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A NEW SYNTHETIC ROUTE TO METHYL (-)-SHIKIMATE BY ASYMMETRIC
DIELS-ALDER REACTION OF (S)_S-3-(2-PYRIDYLSULFINYL)ACRYLATE

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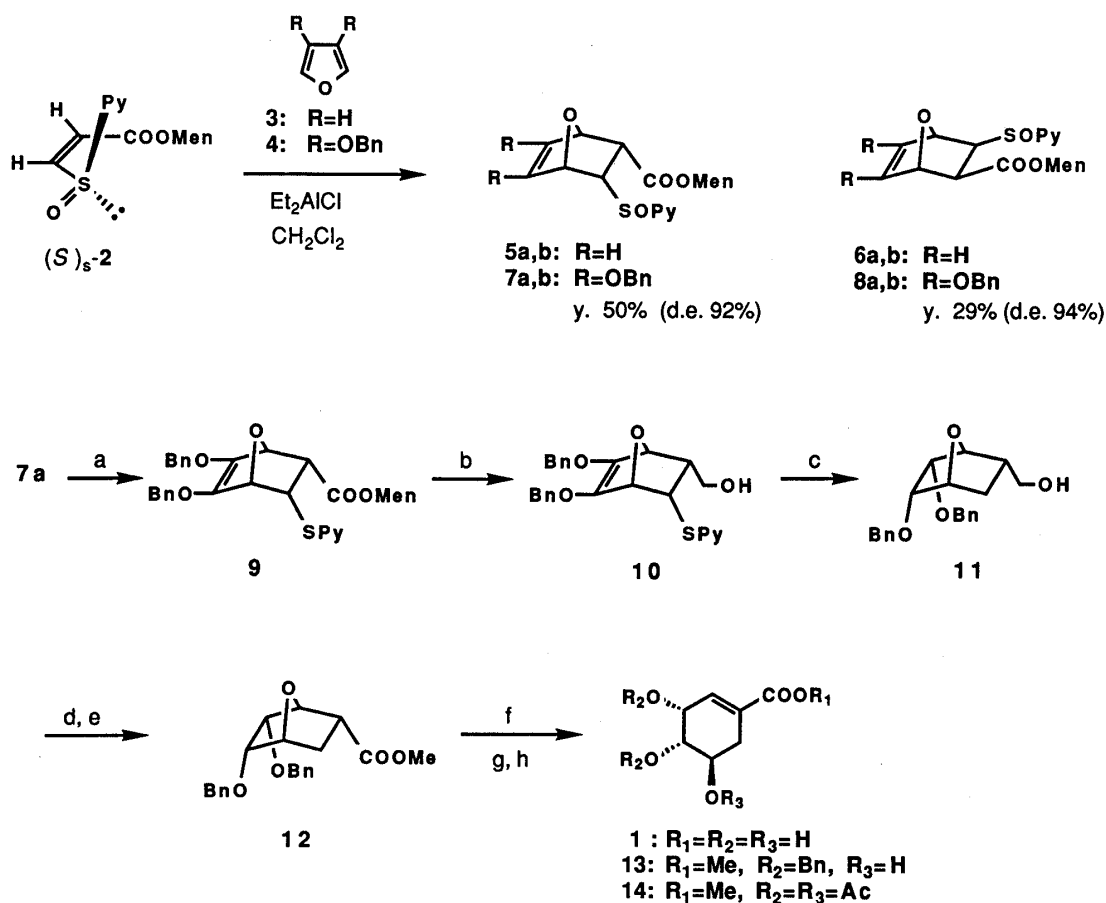
A 7-oxabicyclo[2.2.1]heptene derivative (7a) that substituted effectively for the synthesis of (-)-shikimic acid was prepared by an asymmetric Diels-Alder reaction of (S)_S-3-(2-pyridylsulfinyl)acrylate (2) with 3,4-dibenzyloxyfuran (4). The bicyclic compound (7a) was converted to methyl (-)-triacetylshikimate (14) via the endo-cis dibenzyloxy derivative (11).

KEYWORDS—methyl (-)-shikimate; asymmetric Diels-Alder reaction; chiral sulfoxide; (S)_S-3-(2-pyridylsulfinyl)acrylate; 3,4-dibenzyloxyfuran; stereoselective hydrogenation; endo-cis dibenzyloxy derivative; ring opening

A great variety of the secondary metabolites produced by plants and fungi have provided a rich source of molecules for synthetic and mechanistic studies, and much attention has been paid to the organic synthesis of these metabolites. Of these, (-)-shikimic acid (1) is now one of the key substances in biosynthesis of naturally occurring aromatic and phenolic compounds.¹⁾ Therefore, much information has been accumulated on the total synthesis of this acid (1).²⁾ However, there is little information on its asymmetric synthesis; so far, there have been only two reports, 1) asymmetric Diels-Alder (D-A) reaction of chiral α -hydroxy enone³⁾ and 2) asymmetric hydroxylation of chiral tricarbonyliron complex of dihydrobenzoate.⁴⁾ In this research setting, we have developed a new method for diastereoselective synthesis of the 7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylate system by the asymmetric D-A reaction of (S)_S-3-(2-pyridylsulfinyl)acrylate (2) with furan (3).⁵⁾ This novel asymmetric reaction provides us with a powerful tool for the chiral synthesis of various kinds of natural polyoxygenated cyclohexane derivatives. In this paper, we present the chiral synthesis of methyl (-)-shikimate using the following synthesis strategy: For the purpose of the stereoselective introduction of the vicinal 3,4-diol function of shikimic acid to the 7-oxabicyclo[2.2.1]heptene system, we have chosen 3,4-dibenzyloxyfuran (4) as a diene to form the adduct (7a), because the 5,6-double bond can be expected to be hydrogenated to give the desired endo-cis dibenzyloxy derivative (12). A ring opening of 12 could give a triol corresponding to the absolute configuration of natural (-)-shikimic acid.

The D-A reaction of (S)_S-2 with three equivalents of 3,4-dibenzyloxyfuran (4) in the presence of diethylaluminum chloride at -20°C for 5 days gave the

endo and exo cycloadducts (7) and (8) in 50% and 29% yields, respectively. The configurations of 7 and 8 were assigned by comparing their NMR data with those of the endo and exo adducts (5) and (6).⁵⁾ The diastereoselectivity (d.e.)⁶⁾ was calculated to be no less than 92% for 7 and 94% for 8. The major endo adduct (7a)⁷⁾ ($[\alpha]_D +93.1^\circ$), which has a desired absolute configuration for the synthesis of (-)-shikimic acid,⁸⁾ was reduced with phosphorus tribromide in DMF⁹⁾ to afford the sulfide (9) ($[\alpha]_D -12.2^\circ$) in 84% yield. Treatment of 9 with lithium aluminum hydride gave the primary alcohol (10) ($[\alpha]_D -12.7^\circ$) in 95% yield. The reaction of 10 with Raney nickel (W-2) desulfenylated and hydrogenated the 5,6-double bond to give the endo-cis dibenzyloxy derivative (11) ($[\alpha]_D +55.4^\circ$) in 45% yield. The alcohol (11) was oxidized with Jones reagent. The resulting carboxylic acid was treated with diazomethane to give the methyl ester (12) ($[\alpha]_D -2.1^\circ$) in 67% yield. Ring opening of 12 by lithium hexamethyldisilazide¹⁰⁾ gave the unsaturated ester (13) ($[\alpha]_D -168.7^\circ$) in 56% yield. The dibenzyloxy derivative (13) was debenzylated with trimethylsilyl chloride-sodium iodide¹¹⁾ and the resulting triol was acetylated to give methyl (-)-triacetylshikimate (14), colorless oil, $[\alpha]_D -162.2^\circ$ ($c=0.30$, MeOH), lit.,¹²⁾ $[\alpha]_D -168^\circ$ ($c=0.9$, MeOH),¹³⁾ in 53% yield. The spectral data (IR and NMR) of the synthetic triacetate (14) were identical with those of the authentic sample.



Reagents and conditions: a, PBr₃, DMF, 0°C; b, LAH, Et₂O, rt; c, Raney Ni (W-2), EtOH, rt; d, Jones reagent, acetone, rt; e, CH₂N₂, MeOH-Et₂O; f, LiN(TMS)₂, THF, -78°C; g, TMSCl-NaI, MeCN, rt; h, Ac₂O-Py, rt.

Thus, the method developed in the present studies proposes a new and powerful strategy for the chiral synthesis of a series of the intermediates in the shikimic acid pathway in their natural and artificial forms. Especially, the artificial antipodes of the intermediates may play the role of regulators in this pathway. Our further studies are now in progress on the chiral synthesis of (+)-shikimic acid with the exo adduct (8a) as a starting material.

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- 6) The diastereoselectivity was determined by 270 MHz NMR spectroscopy.
- 7) All new compounds reported here gave satisfactory spectroscopic and analytical data. Optical rotations were taken in CHCl_3 ($c=0.79-2.14$) unless otherwise noted. Some of the spectral data are listed below.
 - (7a). IR(CHCl_3) cm^{-1} : 1728, 1685. NMR(CDCl_3) δ : 3.57(1H, dd, $J=8.4$, 4.3 Hz, 2-H), 4.20(1H, dd, $J=8.4$, 3.8 Hz, 3-H), 4.88(1H, dd, $J=4.3$, 1.5 Hz, 1-H), 5.30(1H, dd, $J=3.8$, 1.5 Hz, 4-H).
 - (8a). IR(CHCl_3) cm^{-1} : 1728, 1683. NMR(CDCl_3) δ : 3.02(1H, d, $J=8.5$ Hz, 2-H), 3.71(1H, d, $J=8.5$ Hz, 3-H), 4.96(1H, d, $J=1.2$ Hz, 1-H), 5.18(1H, d, $J=1.2$ Hz, 4-H).
 - (9). IR(CHCl_3) cm^{-1} : 1724, 1685. NMR(CDCl_3) δ : 3.65(1H, dd, $J=9.2$, 4.0 Hz, 2-H), 4.88(1H, dd, $J=9.2$, 4.1 Hz, 3-H), 4.89(1H, dd, $J=4.0$, 1.2 Hz, 1-H), 5.10(1H, dd, $J=4.1$, 1.2 Hz, 4-H).
 - (10). IR(CHCl_3) cm^{-1} : 3380, 1680. NMR(CDCl_3) δ : 3.00(1H, m, 2-H), 3.11(1H, br s, OH), 3.72(1H, dd, $J=11.2$, 6.4 Hz, CHOH), 3.81(1H, dd, $J=11.2$, 7.8 Hz, CHOH), 4.44(1H, dd, $J=8.3$, 4.2 Hz, 3-H), 4.81(1H, dd, $J=4.1$, 1.2 Hz, 1-H), 5.01(1H, dd, $J=4.2$, 1.2 Hz, 4-H).
 - (11). IR(CHCl_3) cm^{-1} : 3470. NMR(CDCl_3) δ : 1.75(1H, ddd, $J=12.0$, 11.3, 5.3 Hz, exo 6-H), 2.11(1H, dd, $J=12.0$, 5.6 Hz, endo 6-H), 2.53(1H, m, 5-H), 2.94(1H, dd, $J=7.4$, 6.0 Hz, OH), 3.80-4.02(4H, m, 2-H, 3-H, CH_2OH), 4.40(1H, dd, $J=5.3$, 4.8 Hz, 1-H), 4.62(1H, dd, $J=5.1$, 5.1 Hz, 4-H).
 - (12). IR(CHCl_3) cm^{-1} : 1737. NMR(CDCl_3) δ : 1.83(1H, dddd, $J=12.3$, 11.8, 6.0, 1.2 Hz, exo 6-H), 2.76(1H, dd, $J=12.3$, 5.6 Hz, endo 6-H), 3.04(1H, ddd, $J=11.8$, 5.6, 5.5 Hz, 5-H), 3.36(3H, s), 3.81(1H, ddd, $J=8.3$, 4.7, 1.2 Hz, 2-H), 3.91(1H, dd, $J=8.3$, 5.0 Hz, 3-H), 4.50(1H, dd, $J=6.0$, 4.7 Hz, 1-H), 4.82(1H, dd, $J=5.5$, 5.0 Hz, 4-H).
 - (13). IR(CHCl_3) cm^{-1} : 3600, 1715, 1650. NMR(CDCl_3) δ : 2.21(1H, dddd, $J=18.2$, 8.2, 2.4, 1.0 Hz, 6 β -H), 2.48(1H, br s, OH), 2.96(1H, dd, $J=18.2$, 5.7 Hz, 6 α -H), 3.47(1H, dd, $J=9.3$, 3.9 Hz, 4-H), 3.75(3H, s), 6.93(1H, ddd, $J=4.8$, 2.4, 1.2 Hz, 2-H).
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- 13) Methyl (-)-triacetylshikimate (14), prepared from (-)-shikimic acid (Kanto Chemical Co. Inc) according to the procedure reported by Rapoport *et al.*,¹²⁾ showed $[\alpha]_D -161.7^\circ$ ($c=0.64$, MeOH).

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