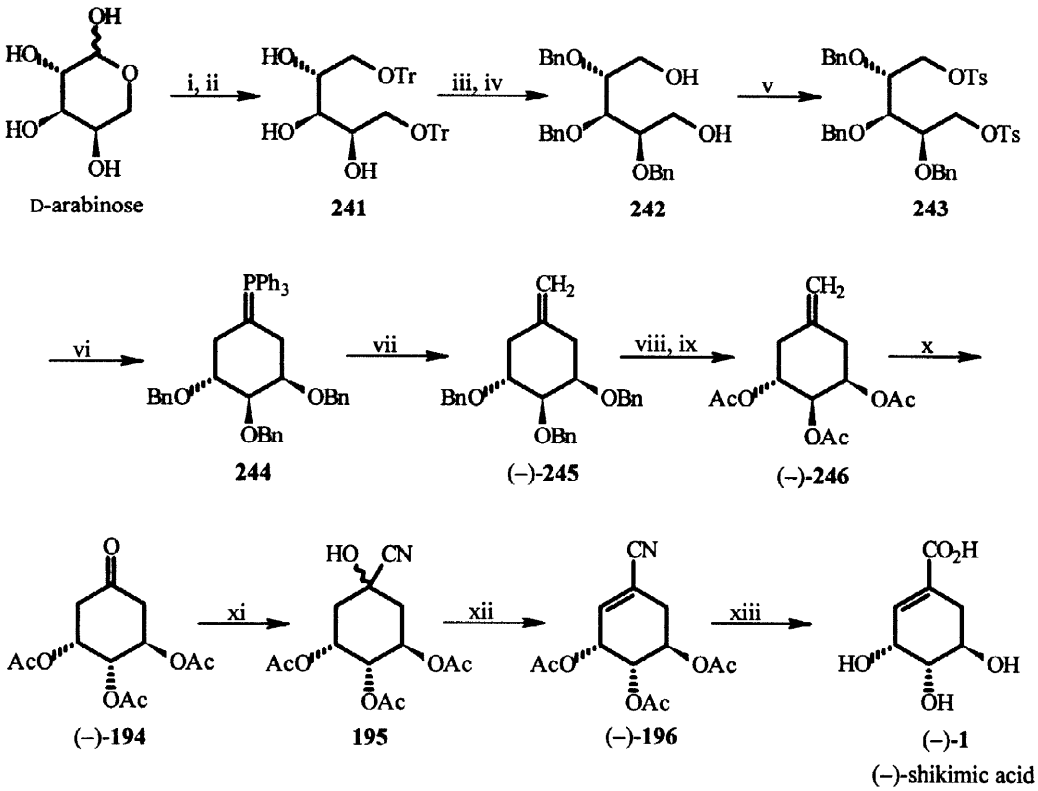


Scheme 45 *Reagents and conditions:* i, aq. TFA, DMSO (74%); ii, TBDMSOTf (75%); iii, Et_2NSF_3 (64%); iv, HCl, MeOH, then aq. HCl (57% for **240**)

5. CHIRAL SYNTHESES FROM CARBOHYDRATES

Carbohydrates, which are naturally abundant and inherently rich in chiral centres, have emerged over the years as an important category of 'chiral templates' in natural product synthesis.[92] Enantiomerically pure shikimic acid and its analogues have consequently been synthesised from carbohydrates.

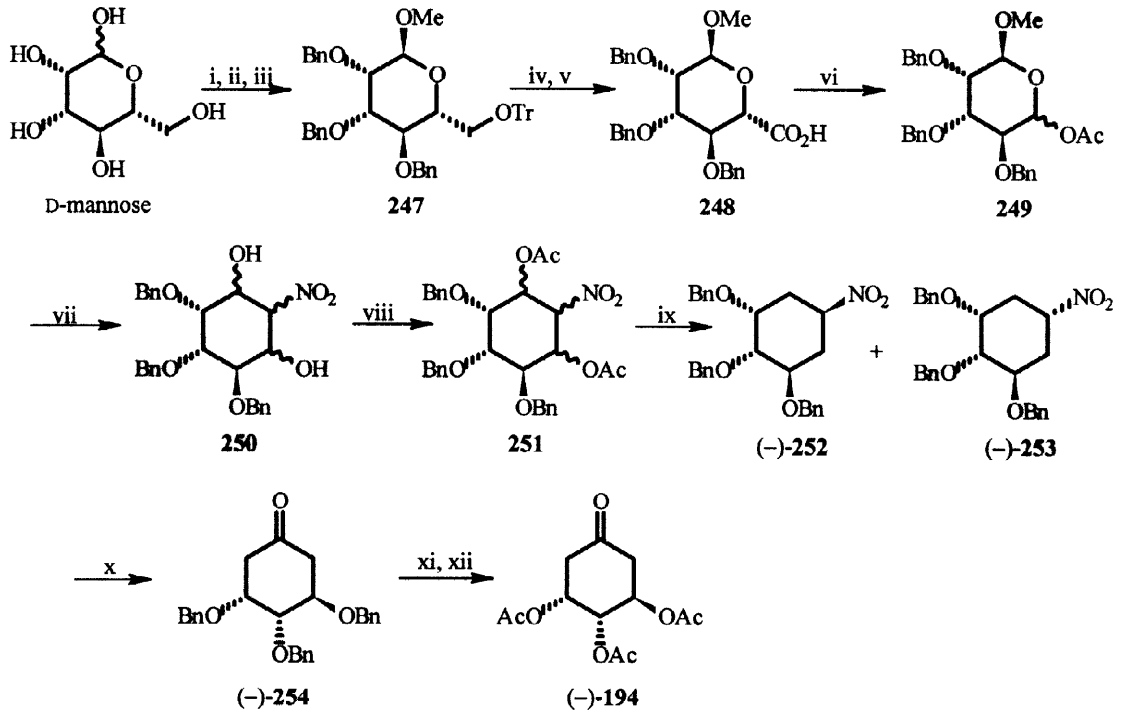
Bestmann and Heid[85] reported an early enantiospecific synthesis of both (–)-shikimic acid **1** (Scheme 46) and (–)-quinic acid **181** from D-arabinose. Catalytic hydrogenation of D-arabinose in the presence of Raney nickel gave arabitol which was tritylated selectively to provide dityrityl **241**. Benzylation and detritylation of **241** gave the diol **242** which was treated with *p*-toluenesulphonyl chloride in pyridine. The resulting ditosylate **243** was reacted with excess of methylenetriphenylphosphorane to form the ylid **244**. Wittig reaction of **244** with formaldehyde furnished the olefin (–)-**245**. Debenzylation of (–)-**245** followed by acetylation and oxidative cleavage produced the ketone (–)-**194**, which was previously prepared by Grewe and Vangermain[83] from (–)-quinic acid **181**. Cyanide addition to (–)-**194** followed by dehydration and hydrolysis gave the free (–)-shikimic acid **1** in an overall yield of 2.5% from D-arabinose. It is interesting to point out that although at that time these authors believed that the dehydration of the cyanohydrin **195** (which itself was later found to be an epimeric mixture[31]) was regiospecific the low yield (30%) of the dehydration step was indicative of the non-regiospecific nature of this reaction, and this was later confirmed by Snyder and Rapoport[31] who found that dehydration produced a *ca.* 1:1 mixture of regio isomers (*vide supra*).



Scheme 46 *Reagents and conditions:* i, Raney nickel, H_2 (96%); ii, TrCl, pyridine (75%); iii, KOH, BnCl (80%); iv, aq. HOAc (69%); v, TsCl, pyridine (76%); vi, $Ph_3P{=}CH_2$; vii, CH_2O (82% two steps); viii, Na, liquid NH_3 (80%); ix, Ac_2O, pyridine (82%); x, OsO_4, $NaIO_4$ (92%); xi, HCN (86%); xii, $POCl_3$, pyridine (30%); xiii, NaOH, H_2O (65%)

Kitagawa and co-workers[93] converted D-mannose to the cyclohexanone (–)-**194** (Scheme 47), an important intermediate in Bestmann and Heid's synthesis of (–)-shikimic acid **1**. Glycosidation of D-mannose with methanol in the presence of a catalytic amount of hydrogen chloride gave the α-pyranoside, which, after selective tritylation of the primary hydroxyl group, was benzylated to provide **247**. Detritylation of **247** followed by Jones oxidation gave the acid **248**. Oxidative decarboxylation of **248** was accomplished using lead tetraacetate[94] to give **249** as an epimeric mixture. Treatment of **249** with nitromethane and sodium methoxide in methanol led to the formation of carbocycle **250** as a mixture of diastereoisomers. Acetylation of **250** and reductive elimination of the resulting acetoxyl groups of **251** with sodium borohydride produced (–)-**252** and (–)-**253** in a ratio of 2:3. Separate treatment of (–)-**252** and (–)-**253** with titanium(III) chloride and ammonium acetate produced the same cyclohexanone (–)-**254**. Debenzylation of (–)-**254** and subsequent acetylation furnished the cyclohexanone (–)-**194**. Following Bestmann and Heid's procedure (*vide supra*), this constituted a formal synthesis of (–)-shikimic acid **1**.

Suami and co-workers[95,96,97] prepared several derivatives of shikimic and *epi*-shikimic acids (Schemes 48, 49, 50 and 51) from D-lyxose, L-arabinose, D-arabinose, D-ribose and D-xylose as key intermediates for the synthesis of pseudosugars.[26]



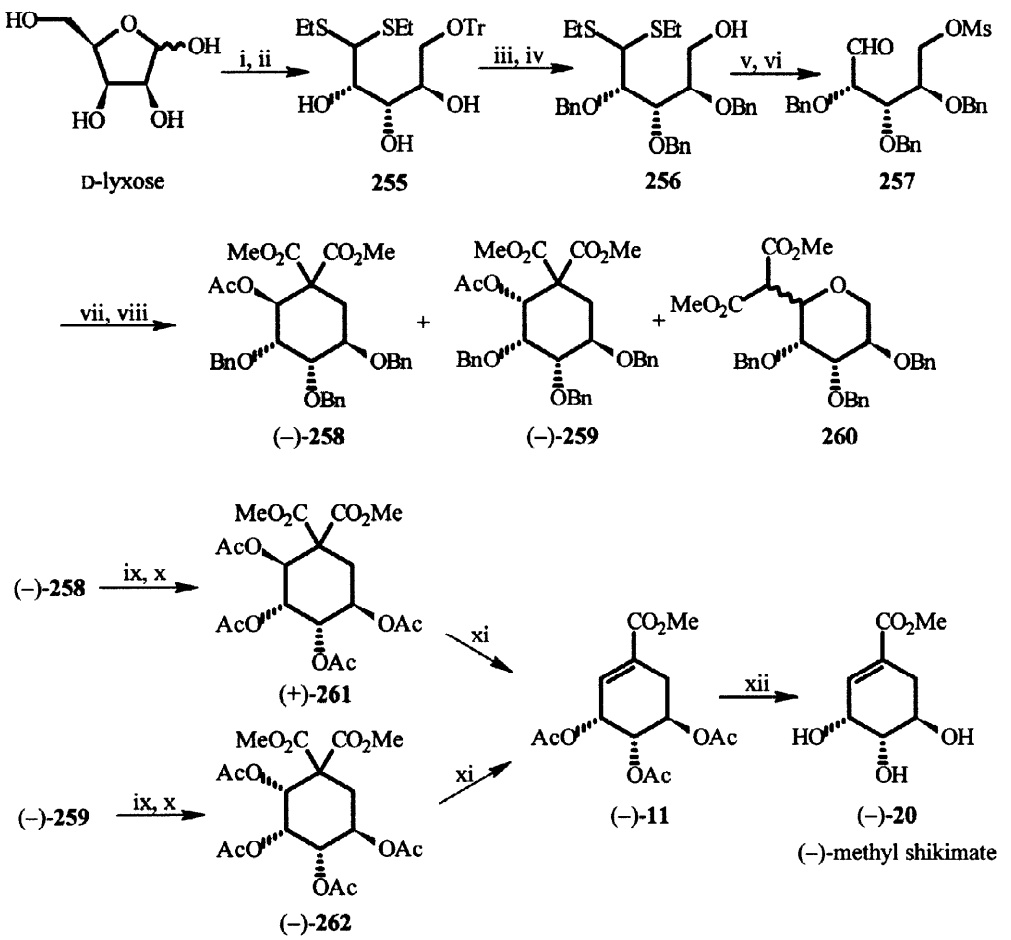
Scheme 47 *Reagents and conditions:* i, MeOH, AcCl; ii, TrCl, pyridine; iii, BnCl, NaOH; iv, aq. H_2SO_4; v, CrO_3, aq. H_2SO_4; vi, $Pb(OAc)_4$, benzene (79%); vii, $MeNO_2$, MeOH, NaOMe (65%); viii, Ac_2O, $BF_3{\cdot}Et_2O$ (97%); ix, $NaBH_4$, EtOH (27% for **252**, 41% for **253**); x, $TiCl_3$, NH_4OAc (72%); xi, debenzylation; xii, acetylation

These authors[95] converted D-lyxose to (−)-methyl shikimate **12** (Scheme 48) *via* a key intermolecular cyclisation of dimethyl malonate with mesylated aldehyde **257** in the presence of sodium hydride. The D-lyxose was treated with ethanethiol to give D-lyxose diethyl dithioacetal which was selectively tritylated to afford the trityl ether **255**. Benzylation of **255** and subsequent removal of the trityl group produced **256**, treatment of which with methanesulphonyl chloride followed by dethioacetalisation gave the aldehyde **257**. The cyclisation gave a separable mixture of three products, (−)-**258**, (−)-**259** and unwanted **260**. The latter resulted from the competitive C-C/C-O bond formation. Separate hydrogenolysis of (−)-**258** and (−)-**259** followed by acetylation afforded the tetraacetates (+)-**261** and (−)-**262**, respectively. The demethoxycarbonylation of both (+)-**261** and (−)-**262** proceeded in very low yields to give the same (−)-methyl 3,4,5-*O*-triacetylshikimate **11**. Deacetylation afforded (−)-methyl shikimate **20**, whose overall yield from D-lyxose was 0.6%.

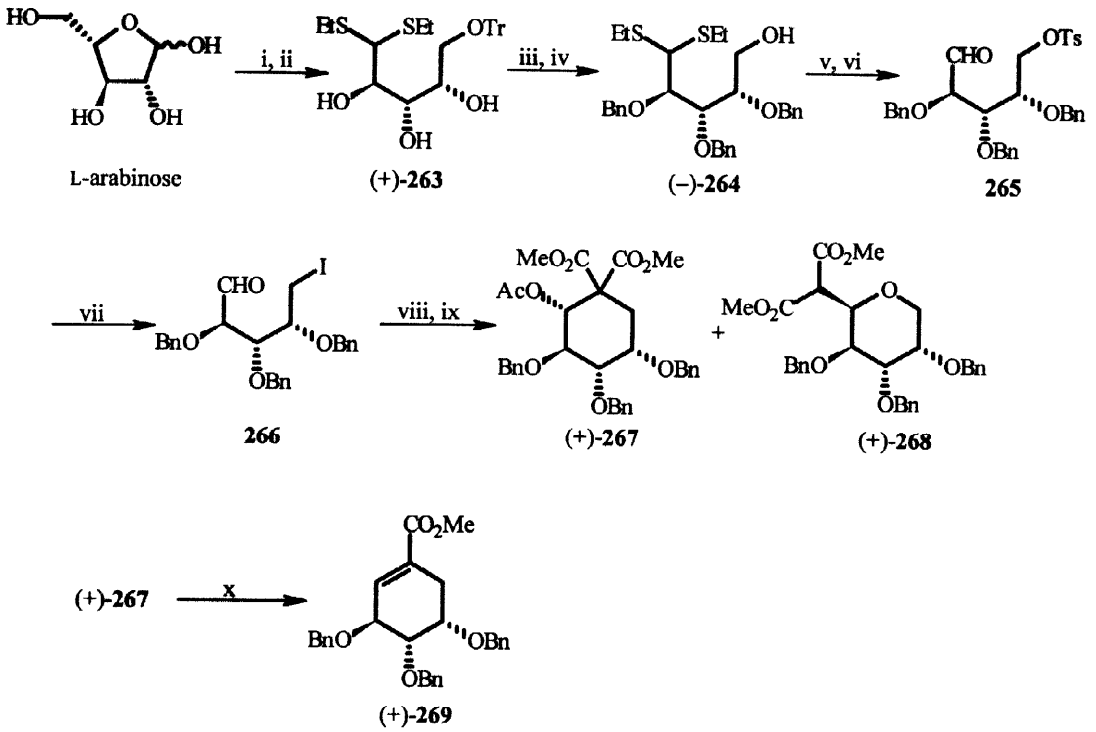
Conversion of L-arabinose to (+)-methyl 3,4,5-tribenzyl-4-*epi*-shikimate **269** (Scheme 49) was also accomplished by the authors using this methodology.[96] The aldehyde **265** was prepared from L-arabinose in much the same fashion as that of aldehyde **257**. Nucleophilic addition of dimethyl malonate to the iodo **266** in the presence of sodium hydride led to the formation of carbocycle (+)-**267** and the unwanted (+)-**268** in a ratio of 1.3:1. Thermal demethoxycarbonylation of (+)-**267** furnished (+)-methyl 3,4,5-*O*-tribenzyl-4-*epi*-shikimate **269**. The overall yield for (+)-**269** from L-arabinose was *ca.* 7%.

Suami and co-workers later modified their approach to carbocyclic formation in order to avoid the competitive C-C/C-O bond formation (Schemes 50 and 51).[97] Stepwise C-C bond formation for the

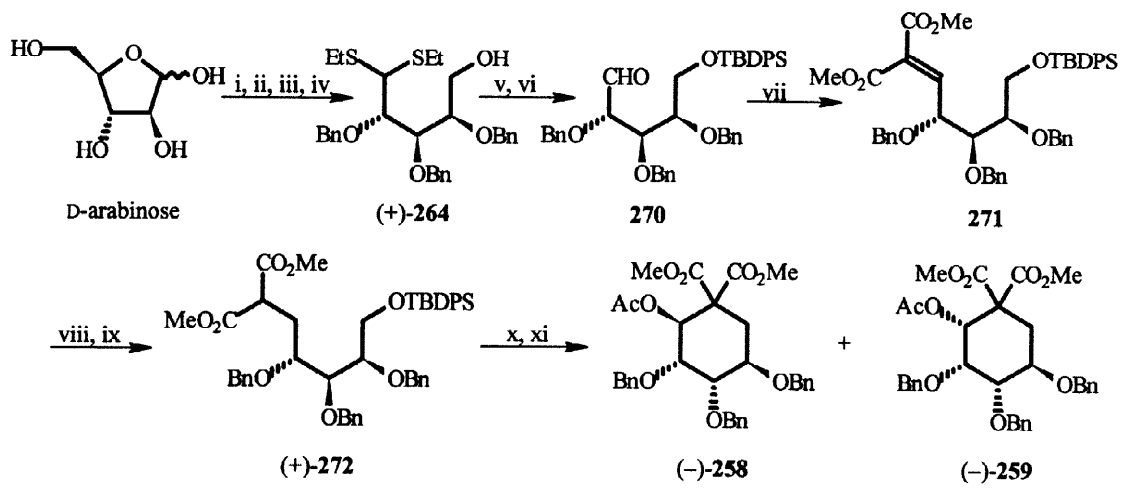
construction of the carbocyclic ring was adopted in these routes. Introduction of the first C-C bond in preparation of the intermediate (+)-**272** was achieved by employing the Knoevenagel condensation of the aldose derived acyclic aldehyde **270** with dimethyl malonate as the key step. The second C-C bond formation for cyclohexane construction featured PCC oxidation of (+)-**272**, which accomplished the aldol cyclisation. In this manner, they prepared exclusively (−)-**258** and (−)-**259** in a ratio of 1:10 from D-arabinose, which provided an alternative route to that from D-lyxose for (−)-methyl shikimate **20**. It has to be pointed out that although this approach eliminated the C-C/C-O bond formation during cyclisation, the overall yield for (−)-**20** from D-arabinose remained as low as 0.6%. By similar transformations, these authors also obtained (−)-methyl 3,4,5-*O*-tribenzyl-5-*epi*-shikimate **274** and (−)-methyl 3,4,5-*O*-tribenzyl-3-*epi*-shikimate **277** from D-ribose and D-xylose in overall yields of 7% and 6%, respectively.



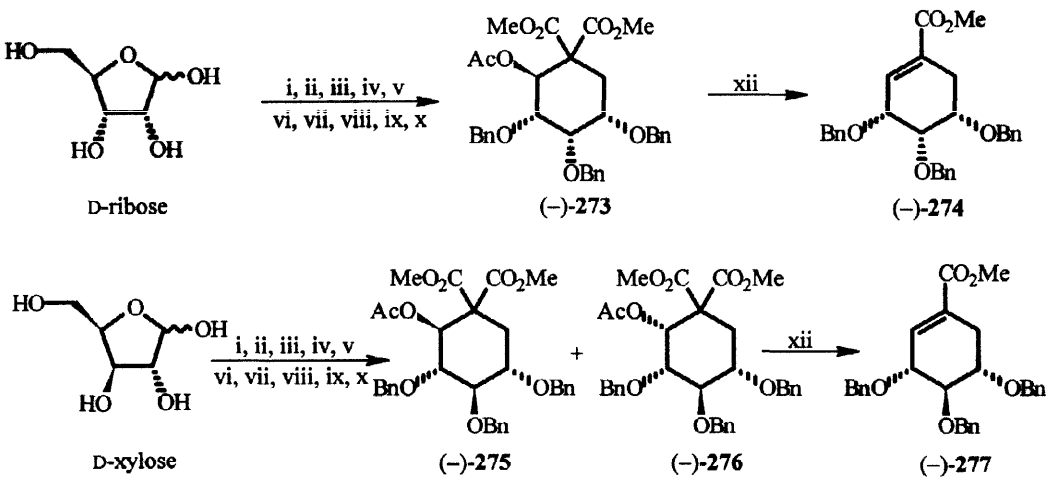
Scheme 48 *Reagents and conditions:* i, conc. HCl, EtSH, 0 °C, 30 min (78%; see: ref. 98a); ii, TrCl, pyridine, DMAP, 70 °C, 14 h (81%); iii, NaH, BnBr, DMF, 17 h; iv, *p*-TsOH, MeOH, EtOAc, 1.5 h (79% two steps); v, MsCl, pyridine, 0 °C, 90 min; vi, $HgCl_2$, $CaCO_3$, MeCN, H_2O, 90 min; vii, NaH, dimethyl malonate, THF; viii, Ac_2O, pridine, 60 °C, 1 h (four steps from **256**, 17% for **258**, 15% for **259** and 8% for **260**); ix, cyclohexene, MeOH, 20% $Pd(OH)_2$-C, reflux, 54 h; x, Ac_2O, pyridine, 15 h (yields for two steps; 54% for **261** and 71% for **262**, respectively); xi, DMSO, H_2O (drops), NaCl, 125 °C, 75 to 90 min (17% for **11** and 47% for recovery of **261**; 13% for **11** and 18% for recovery of **262**); xii, NaOMe, MeOH, 0 °C, 1 h (42%)



Scheme 49 *Reagents and conditions:* i, EtSH, conc. HCl (see: ref. 98b); ii, TrCl, DMAP, pyridine, 70 °C, 18 h (89%); iii, NaH, BnBr, DMF, 32 h; iv, *p*-TsOH, MeOH, EtOAc, 2 days (61% two steps); v, *p*-TsCl, DMAP, pyridine, 18 h; vi, $HgCl_2$, $CaCO_3$, MeCN, H_2O, 2 h; vii, 2-butanone, NaI, reflux, 18 h (50% for three steps); viii, NaH, THF, dimethyl malonate, 3 h; ix, Ac_2O, pyridine, DMAP (two steps, 43% for **267** and 33% for **268**); x, DMSO, H_2O, NaCl, 110 °C to 170 °C, 4 h (75%)



Scheme 50 *Reagents and conditions:* i, conc. HCl, EtSH (see: ref. 98b); ii, TrCl, DMAP, pyridine (81%); iii, NaH, BnBr, DMF; iv, *p*-TsOH, MeOH, EtOAc (64% two steps); v, TBDPSCl, imidazole, DMF (93%); vi, $HgCl_2$, $CaCO_3$, MeCN, H_2O; vii, dimethyl malonate, Ac_2O, pyridine; viii, Raney nickel T-4, H_2 (1 atm); ix, Bu_4NF, THF (62% four steps); x, PCC, molecular sieves, CH_2Cl_2, 15 h; xi, Ac_2O, pyridine (two steps, 5% for **258** and 48% for **259**)

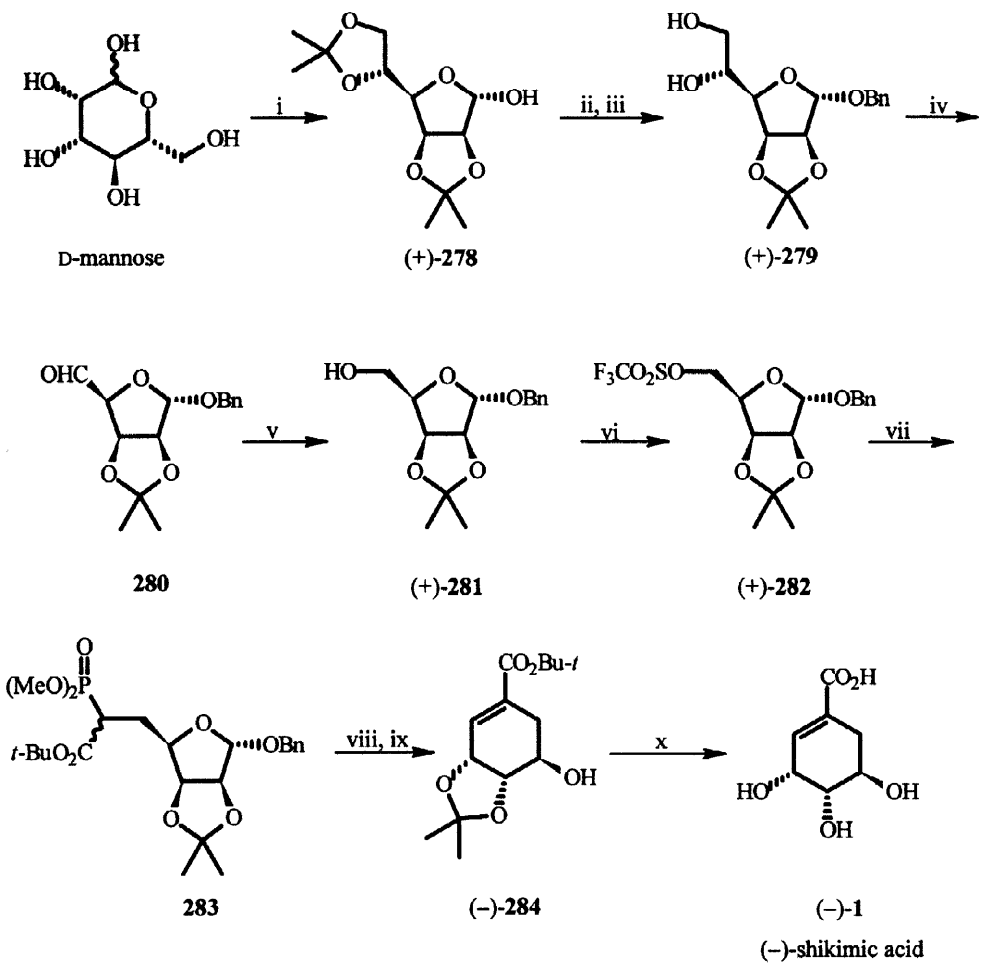


Scheme 51 *Reagents and conditions:* i, conc. HCl, EtSH (61% for ribose, see: ref. 98c; 80% for xylose, see: ref. 98d); ii, TrCl, DMAP, pyridine (92% for ribose; 78% for xylose); iii, NaH, BnBr, DMF; iv, *p*-TsOH, MeOH, EtOAc (two steps. 61% for ribose; 67% for xylose); v, TBDPSCl, imidazole, DMF (98% for ribose; 98% for xylose); vi, $HgCl_2$, $CaCO_3$, MeCN, H_2O; vii, dimethyl malonate, Ac_2O, pyridine (two steps, 85% for ribose; for the xylose, a catalytic amount of Et_3N was used for the reaction); viii, Raney nickel T-4, H_2 (1 atm) (78% for ribose); ix, Bu_4NF, THF (68% for ribose; 53% for xylose for four steps); x, PCC, molecular sieves, CH_2Cl_2; xi, Ac_2O, pyridine (two steps. 69% for **273**; 34% for **275** and 21% for **276**); xii, DMSO, H_2O, NaCl, 120 °C to 170 °C (70% for **274**; 48% for **277**)

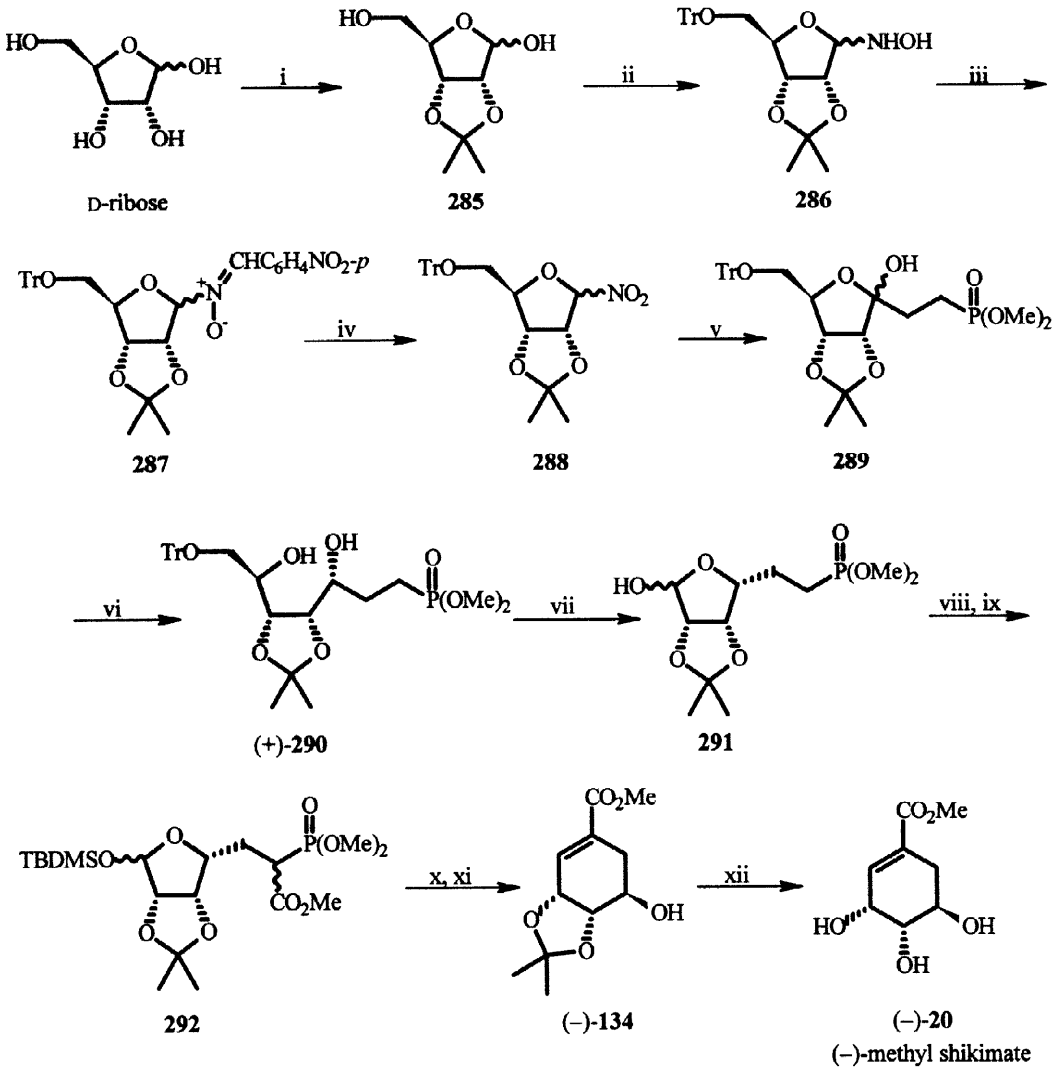
Fleet and co-workers[99] accomplished an efficient synthesis of (–)-shikimic acid **1** in an overall yield of 39% from D-mannose *via* an intramolecular Wadsworth-Emmons olefination[100] as a key reaction (Scheme 52). The *lyxo*-alcohol (+)-**281**[101] was prepared from D-mannose in 66% overall yield *via* the diacetonide (+)-**278**.[102] Treatment of (+)-**281** with trifluoromethanesulphonic anhydride in pyridine gave quantitatively the trifluoromethanesulphonate (+)-**282**, which was reacted with the sodium salt of *t*-butyl dimethylphosphonoacetate in the presence of a crown ether to form the phosphonate **283** as a diastereoisomeric mixture with regard to the stereochemistry at C-6. Removal of the benzyl group in **283** by hydrogenolysis, followed by intramolecular Wadsworth-Emmons olefination[100] of the resulting lactol, afforded (–)-*t*-butyl 3,4-*O*-isopropylideneshikimate **284**. Deprotection using aqueous trifluoroacetic acid produced quantitatively (–)-shikimic acid **1**.

Another intramolecular Wadsworth-Emmons olefination[100] based approach to the synthesis of (–)-methyl shikimate **20** from D-ribose (Scheme 53) was reported by Mirza and Vasella,[103] which was contemporaneous with that of Fleet and co-workers. The acetonide **285**,[104] prepared from isopropylidenation of D-ribose, was treated sequentially with trityl chloride and hydroxylamine hydrochloride in pyridine in a one-pot procedure to give the oxime **286**.[105a] Reaction of oxime **286** with *p*-nitrobenzaldehyde led to the formation of nitrone **287** as an isomeric mixture. Ozonolysis of nitrone **287** afforded the 1-deoxy-1-nitroribose **288** as a mixture of anomers.[105b] Chain elongation of **288** *via* Micheal addition to diethyl vinylphosphonate followed by heating the resulting product in moist formamide in the presence of sodium hydrogen carbonate furnished the heptulosephosphonate **289** as an anomeric mixture. Diastereoselective reduction of **289** with

sodium borohydride in either ethanol or methanol afforded predominantly the diol (+)-**290**. Detritylation of (+)-**290** with either zinc bromide or aqueous acetic acid followed by periodate cleavage of the resulting triol gave lactol **291** as an anomeric mixture. Silylation of the anomeric hydroxyl group in **291** produced a 6.8:1 mixture of α- and β-anomers, which were separated and treated separately with butyllithium and methyl chloroformate to give ester **292** as a mixture with both α- and β-anomers each containing a 1:1 mixture of diastereoisomers due to the newly formed chiral centre at C-6. The mixture of **292** was desilylated to generate the lactol which was treated with sodium methoxide to induce the cyclisation to form the (−)-methyl 2,3-*O*-isopropylideneshikimate **134**. Deacetonation afforded (−)-methyl shikimate **20**. As the authors claimed that the yield for conversion of D-ribose to 1-deoxy-1-nitroribose **288** was 75%, therefore the overall yield of (−)-methyl shikimate **20** from D-ribose was 38%.



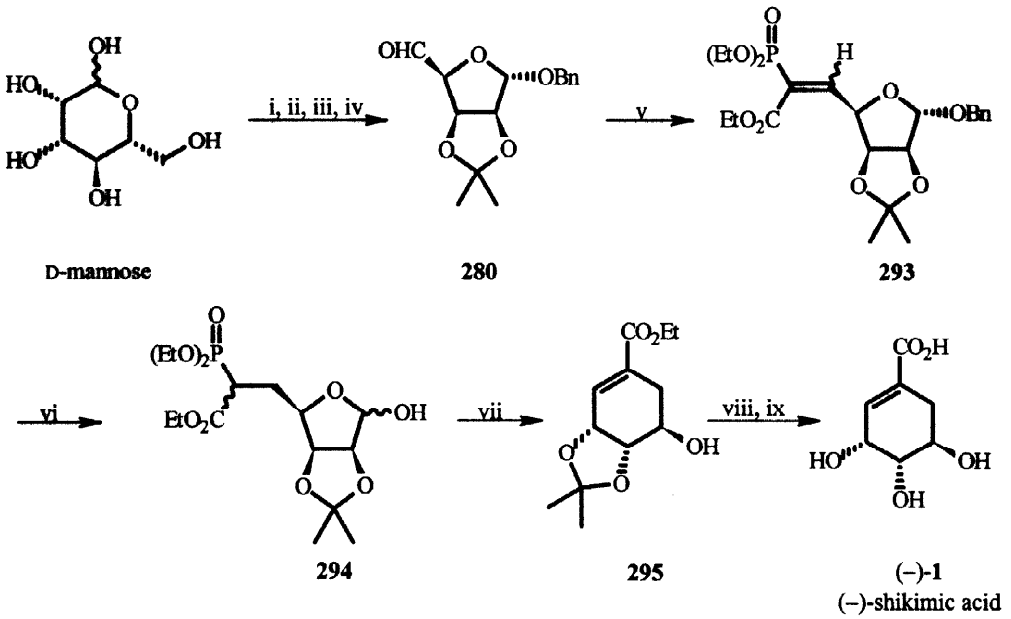
Scheme 52 *Reagents and conditions:* i, acetone, conc. H_2SO_4 (cat), rt; ii, BnCl, NaH, DMF, rt; iii, conc. HCl, MeOH, H_2O; iv, $NaIO_4$, H_2O, rt; v, $NaBH_4$, EtOH (66% from D-mannose); vi, $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, −30 °C (100%); vii, NaH, *t*-butyl dimethylphosphonoacetate, DMF, 15-crown-5 (81%); viii, Pd-C (10%), MeOH, H_2 (1 atm), rt; ix, NaH, THF (73% two steps); x, aq. TFA, rt, 12 h (100%)



Scheme 53 *Reagents and conditions:* i, acetone, conc. H_2SO_4; ii, TrCl, pyridine, then MeOH, NH_2OH·HCl (61%; Note: two separate reactions may give a higher overall yield); iii, *p*-$O_2NC_6H_4CHO$, CH_2Cl_2, reflux; iv, O_3, CH_2Cl_2, −78 °C (90%, two steps); v, Bu_4NF, diethyl vinylphosphonate, THF, 0 °C, 1 h, then $HCONH_2$, $NaHCO_3$, 60 °C, 24 h (87%, 5.5:1 mixture of anomers); vi, $NaBH_4$, EtOH, 0 °C (73.5% for **290** and 18.5% for the other isomer) or $NaBH_4$, MeOH, 0 °C (97% total yield, the ratio of **290** and its corresponding isomer as 22:1); vii, $ZnBr_2$, CH_2Cl_2, rt, 30 min then MeOH, H_2O, $NaIO_4$, 10 min (85%, 4.9:1 mixture of anomers) or aq. AcOH, rt, 6 h, evaporation, then MeOH, 0 °C, $NaHCO_3$, $NaIO_4$, H_2O, 10 min (76%, mixture of anomers); viii, TBDMSCl, imidazole, CH_2Cl_2, rt (12% for the β-anomer, and 81% for the α-anomer); ix, BuLi, THF, methyl chloroformate, −78 °C (95% for the β-anomer as mixture of diasereoisomers; 94% for the α-anomer as mixture of diastereoisomers); x, Bu_4NF, THF, rt, 1 h; xi, NaOMe, MeOH, rt, 1 h (86% two steps); xii, Dowex (50W, H^+ form), MeOH, rt, 1 h (97%)

Mirza and Harvey[106] later published another synthesis of (–)-shikimic acid **1** (Scheme 54) from D-mannose *via* the *lyxo*-aldehyde **280**.[101] They used a Knoevenagel reaction for the two-carbon chain extension of **280** and intramolecular Wadsworth-Emmons olefination[100] to form the carbocycle. This work

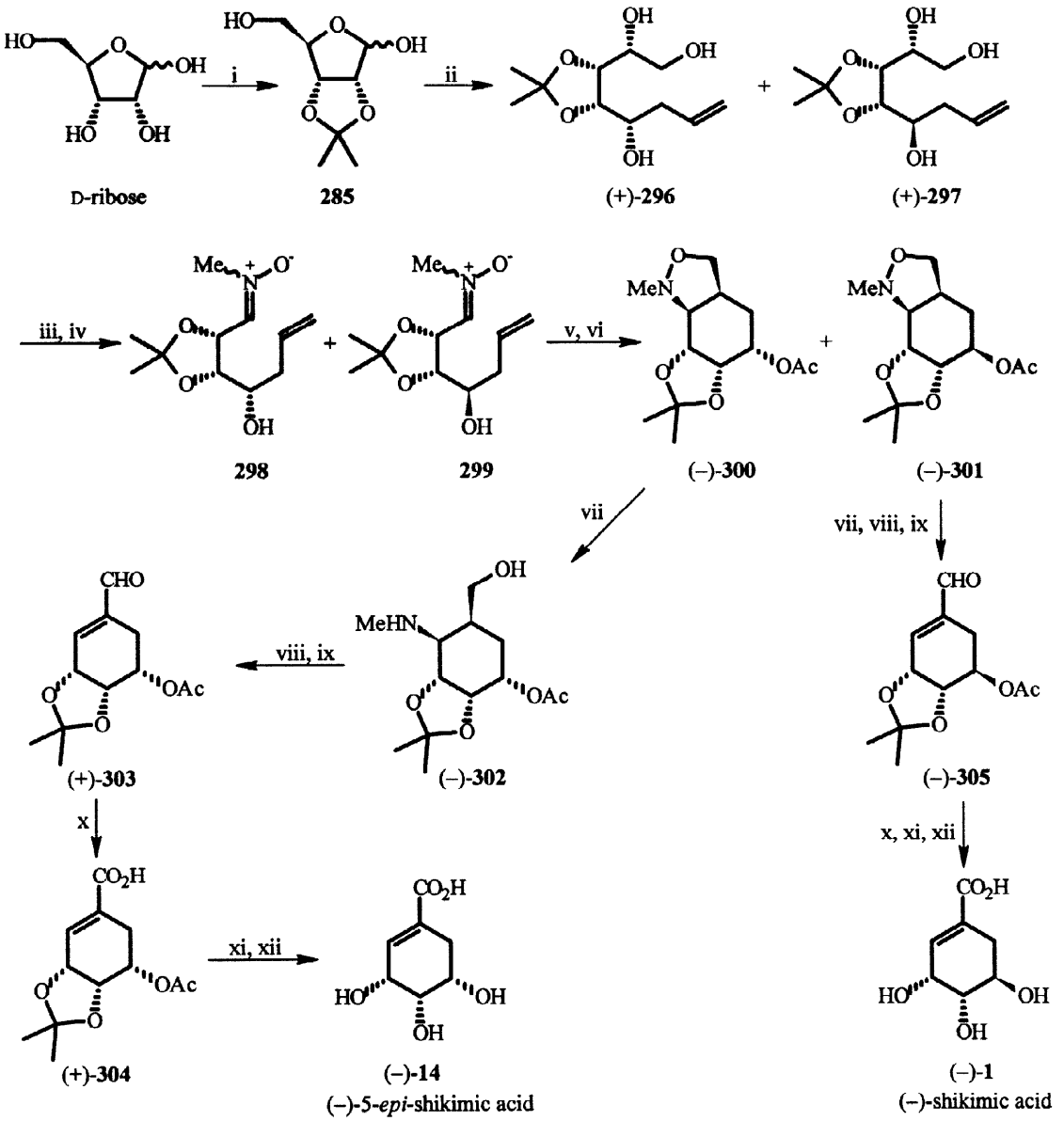
was very similar to that of Fleet and co-workers with only slight difference in the method of carbon chain elongation. Condensation of *lyxo*-aldehyde **280**, preapred from D-mannose in four steps,[101] with triethyl phophonoacetate in the presence of *N*-methylmorpholine and titanium(IV) chloride gave **293** as a 2:1 mixture of *E*- and *Z*-isomers. Hydrogenation of **293** yielded the lactol **294** as an isomeric mixture because of the chirality at C-1 and C-6. Intramolecular cyclisation of lactol **294** in the presence of sodium ethoxide gave, after deprotection, (−)-shikimic acid **1**. In this synthesis, the overall yield for (−)-shikimic acid **1** from D-mannose was between 26% and 29%.



Scheme 54 *Reagents and conditions:* i, acetone, conc. H_2SO_4 (cat), rt; ii, BnCl, NaH, DMF, rt; iii, conc. HCl, MeOH, H_2O; iv, $NaIO_4$, H_2O, rt; v, triethyl phosphonoacetate, *N*-methylmorpholine, $TiCl_4$, CCl_4, THF (79%, *E*:*Z* = 2:1); vi, Pd-C, H_2, EtOH; vii, NaOEt, EtOH (60% two steps); viii, NaOH, EtOH; ix, Dowex 50WX4, H_2O (87% two steps)

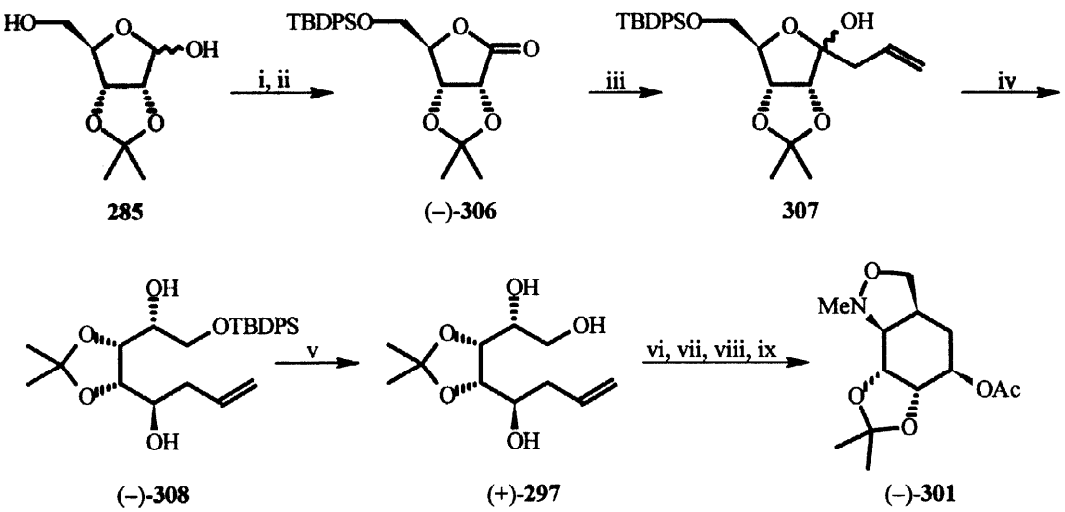
A recent synthesis of (−)-5-*epi*-shikimic acid **14** and (−)-shikimic acid **1** (Schemes 55 and 56) from D-ribose by Singh, Wightman and co-workers[107] utilised an intramolecular nitrone cycloaddition reaction as a key step to establish the carbocyclic ring. Reaction of 2,3-*O*-isopropylidene-D-ribose **285**[104] with excess of allylmagnesium chloride gave a 5:1 mixture of diastereoisomeric triols (+)-**296** and (+)-**297**. Sodium periodate cleavage of the triols and treatment of the resulting lactols with excess of *N*-methylhydroxylamine hydrochloride in pyridine led to the formation of nitrones **298** and **299**, which, upon refluxing in toluene, underwent intramolecular nitrone cycloaddition to produce stereospecifically the isoxazolidines. Acetylation of this mixture gave the isoxazolidines (−)-**300** and (−)-**301**, which were separated by crystallisation and column chromatography. Hydrogenation of (−)-**300** in the presence of Pearlman's catalyst (20% palladium hydroxide on carbon) and methylation of the resulting amino alcohol (−)-**302** afforded the quaternary ammonium salt which was oxidised under Swern[87] conditions to give the α,β-unsaturated aldehyde (+)-**303**. Further oxidation of (+)-**303** with sodium chlorite and hydrogen peroxide under buffered conditions furnished the acid (+)-**304**. Consecutive deprotection of acid (+)-**304** gave (−)-5-*epi*-shikimic acid **14**. (−)-Shikimic acid

1 was obtained by a similar sequence of reactions on the other diastereoisomer (–)-**301**. This route from D-ribose gave (–)-5-*epi*-shikimic acid **14** and (–)-shikimic acid **1** in overall yields of 16% and 3%, respectively.



Scheme 55 *Reagents and conditions:* i, acetone, H_2SO_4 (cat.), rt, 4 h (73%); ii, allylmagnesium chloride, THF, 0 °C to rt, 14 h (mixture of diastereoisomers, **296**:**297** = 5:1); iii, $NaIO_4$, H_2O, rt, 2 h (94% total mixture, two steps); iv, MeNHOH·HCl, pyridine, rt, 17 h; v, toluene, reflux, 16 h (91% mixture, two steps); vi, Ac_2O, DMAP, pyridine, rt, 9 h (67% for **300** and 11% for **301**) vii, $Pd(OH)_2$-C (20%), H_2 (2 atm), MeOH, 30 h (100% from **300**; 100% from **301** being hydrogenated for 2 days); viii, MeI, K_2CO_3, THF, rt, 30 h (87% from **302**; 80% from the other); ix, DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, 55 min, then Et_3N, –78 °C to rt (79% for **303**; 71% for **305**); x, $NaClO_2$, NaH_2PO_4, H_2O_2, MeCN, H_2O, rt, 2 h (67% from **303**; 91% from **305**); v, K_2CO_3, MeOH, H_2O, rt, 12 h; vi, aq. TFA, rt, 10 h (two steps, 80% for **14**; 79% for **1**)

These authors also achieved exclusive conversion of D-ribose to (–)-shikimic acid **1** (Scheme 56) *via* a lactone route that established at an early stage the stereochemistry appropriate for further transformation into shikimic aicd. The lactone (–)-**306**, prepared from acetonide **285** by sequential silylation and potassium permanganate oxidation, was treated with allylmagnesium chloride in THF at –78 °C to give the lactol **307**, which was reduced with DIBAL-H to produce exclusively the diol (–)-**308**. Desilylation of (–)-**308** gave the triol (+)-**297**, which was subjected to a sequence of reactions similar to those of the previous diastereoisomeric mixture to furnish the isoxazolidine (–)-**301**. This lactone route delivered (–)-shikimic acid **1** in 10% overall yield from D-ribose.



Scheme 56 *Reagents and conditions:* i, TBDPSCl, CH_2Cl_2, Et_3N, DMAP, rt, 3 h (98%); ii, $KMnO_4$, acetone, reflux, 2 h (74%); iii, allylmagnesium chloride, THF, –78 °C, 3 h (87%); iv, DIBAL-H, toluene, –78 °C, 3 h (88%); v, Bu_4NF, THF, rt, 10 h (72%); vi, $NaIO_4$, H_2O, rt, 2 h (92%); vii, MeNHOH·HCl, pyridine, rt, 20 h (100%); viii, toluene, reflux, 18 h (95%); ix, Ac_2O, DMAP, pyridine, rt, 10 h (93%)

6. CONCLUSION

This review has surveyed chemical syntheses of shikimic acid, and covered literature through early 1997. Among various methods reported for assembling shikimic acid from acyclic precursors, the Diels–Alder reaction remains the most important one. Its utilisation ranges from early syntheses of racemic shikimic acid to later chiral ones with the use of chiral auxiliaries (Schemes 18, 19 and 20) and more recently chiral catalysts (Scheme 21). The current enthusiasm in the use of arene *cis*-dihydrodiols also led to several syntheses of shikimic acid and its analogues dealing mainly with the installation of the carboxylic group on the carbocyclic ring (Sec. 3.2). As quinate-shikimate conversion does not require formation of new carbon-carbon bond, (–)-quinic acid is therefore well suited as a convenient precursor for preparing shikimic acid analogues (Sec. 4). In the case of carbohydrates, an important feature in their conversion to chiral shikimic acid is the formation of the carbocycles. Currently, the intramolecular olefination based syntheses stand to be the most efficient in this category. With the continued interest in the search of biologically active shikimic acid

analogues and also as a showcase for new synthetic methodologies, more reports on the syntheses of shikimic acid and its analogues will be forthcoming in the future.

Note added in proof

Garretero and co-workers have recently reported the enantioselective synthesis of (+)-shikimic acid and (+)-5-*epi*-shikimic acid by asymmetric Diels–Alder reaction of (S)-α-sulphinylacrylates and furan (Adrio, J.; Carretero, J. C.; García Ruano, J. L.; Martín Cabrejas, L. M. *Tetrahedron: Asymmetry*, **1997**, 8, 1623). Gotor and co-workers have prepared (−)-methyl 5-*epi*-shikimate from (−)-quinic acid *via* (−)-methyl shikimate (Fernández, S.; Díaz, M.; Ferrero, M.; Gotor, V. *Tetrahedron Lett.*, **1997**, 38, 5225).

7. REFERENCES AND NOTES

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2. This author, J. F. Eykman, is sometimes referred in the literature as J. F. Eijkman. However, in most reviews and books on this subject his name had unfortunately been misspelled as J. F. Eykmann.
3. *Illicium religiosum* Sieb. et Zucc., synonym *Illicium anisatum* L., is an evergreen tree which is native to China and was introduced into Japan at an early date by Buddhist priests. It is called *Mang ts'ao* (or *Mang cao*) in Chinese, *Shikimi-no-ki* in Japanese, and commonly known as Japanese star anise. In China this poisonous plant has been used locally as a medicine and also used to kill fish. In Japan it is often planted in cemeteries and Buddhist temple grounds as an offering flower and used in religious ceremonies, whence the name *Illicium religiosum*. Sometime, the name *Illicium anisatum* L. was used improperly to refer to the Chinese star anise which should be termed as *Illicium verum* Hook. The Chinese star anise (*Illicium verum* Hook.) and the Japanese star anise (*Illicium religiosum* Sieb. et Zucc., *Illicium anisatum* L.) are different, although their fruits are barely distinguishable. In Asia the fruit of the former is used as a spice, and in the West it is used to aromatise cordials and liqueurs. In the last century, mistaken identity and intentional mixing of the two fruits as an adulterated spice often resulted in many cases of poisoning, which was also the reason behind Eykman's investigation into the chemical constituents of *Illicium religiosum* Sieb. et Zucc. (see: Eykman, J. F. *Pharm. J. Trans.*, **1881**, 11, 1046). Eykman isolated (−)-shikimic acid **1** from the fruit of *Illicium religiosum* Sieb. et Zucc. in 1885 (see: ref. 1), and in the following year he also obtained (−)-shikimic acid **1** from the fruit of *Illicium verum* Hook. which he at that time termed as *Illicium anisatum* in his article (see: Eykman, J. F. *Recl. Trav. Chim. Pays-Bas*, **1886**, 5, 299).
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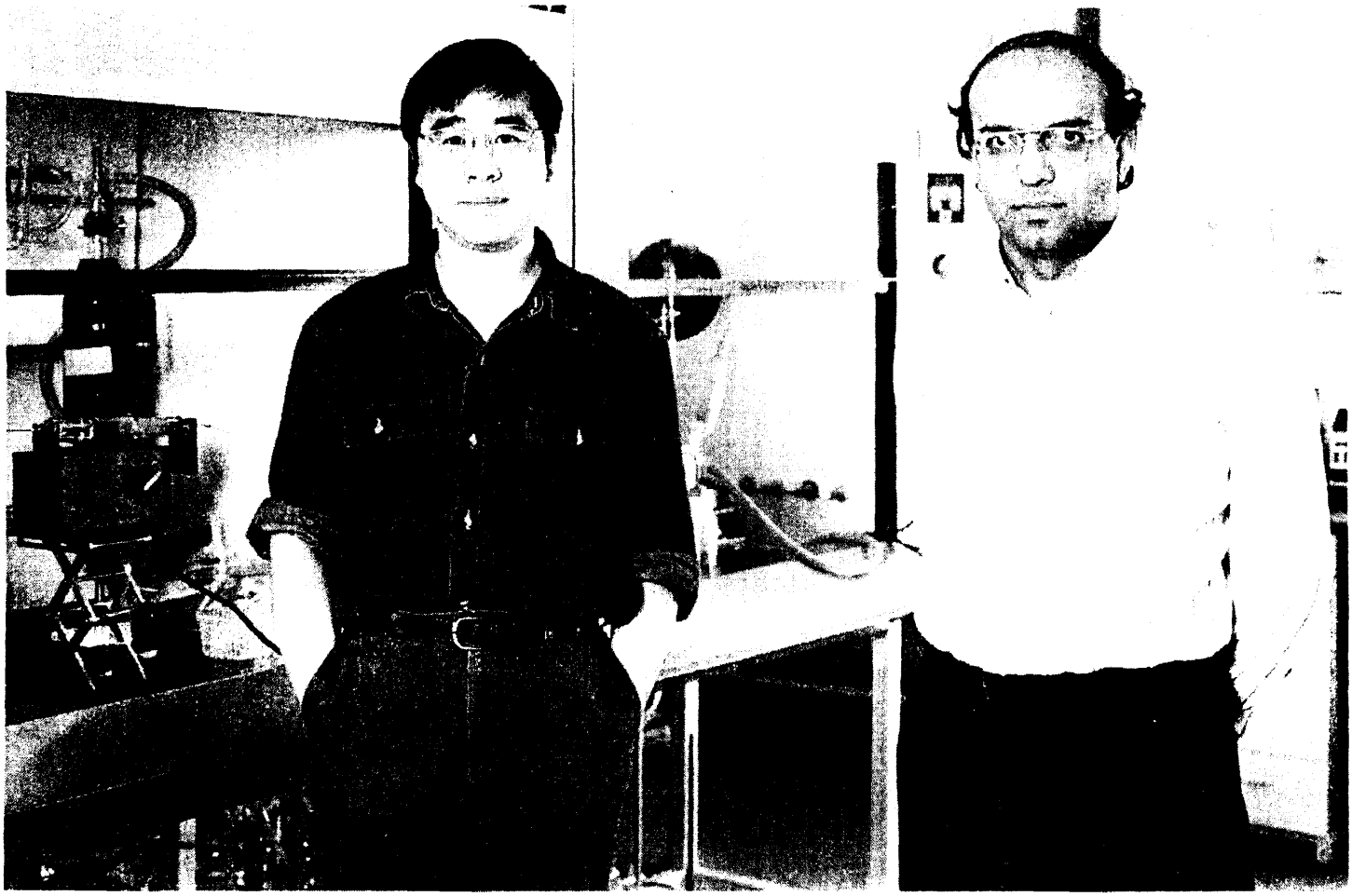
Biographical sketch



Shende Jiang Gurdial Singh

Shende Jiang was born in 1963 in Shandong, China. He studied chemistry (B.Sc. in 1983) at Liaocheng Teachers College and medicinal chemistry (M.Sc. in 1986) under the supervision of Professor Huicai Wang at Shandong Medical University. From 1986 to 1988 he was a lecturer at Shandong Teachers University. He was the recipient of a Leverhulme Trust Fellowship (1988-1991) at the University of Nottingham where he initially conducted research under Professor J. E. Thomas and the late Professor M. D. Stephens on the comparative adult education of China and Japan, and later joined Dr. J. S. Clark's group working on the asymmetric synthesis of heterocycles by sigmatropic rearrangement of ylides generated from rhodium carbenoids. In 1991 he moved to Nottingham Trent University working with Dr. I. G. C. Coutts on the design and synthesis of heterocycles as calmodulin antagonists and a year later he joined Professor G. Singh's group at the University of Teesside working on the synthesis of shikimic acid and analogues from carbohydrates for which he was awarded a Ph.D. in early 1996. He moved with Professor Singh to the University of Sunderland and is currently a postdoctoral research worker.

Gurdial Singh received his B.Sc. (Hons) in chemistry from the University of Liverpool in 1977 and Ph.D. in organic chemistry in 1980 from UMIST under the supervision of Professor R. Ramage working in the area of β-lactam chemistry. After two years of postdoctoral work with Professor M. M. Campbell at the University of Bath as a Pfizer Postdoctoral Fellow, he was appointed lecturer at Heriot-Watt University in 1982. He moved to the University of Teesside in 1984 as senior lecturer in organic chemistry and was promoted to reader in 1991. He assumed his present position as research professor of organic chemistry at the University of Sunderland in 1996. His research interests include peptide synthesis, antibiotics, conducting polymers, shikimate pathway, and natural product synthesis using carbohydrates.