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Enantioselective synthesis of (+)-shikimic acid and (+)-5-*epi*-shikimic acid by asymmetric Diels–Alder reaction of (*S*)-α-sulfinylacrylates

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Abstract: Enantiopure (*S*) benzyl and *t*-butyl 2-*p*-tolylsulfinylpropenoates (**1** and **2**) were readily prepared by Mannich condensation of (*R*) *p*-tolylsulfinylacetates (CH_2O+Me_2NH), followed by *in situ* nitrogen quaternization. These new chiral dienophiles reacted with furan at high pressures (4–13 Kbar) at rt to afford mainly a 2:1 mixture of both *endo* adducts (*endo*-**B**+*endo*-**A**). Enantiopure *endo*-**4B** and *endo*-**4A** were stereoselectively transformed into (+)-shikimic acid and (+)-5-*epi*-shikimic acid respectively, by dihydroxylation of the double bond, removal of the sulfinyl group, basic opening of the oxabicyclic skeleton and hydrolysis of the ester moiety. © 1997 Elsevier Science Ltd

(−)-Shikimic acid is a key biosynthetic intermediate which plays a central role in the biosynthesis of aromatic aminoacids (phenylalanine, tyrosine and tryptophan) and a wide range of secondary metabolites such as folic acid and isoprenoid quinones.[1] As the shikimate pathway is exclusively utilized by plants, fungi and micro-organisms, the discovery of specific enzyme inhibitors could lead to new valuable herbicidal or antibiotic compounds. Owing to this biological significance, in recent years the enantioselective synthesis of shikimic acid, stereoisomers and derivatives has attracted great attention.[2]

In connection with our current interest concerning the use of enantiopure vinyl sulfoxides as versatile dienophiles in asymmetric Diels–Alder reactions,[3] we wish to report a very short synthesis of (+)-shikimic acid and (+)-5-*epi*-shikimic acid based on the Diels–Alder reaction of (*S*)-α-*p*-tolylsulfinyl acrylates[4] with furan (Scheme 1). From the oxanorbornenic adduct, enantiopure shikimic acid could be readily prepared by reductive elimination of the sulfinyl moiety, opening of the oxabicyclic structure and dihydroxylation of the double bond.[5] The inversion of the last two steps, dihydroxylation followed by cleavage of the oxide bridge, could furnish its C-5 epimer. Close to this synthetic approach, but in its racemic version Campbell et al had previously reported the synthesis of (±)-methyl shikimate and stereoisomers from the adducts obtained in the catalyzed Diels–Alder reaction of methyl acrylate with furan.[6]

As depicted in Scheme 2, the (*S*)-α-*p*-tolylsulfinyl acrylates **1** and **2** were readily prepared from the corresponding (*R*)-α-tolylsulfinyl acetates[7] in a *one-pot* experimental procedure. Mannich condensation of the (*R*)-sulfinyl acetates (CH_2O, Me_2NH, CH_3CN, rt) and further *in situ* nitrogen quaternization (MeI, $CaCO_3$, CH_3CN, rt) afforded acrylates **1** and **2** in reasonable yields after chromatography (55% and 53% respectively). The enantiomeric excess of both dienophiles, determined by ^1H NMR in the presence of Eu(hfc)$_3$, was very high (ee≥98%).

All our attempts to achieve the Diels–Alder reaction of dienophiles **1** and **2** with furan under thermal or Lewis acids catalyzed conditions were completely unsuccessful. In the absence of Lewis acid no reaction was observed at all, whereas in the presence of ZnI_2[8] or $TiCl_4$[9] a slow decomposition of the dienophile was observed. On the contrary, this cyclization took place cleanly at high pressures (4–13 kbar in CH_2Cl_2) in the absence of catalysts.[10] In Table 1 are summarized the most significant results.

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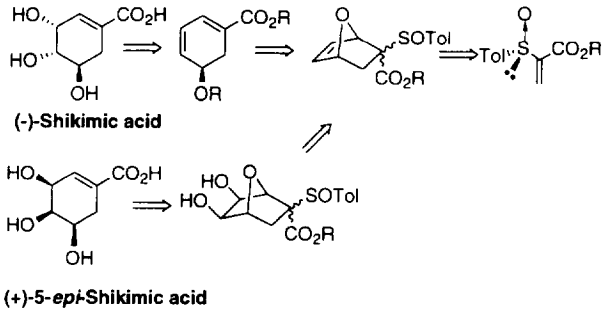
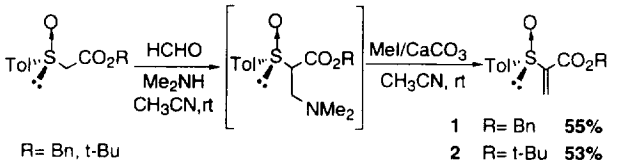
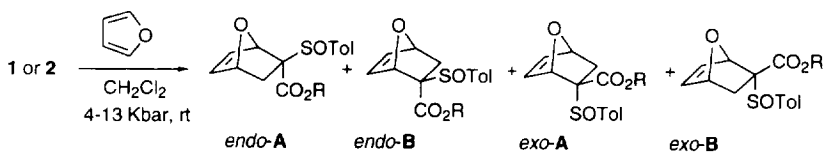


Scheme 1.



Scheme 2.

Table 1. Diels–Alder reactions of dienophiles **1** and **2** with furan at high pressures



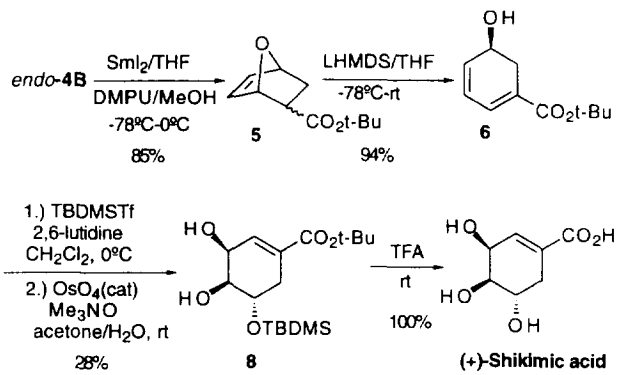
Entry	Dienophile	R	Adduct	P (Kbar)[a]	t (h)	Conversion (%)[b]	product ratio[b] *endo*-**A**/*endo*-**B**/*exo*-**A**/*exo*-**B**
1	**1**	Bn	**3**	13	24	95	24/44/11/21
2	**1**	Bn	**3**	4	72	68	34/66/--/--[c]
3	**2**	t-Bu	**4**	13	24	95	24/44+*bis*-adducts
4	**2**	t-Bu	**4**	8	6	90	22/45/15/18
5	**2**	t-Bu	**4**	4	17	60	29/44/12/15
6	**2**	t-Bu	**4**	4	120	65	29/59/4/8

[a]CH_2Cl_2 as solvent except for entries 4 and 6 (furan as solvent). [b]Determined by ^1H NMR.
[c]The *exo* adduct ratio could not be evaluated.

The cycloaddition was in all cases moderately stereoselective, giving a mixture of the four possible adducts, predominating the *endo* adducts[11] (*endo* **A**+*endo* **B**). Interestingly, the ratio *endo*-**B**/*endo*-**A**=2:1 remained practically unchanged regardless the dienophile and pressure used. Although conversions at 13 kbar are higher than at 4 kbar (compare entries 1–2 and 3–4), the formation at 13 Kbar of significant amounts of *bis*-adducts makes difficult the further adduct purification and decreases the yield.[12] Also we observed that adducts **3** were very prone to give the retro-Diels–Alder reaction at atmospheric pressure. In fact, even when the mixture of adducts **3** obtained after cycloaddition was immediately purified by flash chromatography at low temperature (0°C) the dienophile **1** was mostly

recovered. Fortunately the stability of adducts **4** is much higher, both major adducts, *endo*-**4A** and *endo*-**4B**, can be separated by flash chromatography at 0°C and stored at −20°C for weeks. On the other hand, the spontaneous retro-Diels–Alder reaction at atmospheric pressure that the adducts **3** and **4** suffer would explain the failure of all the Diels–Alder reaction trials carried out under thermal or catalyzed conditions.

In Scheme 3 is summarized the transformation of *endo*-**4B** to (+)-shikimic acid. Reductive elimination of the sulfinyl group with SmI_2 took place without cleavage of the contiguous C–O bond, affording the enantiopure oxanorbornene **5** in excellent yield (85%).[13] **5** was converted to the (+)-*t*-butyl shikimate **8** (28% overall yield)[14] according to the procedure reported by Campbell in their racemic synthesis of related compounds:[6a] cleavage of the oxide bridge by reaction with LHMDS in THF at −78°C, protection of the resulting cyclohexadienol **6** as its TBDMS derivative **7** (TBDMSTf, lutidine, CH_2Cl_2, 0°C) and stereoselective dihydroxylation with OsO_4 (cat)/Me_3NO gave the diol **8**. Finally, the deprotection of the *t*-butyl ester and the silyl ether was carried out simultaneously by treatment with TFA at rt to afford enantiomerically pure (+)-shikimic acid.[15]



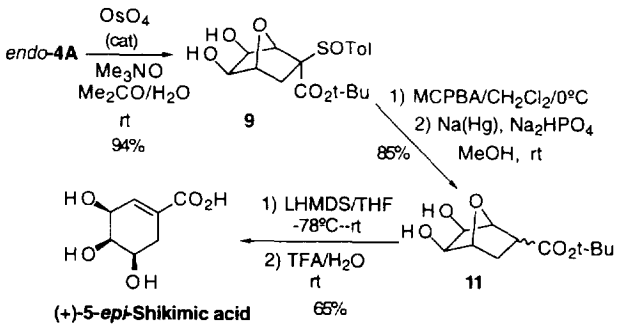
Scheme 3.

In a similar way, carrying out firstly the dihydroxylation reaction and secondly the opening of the bicyclic skeleton, *endo*-**4A** was converted to (+)-5-*epi*-shikimic acid (Scheme 4). Like in other oxanorbornens,[4b,6a] *cis* dihydroxylation of *endo*-**4A** with OsO_4 (cat)/Me_3NO afforded a single diol **9**. As the direct desulfinylation of **9** with SmI_2 and Al(Hg) occurred with poor yields, **9** was oxidized with MCPBA (CH_2Cl_2, 0°C) to the corresponding sulfone **10** and then desulfonylated by treatment with Na(Hg) (Na_2HPO_4, MeOH, rt). Thus, diol **11** was obtained as a mixture of *endo*+*exo* isomers in 85% yield after purification. Finally, opening of the oxanorbornane skeleton with LHDMS (3 equiv, THF, −78°C) and deprotection of the *t*-butyl ester (TFA, H_2O, rt) afforded cleanly enantiopure (+)-5-*epi*-shikimic acid[16] (52% overall yield for the sequence shown in Scheme 4).

In summary (+)-shikimic acid[17] and (+)-5-*epi*-shikimic acid were enantioselectively prepared in few steps from the *endo* adducts obtained in the Diels–Alder reactions performed at high pressure of enantiopure α-sulfinyl acrylates with furan.

Experimental

Melting points are uncorrected. ^1H NMR (200, 300 MHz) spectra and ^{13}C NMR (50 MHz) spectra were recorded in $CDCl_3$. Both chemical shifts (ppm downfield from internal tetramethylsilane) and coupling constants (Hz) were obtained by first order analysis of spin patterns. Mass spectra (MS) were recorded with electron impact (EI, 70 eV). Mass data are reported in mass units (*m/z*), and the values in brackets report the relative intensity from the base peak (as 100%). High-resolution mass spectra were determined at an ionizing voltage of 70 eV. High pressure reactions were performed in a UNIPRESSEQUIPMENT 101 LV 30/16 in polyethylene vials.



Scheme 4.

Analytical thin-layer chromatography was performed on DC-Alufolien 0.2 mm silica gel 60-F plates (MERCK). Visualization was accomplished with UV light and ethanolic phosphomolybdic acid solution followed by heating. Flash chromatography was performed by using silica gel (MN-Kieselgel 60, 230–400 mesh). All solvents were dried before use. THF and Et_2O were distilled from sodium-benzophenone under argon. CH_2Cl_2 and $CHCl_3$ were distilled from P_2O_5. DMPU and MeOH were distilled from CaH_2, 2,6-lutidine was distilled from KOH.

Adducts *endo*-**3A** and *endo*-**3B** have been only described with ^1H NMR due to their rapid retro Diels–Alder reaction.

(S) Benzyl 2-p-tolylsulfinylpropenoate ***1***

To a solution of (+)-(*R*)-benzyl *p*-tolylsulfinylacetate[3j] (756 mg, 2.62 mmol, 1.0 equiv) in CH_3CN (15 ml) cooled to 0°C were added, sequentially, HMe_2N (40% H_2O) (986 µl, 7.86 mmol, 3.0 equiv) and HCHO (37% H_2O) (590 µl, 7.86 mmol, 3.0 equiv). The mixture was stirred at 0°C for 6 h, and then H_2O was added (20 ml). The solution was extracted with CH_2Cl_2 (3×50 ml) and the combined organic layer were dried ($MgSO_4$) and concentrated. The residue was dissolved in CH_3CN (15 ml) and iodomethane (815 µl, 13.1 mmol, 5.0 equiv) and $CaCO_3$ (787 mg, 7.86 mmol, 3.0 equiv) were added. The mixture was stirred for 8 h at rt. Then, H_2O (20 ml) was added and the solution was extracted with CH_2Cl_2 (3×50 ml). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (hexane–ethyl acetate 3:1) to give 417 mg of **1** as a yellow oil. Yield: 55%. $[\alpha]_D^{20}$=+173.2 (c=1.0, $CHCl_3$), ee≥97% [by using Eu(hfc)$_3$ as chiral shift reagent]. IR ($CHCl_3$): 3010, 2980, 1710, 1595, 1490, 1440, 1375, 1270, 1220, 1110, and 1040 cm^{-1}. ^1H NMR δ: 2.37 (s, 3H), 5.05 and 5.17 (AB system, 2H, J=12.2 Hz), 6.80 (s, 1H), 6.89 (s, 1H), 7.17 (half of an AA′BB′ system, 2H), 7.20–7.34 (m, 5H) and 7.51(half of an AA′BB′ system, 2H). ^{13}C NMR δ: 21.2, 67.0, 125.9, 128.2, 128.3, 129.6, 134.4, 139.4, 142.1, 147.1 and 162.1. MS (EI): 300 (5.7, M^+), 252 (3.0), 149 (6.3), 140 (24.3), 139 (23.6), 117 (9.4), 91 (100.0), and 77 (9.3). HRMS: exact mass calcd for $C_{17}H_{16}O_3S$ (M^+) 300.0820, found 300.0821.

(S) t-Butyl 2-p-tolylsulfinylpropenoate ***2***

To a solution of (*R*) *t*-Butyl *p*-tolylsulfinylacetate[18] (1.64 g, 6.46 mmol, 1.0 equiv) in CH_3CN (31 ml) cooled to 0°C were added, sequentially, HMe_2N (40% H_2O) (2.1 ml, 19.4 mmol, 3.0 equiv) and HCHO (37% H_2O) (1.5 ml, 19.4 mmol, 3.0 equiv). The mixture was stirred at 0°C for 6 h, and then H_2O was added (20 ml). The solution was extracted with CH_2Cl_2 (3×50 ml) and the combined organic layer were dried ($MgSO_4$) and concentrated. The residue was dissolved in CH_3CN (31 ml) and iodomethane (2 ml, 32.3 mmol, 5.0 equiv) and $CaCO_3$ (1.94 g, 19.4 mmol, 3.0 equiv) were added. The mixture was stirred for 5 h at rt. Then, H_2O (30 ml) was added and the solution was extracted with CH_2Cl_2 (3×100 ml). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (hexane–ethyl acetate 4:1) to give 417 mg of **1** as a white solid. Yield: 53%. mp: 37–38°C. $[\alpha]_D^{20}$=+224.8 (c=1.57, $CHCl_3$), ee≥97% [by using Eu(hfc)$_3$

as chiral shift reagent]. IR ($CHCl_3$): 3030, 2980, 1700, 1370, 1290, 1260, 1120, 1040, 970, and 840. ^1H NMR ($CDCl_3$) δ:1.34 (s, 9H), 2.39 (s, 3H), 6.70 (s, 1H), 6.82 (s, 1H), 7.27 (half of an AA′BB′ system, 2H) and 7.58 (half of an AA′BB′ system, 2H). ^{13}C NMR ($CDCl_3$) δ: 21.3, 27.6, 83.1, 126.2, 127.4, 129.6, 139.7, 142.2, 148.2, and 160.7.MS (EI): 266 (10.9, M^+), 210 (34.6), 162 (60.3), 149 (33.7), 139 (100.0), 123 (23.0), 91 (37.8), 77 (13.2), 65 (25.0), and 57 (90.7). HRMS: exact mass calcd for $C_{14}H_{18}O_3S$ (M^+) 266.0976, found 266.0977.

General procedure for the Diels–Alder reactions of ***1*** *and* ***2*** *with furan under high pressures*

In a polyethylene high pressure tube were placed dienophile **1** or **2** (150–200 mg) in furan (1 ml). The reaction was pressured at 4 Kbar for 5 days at rt. Then, the mixture was carefully concentrated (without heating) and the residue was immediately analyzed by ^1H NMR. The mixture of adducts **3** or **4** (mainly *endo* adducts) was purified by flash chromatography at low temperature (0–5°C) (hexane–ethyl acetate 4:1). Conversion=60–65%. For the ratio of isomers see Table 1.

*(R_1,S_2,R_4,S_S) 2-Benzyl 2-*p*-tolylsulfinyl-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylate* endo-***3A***

^1H NMR ($CDCl_3$) δ: 1.90 (d, 1H, J=12.5 Hz), 2.39 (s, 3H), 2.78 (dd, 1H, J=4.7 y 12.6 Hz), 4.81 (AB system, 2H, J=12.4 Hz), 5.15 (m, 1H), 5.27 (m, 1H), 6.17 (dd, 1H, J=5.6 y 1.8 Hz), 6.65 (dd, 1H, J=1.8 and 5.6 Hz), 7.29 (half of an AA′BB′ system, 2H, J=8.1 Hz) and 7.55 (half of an AA′BB′ system, 2H).

*(S_1,R_2,S_4,S_S) 2-Benzyl 2-*p*-tolylsulfinyl-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylate* endo-***3B***

^1H NMR ($CDCl_3$) δ: 1.93 (d, 1H, J=12.5 Hz), 2.15 (dd, 1H, J=4.7 and 12.5 Hz), 2.37 (s, 3H), 4.71 y 4.87 (AB system, 2H, J=12.1 Hz), 5.18 (bd, 1H, J=7.2 Hz), 5.64 (d, 1H, J=1.1 Hz), 6.15 (dd, 1H, J=1.7 and 5.6 Hz), 6.53 (dd, 1H, J=1.6 and 5.5 Hz), 7.17–7.35 (m, 7H) and 7.45 (half of an AA′BB′ system, 2H).

*(R_1,S_2,R_4,S_S) 2-t-Butyl 2-*p*-tolylsulfinyl-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylate* endo-***4A***

$[\alpha]_D^{20}$=−124.5 (c=1, $CHCl_3$). IR ($CHCl_3$): 2960, 1710, 1360, 1270, 1150, 1050, 910 and 840. ^1H NMR ($CDCl_3$) δ:1.26 (s, 9H), 1.95 (d, 1H, J=12.6 Hz), 2.41 (s, 3H), 2.73 (dd, 1H, J=4.7 and 12.6 Hz), 5.15 (dd, 1H, J=4.7 and 1.8 Hz), 5.29 (dd, 1H, J=1.8 Hz), 6.27 (dd, 1H, J=1.8 and 5.6 Hz), 6.56 (dd, 1H, J=1.8 and 5.6 Hz), 7.29 (half of an AA′BB′ system, 2H) and 7.55 (half of an AA′BB′ system, 2H, J=8.2 Hz). ^{13}C NMR ($CDCl_3$): 21.6, 27.5, 29.7, 76.6, 79.3, 82.6, 125.9, 129.2, 132.9, 137.9, 140.1, 142.3 and 165.6. HRMS: exact mass calcd for $C_{18}H_{22}O_4S$ (M^+) 334.1239, found 334.1239.

*(S_1,R_2,S_4,S_S) 2-t-Butyl 2-*p*-tolylsulfinyl-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylate* endo-***4B***

$[\alpha]_D^{20}$=+33.25 (c=1.2, $CHCl_3$). IR ($CHCl_3$): 2990, 1710, 1370, 1240, 1150, 1050, 910 and 840. ^1H NMR ($CDCl_3$) δ: 1.26 (s, 9H), 1.82 (d, 1H, J=12.5 Hz), 2.15 (dd, 1H, J=4.7 and 12.5 Hz), 2.37 (s, 3H), 5.10 (dd, 1H, J=1.1 and 4.7 Hz), 5.54 (d, 1H, J=1.1 Hz), 6.32 (dd, 1H, J=1.8 y 5.7 Hz), 6.53 (dd, 1H, J=1.8 and 5.7 Hz), 7.25 (half of an AA′BB′ system, 2H) and 7.52 (half of an AA′BB′ system, 2H). ^{13}C NMR ($CDCl_3$) δ:21.1, 27.6, 32.1, 79.6, 79.8, 82.2, 125.1, 129.2, 133.0, 137.1, 139.3, 141.6 and 165.0. MS (EI): 334 (0.2, M^+), 266 (11.0), 210 (38.0), 193 (22.1), 162 (61.4), 139 (98.0), 123 (24.6), 91 (42.7), 77 (16.0) and 57 (100.0). HRMS: exact mass calcd for $C_{18}H_{22}O_4S$ (M^+) 334.1239, found 334.1238.

(S_1,S_4) t-Butyl 7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylate endo-***5***+exo-***5***

To a solution of *endo*-**4B** (440 mg, 1.32 mmol, 1.0 equiv) in THF (10 ml) cooled to −78°C and under argon atmosphere, were added sequentially MeOH (270 μl, 6.60 mmol, 5.0 equiv), DMPU (794 μl, 6.60 mmol, 5.0 equiv) and freshly prepared SmI_2 0.1M (51 ml, 5.1 mmol, 4.0 equiv). The mixture was stirred for 1 h and was allowed to stand at 0°C. Then, a solution of 30% Na_2SO_3 (40 ml) was added, and the mixture was extracted with CH_2Cl_2 (3×50 ml). The combined organic layers were dried and concentrated. The residue was purified by flash chromatography (hexane–ethyl acetate 8:1) to give 220 mg of **5** as a yellow oil. Yield: 85%. IR ($CHCl_3$): 2940, 1710, 1450, 1370, 1220, 1150,

1020, 900 and 850 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.38 (s, 3H), 1.44 (s, 9H), 1.50 (m, 2H), 2.00 (m, 2H), 2.30 (dd, 1H, J=3.9 Hz, H_{2exo}), 3.01 (m, 1H, H_{2endo}), 4.9 5.1 (m, 4H), 6.19 (dd, 1H, J=1.4 and 5.8 Hz, H_{5endo}), 6.32 (m, 2H, H_5 and $_{6exo}$) and 6.40 (dd, 1H, J=1.7 and 5.8 Hz, H_{6endo}). ^{13}C NMR ($CDCl_3$) δ: 27.7, 28.0, 43.4, 43.6, 77.7, 78.6, 78.8, 80.3, 80.8, 132.1, 134.5, 136.7, 171.0 and 172.8. MS (EI): 196 (0.1, M^+), 140 (9.1), 123 (6.3), 68 (100.0) and 57 (48.0).

(S) t-Butyl 5-hydroxy-1,3-cyclohexadien-1-carboxylate ***6***

A solution of **5** (220 mg, 1.12 mmol, 1.0 equiv) in THF (6 ml) was added dropwise, under argon atmosphere, to a freshly prepared solution of 0.5 M LHMDS (2.5 ml, 1.23 mmol, 1.1 equiv) in THF at −78°C. The reaction mixture was stirred for 2 h and was allowed to stand at rt. Then, saturated NH_4Cl (2 ml) was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3×10 ml). The combined organic layer was dried and concentrated. The residue was purified by flash chromatography (hexane–ethyl acetate 3:1) to give 206 mg of **6** as a colorless oil. Yield: 94%. $[\alpha]_D^{20}$=−120.8 (c=2.1, EtOH). IR ($CHCl_3$): 3590, 2940, 1630, 1370, 1290, 1160, 1010 and 850 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.49 (s, 9H), 2.59 (ddd, 1H, J=2.3, 7.4 and 18.8 Hz), 2.89 (ddd, 1H, J=1.0, 5.3 and 18.8 Hz), 4.38 (m, 1H), 6.22 (m, 2H) and 7.00 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 27.9, 30.8, 63.1, 80.3, 124.3, 128.3, 130.5, 133.1 and 166.2. MS (EI): 194 (8.7, M^+-2), 140 (28.6), 138 (41.4), 121 (28.1), 111 (8.7), 95 (27.4) and 57 (100.0). HRMS: exact mass calcd for $C_7H_8O_3$ (M^+-t-Bu) 140.0473, found 140.0460.

(S_3,S_4,S_5) t-Butyl 5-t-butyldimethylsilyloxy-3,4-dihydroxy-1-cyclohexen-1-carboxylate ***8***

t-Butyldimethylsilyltriflate (185μl, 0.80 mmol, 1.4 equiv) was added to 2,6-lutidine (144 μl, 1.23 mmol, 2.1 equiv) at 0°C and the mixture stirred for 30 min. A solution of **6** (112 mg, 0.57 mmol, 1.0 equiv) in CH_2Cl_2 (1.4 ml) was added dropwise and the mixture stirred for further 30 min. Then, the reaction mixture was poured into ice and a saturated solution of $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×5 ml). The combined organic layer was dried and concentrated to yield **7** as an oil being used directly in the next step. ^1H NMR ($CDCl_3$) δ: 0.03 (s, 6H), 0.88 (s, 9H), 1.49 (s, 9H), 2.59 (dd, 2H, J≃1.7 and 9.0 Hz), 4.51 (dt, 1H, J=2.1 and 8.9 Hz), 6.02 (m, 2H) and 6.90 (m, 1H). The crude was dissolved in a mixture of acetone (5 ml) and water (0.7 ml). Then, OsO_4 (114 μl, 4% solution in H_2O) and Me_3NO (73 mg, 0.66 mmol) were added and the reaction mixture was left stirring overnight. Then, Na_2SO_3 was added and the mixture was concentrated and purified by flash chromatography (hexane–ethyl acetate 4:1) to give 34 mg of **8** as a colorless oil. Overall yield 28%. $[\alpha]_D^{20}$=+86.15 (c=0.26, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 0.11 (s, 6H), 0.89 (s, 9H), 1.48 (s, 9H), 2.14 (bdd, 1H, J=3.5 and 9.0 Hz), 2.69 (dd, J=3.1 and 9.4 Hz), 3.62 (ddd, J=1.9, 4.2 y 6.2 Hz), 4.04 (m, 1H), 4.48 (c, 1H, J=4.0 Hz) and 6.78 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 18.0, 25.7, 28.0, 32.4, 65.9, 68.2, 72.9, 80.9, 132.4, 134.3 and 165.5. MS (EI): 345 (2.4,M^++1), 231 (12.7), 213 (100.0) and 195 (5.8).

(+)-Shikimic acid

To a solution of **8** (25 mg, 0.07 mmol, 1.0 equiv) in CH_2Cl_2 (1 ml) was added dropwise TFA (140 μl) at rt. The reaction mixture was stirred for 15 min and then, water (2 ml) was added. The aqueous layer was separated and concentrated to give 12.1 mg of (+)-shikimic acid. Yield: 100%. $[\alpha]_D^{20}$=+154.4 (0.68, H_2O); $[\alpha]_D^{20}$ lit. (−)-shikimic acid=−179.7 (4.40, H_2O).[15] ^1H NMR (300 MHz, D_2O) δ: 2.20 (ddt, 1H, J=2.0, 6.4 and 17.8 Hz), 2.72 (ddt, 1H, J=1.6, 5.2 y 18.2 Hz), 3.75 (dd, 1H, J=4.2 and 8.2), 4.01 (m, 1H), 4.43 (m, 1H), 6.81 (q, 1H, J=1.8). ^{13}C NMR (D_2O) δ: 30.2, 65.7, 66.5, 70.9, 129.6, 137.2 and 170.0.

*(R_1,S_2,R_4,R_5,R_6,S_S) t-Butyl 5,6-dihydroxy-7-oxa-2-*p*-tolylsulfinylbicyclo[2.2.1]heptan-2-carboxylate* ***9***

To a solution of adduct *endo*-**4A** (200 mg, 0.6 mmol, 1.0 equiv) in acetone (4.5 ml) and H_2O (0.5 ml), were added sequentially, Me_3NO (74 mg, 0.66 mmol, 1.1 equiv) and OsO_4 (106 μl, 4%

solution in H_2O). The mixture was stirred for 4 h at rt. Then, Na_2SO_3 was added and the mixture was stirred for 30 min. The reaction mixture was concentrated and purified by flash chromatography (ethyl acetate) to give 207.5 mg of **9**. Yield: 94%. $[\alpha]_D^{20}$=+40.0 (c=1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 1.31 (s, 9H), 1.96 (d, 1H, J=13.8 Hz), 2.39 (s, 3H), 2.63 (dd, 1H, J=6.0 and 13.8 Hz), 3.25 (bs, 2H), 3.92 (bc, 2H, J=5.7), 4.55 (bd, 1H, J=5.7), 4.74 (bs, 1H), 7.27 (half of an AA′BB′ system, 2H) and 7.49 (half of an AA′BB′ system, 2H). ^{13}C NMR ($CDCl_3$) δ: 23.45, 29.3, 29.4, 73.1, 74.4, 76.3, 84.1, 84.6, 87.5, 125.7, 129.1, 136.8, 142.2 and 164.1. MS (EI): 312 (2.6, M^+−*t*-Bu+1), 173 (7.4), 139 (60.3), 124 (9.7), 113 (54.8), 95 (100.0), 77 (23.1) and 57 (98.7). HRMS: exact mass calcd for $C_{14}H_{16}O_6S$ (M^+−*t*-Bu+1) 312.0667, found 312.0660.

(R_1,S_2,R_4,R_5,R_6) t-*Butyl 5,6-Dihydroxy-7-oxa-2*-p-*tolylsulfonylbicyclo [2.2.1]heptan-2-carboxylate* ***10***

To a suspension of MCPBA (55–65% in water, 1.1 equiv) in CH_2Cl_2 (1 ml) at 0°C, was added a solution of diol **9** (207 mg, 0.56 mmol, 1.0 equiv) in CH_2Cl_2. The mixture was stirred for 1 h. Then, 50% Na_2SO_3 (2 ml) was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×5 ml). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was used without further purification. Yield: 94%. ^1H NMR ($CDCl_3$) δ: 1.49 (s, 9H), 2.25 (d, 1H, J=13.8 Hz), 2.49 (s, 3H), 2.74 (dd, 1H, J=6.0 and 13.8 Hz), 3.87 (c, 2H, J=5.6 Hz), 4.47 (d, 1H, J=6.0 Hz), 7.53 (AA′BB′, 2H, arom). ^{13}C NMR ($CDCl_3$) δ: 21.5, 27.4, 30.9, 72.1, 73.5, 79.4, 83.0, 84.7, 85.7, 129.9, 130.2, 134.8, 145.4 and 164. MS (EI): 328 (1.3, M^+−*t*-Bu+1), 293 (13.2), 225 (10.3), 173 (55.0), 155 (55.0), 139 (50.8), 113 (59.8), 91 (74.1) and 57 (98.7). HRMS: exact mass calcd for $C_{14}H_{16}O_7S$ (M^+−*t*-Bu+1) 328.0617, found 328.0612.

(S_1,R_4,R_5,R_6) t-*Butyl 5,6-dihydroxy-7-oxabicyclo[2.2.1]heptan-2-carboxylate* ***11***

To a solution of sulfone **10** (48 mg, 0.12 mmol, 1.0 equiv) in MeOH (2 ml) were added Na_2HPO_4 (0.48 mmol, 4.0 equiv) and 6% Na(Hg) in excess, at rt and under argon atmosphere. The mixture was stirred for 3 h. Then, H_2O (2 ml) was added. The aqueous layer is extracted with CH_2Cl_2 (3×10 ml) and the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by preparative chromatography (eluent: ethyl acetate) to give 26.6 mg of **11** as an equimolecular mixture of epimers at C_2. Yield: 85%. ^1H NMR ($CDCl_3$): *endo*-**11**: 1.45 (s, 9H), 1.78 (m, 2H), 2.88 (m, 1H), 3.4 (bs 2H), 3.94 (m, 2H), 4.39 (m, 2H) and 4.47 (m, 1H). *exo*-**11**: 1.44 (s, 9H), 1.54 (dd, 1H, J=9.1 and 13.0 Hz), 2.01 (m, 1H), 2.41 (dd, 1H, J=4.8 and 9.1 Hz), 3.4 (bs, 2H), 3.86 (m, 2H), 4.39 (m, 2H) and 4.55 (s, 1H). ^{13}C NMR ($CDCl_3$): 22.3, 23.0, 38.1, 39.1, 66.1, 68.4, 68.5, 70.7, 71.3, 72.0, 75.4, 78.7, 165.0 and 166.2. MS (EI): 174 (25.3 M^+−*t*-Bu+1), 156 (33.4), 138 (25.5), 115 (26.8), 97 (48.2) and 57 (100.0). HRMS: exact mass calcd for $C_7H_{10}O_5$ (M^+−*t*-Bu+1) 174.0528, found 174.0528.

(S_3,R_4,R_5)-t-*Butyl-3,4,5-trihydroxy-1-cyclohexen-1-carboxylate* ***12***

The experimental procedure was the same as in the case of compound **6**. Yield: 65%. $[\alpha]_D^{20}$=+43.0 (c=1.0, $CHCl_3$). ^1H NMR (D_2O): 1.51 (s, 9H), 2. 39 (ddt, 1H, J=3.0, 7.9 and 17.2 Hz), 2.52 (bdd, 1H, J=6.1 and 17.2 Hz), 3.34 (m, 1H), 3.80 (d, 1H, J=1.9 Hz), 3.83 (d, 1H, J=1.9 Hz), 3.87 (d, 1H, J=1.9 Hz), 3.83 (m, 1H), 3.97 (m, 1H), 4.33 (m, 1H) and 6.61 (m, 1H). ^{13}C NMR (acetone-d_6): 7.4, 8.5, 47.3, 47.5, 50.1, 59.6, 109, 116.9 and 145.2. MS (EI): 174 (6.5 M^+−*t*-Bu+1), 157 (22.1), 138 (13.7), 115 (11.3), 97 (24.9) and 57 (100.0). HRMS: exact mass calcd for $C_7H_{10}O_5$ (M^+−*t*-Bu+1) 174.0528, found 174.0529.

*(+)-5-*epi-*Shikimic acid*

$[\alpha]_D^{20}$=+51.0 (0.3, MeOH). $[\alpha]_D^{20}$ lit. (−)-isomer[16]=−57.6 (c=0.8, MeOH). ^1H NMR (D_2O): 2.06 (ddt, 1H, J=17.1, 7.8 and 3.0 Hz), 2.40 (bdd, 1H, J=17.0 and 6.1 Hz), 3.78 (dd, J=7.8, 1.6 Hz), 3.87 (m, 1H), 4.29 (m, 1H) and 6.52 (m, 1H).

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5. During the preparation of this article, Evans and col. have just published a highly efficient enantioselective synthesis of (+)-shikimic acid based on the Diels–Alder reaction between acryloyl oxazolidinone and furan, catalyzed by a homochiral bis (4-*tert*-butyloxazoline) Cu(II) complex. See Evans, D. A.; Barnes, D. M. *Tetrahedron Lett.* **1997**, *38*, 57.
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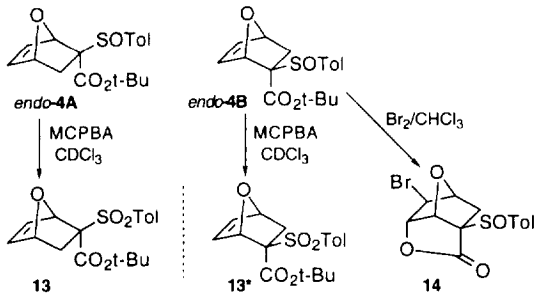
7. The enantiopure (*R*) benzyl or *t*-butyl sulfinylacetates were prepared by Andersen reaction of the magnesium enolate of benzyl or *t*-butyl acetate with (*S*)-menthyl *p*-toluenesulfinate as it is described in ref. 3j (for the preparation of (*S*)-menthyl *p*-toluenesulfinate, see: Solladie, G. *Synthesis* **1981**, 185). As both enantiomers of menthol are commercially available, the sulfinylacetates of (*S*) configuration can be equally prepared from (*R*)-menthyl *p*-toluenesulfinate.
8. ZnI_2 is usually used as catalyst in the Diels–Alder reaction of acrylates with furan (see ref. 6a).
9. According with our previous work on the Diels–Alder reaction of vinylsulfoxides, $TiCl_4$ is by far the most effective catalyst for the cycloadditions of sulfinyl maleates and sulfinyl trialkoxycarbonyl ethenes (see refs 3d and 3j).
10. Decomposition was observed in the Diels–Alder reactions carried out at high pressure in the presence of ZnI_2.
11. The *endo*-configuration of adducts *endo*-**4A** and *endo*-**4B** have been chemically proved by their oxidation with m-CPBA (CH_2Cl_2, 0°C) to both enantiomers of the same sulfone **13** and by intramolecular bromolactonization (Br_2, $CHCl_3$, rt) of *endo*-**4B** to give bromolactone **14**.



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13. Arai, Y.; Matsui, M.; Koizumi, T. *J. Chem. Soc. Perkin Trans. I*, **1990**, 1233.
14. This moderate overall yield is mainly due to the competitive formation of *t*-butyl benzoate as a result of the aromatization of **6** and **7**. Very similar yields have been reported for related cyclohexadienols (see ref. 6).
15. (+)-Shikimic acid $[\alpha]_D^{20}$ exp.=+154.4 (0.68, H_2O); (+)-shikimic acid $[\alpha]_D^{20}$ lit.=−179.7 (4.40, H_2O); Pawlak, J. L.; Berchtold, G. A. *J. Org. Chem.* **1987**, *52*, 1765. The difference between the experimental and literature values of optical rotation can be explained as a consequence of the concentration of the samples.
16. (+)-5-*epi*-Shikimic acid, $[\alpha]_D^{20}$ exp.=−51.0 (c 0.3, MeOH); (−)-5-*epi*-shikimic acid, $[\alpha]_D^{20}$ lit.=−57.6 (c 0.8, MeOH); Jiang, S.; Mekki, B.; Singh, G.; Wightman, R.H. *Tetrahedron Lett.* **1994**, *35*, 5505.
17. Although this publication describes the enantioselective synthesis of (+)-shikimic acid, the non natural enantiomer, the synthesis of the natural (−)-enantiomer and its corresponding (−)-C-5 epimer would be accomplished in an identical way starting from (*R*) *t*-butyl α-*p*-tolylsulfinylacrylate instead of its (*S*)-enantiomer. To this effect it is important to note that both enantiomeric dienophiles are equally available (see ref. 7).
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