Supplementary Material Available: ^1H NMR and mass spectroscopic data of remaining products (6 pages). Ordering information is given on any current masthead page.

Registry No. 1 (R = $Me(CH_2)_9$, R^1 = Me), 67217-00-9; 1 (R = $Me(CH_2)_9$, R^1 = CH_2=$CHCH_2$), 28783-83-7; 1 (R = Me_2C=$CH(CH_2)_2$, R^1 = Me), 100011-01-6; 1 (R = $PhOCH_2$, R^1 = Me), 32017-84-8; 1 (R = $PhOCH_2$, R^1 = CH_2=$CHCH_2$), 20040-20-4; 1 (R = $ClCH_2$, R^1 = Me), 4151-97-7; 1 (R = $ClCH_2$, R^1 = $PhCH_2$), 13991-52-1; 1 (R = $AcOCH_2$, R^1 = Me), 89534-59-8; 1 (R = $AcOCH_2$, R^1 = CH_2=$CHCH_2$), 100011-03-8; 1 (R = $HO(CH_2)_9$, R^1 = Me), 111903-73-2; 1 (R = $MeO(CH_2)_9$, R^1 = Me), 111903-75-4; 1 (R = $MeOCO(CH_2)_8$, R^1 = Me), 100011-04-9; 1 (R = Ph, R^1 = Me), 3587-84-6; 2 (R = $Me(CH_2)_9$, R^1 = Me), 56256-81-6; 2 (R = $Me(CH_2)_9$, R^1 = CH_2=$CHCH_2$), 111903-71-0; 2 (R = Me_2C=$CH(CH_2)_2$, R^1 = Me), 100011-02-7; 2 (R = $PhOCH_2$, R^1 = Me), 40453-79-0; 2 (R = $PhOCH_2$, R^1 = CH_2=$CHCH_2$), 111903-72-1; 2 (R = $HO(CH_2)_9$, R^1 = Me), 111903-74-3; 2 (R = $MeO(CH_2)_9$, R^1 = Me), 111903-76-5; 2 (R = $MeOCO(CH_2)_8$, R^1 = Me), 111903-77-6; 2 (R = Ph, R^1 = Me), 2979-22-8; 3, 111933-41-6; 3 (acetate), 111903-79-8; 4 (R = $PhCH_2$), 111903-91-4; 4 (R = Bu), 111903-92-5; 5 (R = $PhCH_2$), 58021-03-7; $Me(CH_2)_9\overline{CHCH_2O}$, 2404-44-6; Me_2C=$CH(CH_2)_2\overline{CHCH_2O}$, 98322-92-0; $PhOCH_2\overline{CHCH_2O}$, 122-60-1; $ClCH_2\overline{CHCH_2O}$, 106-89-8; $AcOCH_2\overline{CHCH_2O}$, 6387-89-9; $HO(CH_2)_9\overline{CHCH_2O}$, 15764-66-6; $MeO(CH_2)_9\overline{CHCH_2O}$, 111903-70-9; $MeOCO(CH_2)_8\overline{CHCH_2O}$, 22663-09-8; $Ph\overline{CHCH_2O}$, 96-09-3; MeOH, 67-56-1; CH_2=$CHCH_2OH$, 107-18-6; $PhCH_2OH$, 100-51-6; Sn, 7440-31-5; $Me(CH_2)_4\overline{CHCH(Me)O}$, 3234-26-2; $Me(CH_2)_4CH(OH)CH(OMe)Me$, 111903-80-1; $Me(CH_2)_4CH(OMe)CH(OH)Me$, 111903-81-2; $Me_2\overline{CCH(Et)O}$, 1192-22-9; $Me_2\overline{CCH(CH_2CH_2CH(Me)Et)O}$, 60814-44-0; Me_2C=$CH(CH_2)_2\overline{C(Me)CH(CH_2OMe)O}$, 111903-82-3; Me_2C=$CH(CH_2)_2\overline{C(Me)CH(SO_3Me)O}$, 111903-83-4; CH_2=$CHCH_2OC(Me_2)CH(OH)Et$, 111903-84-5; $PhCH_2OC(Me_2)CH(OH)Et$, 111933-42-7; $MeOC(Me_2)CH(OH)(CH_2)_2CH(Me)Et$, 60814-45-1; Me_2C=$CH(CH_2)_2C(Me)(OMe)CH(OH)CH_2OH$, 111903-85-6; Me_2C=$CH(CH_2)_2C(Me)(OMe)CH(OH)CH_2OMe$, 111903-86-7; Me_2C=$CH(CH_2)_2C(Me)OMe)CH(OH)CH_2SO_3Me$, 111903-87-8; $Me(CH_2)_{10}\overline{C(Me)CH_2O}$, 111903-88-9; $PhCH_2OCH_2\overline{C(Me)CH_2O}$, 97389-48-5; $BuOCH_2\overline{C(Me)CH_2O}$, 111903-89-0; $Me(CH_2)_{10}C(Me)(OMe)CH_2OH$, 111903-90-3; 1-[(methylsulfonyl)oxy]-2-hexene oxide, 111903-78-7; cyclohexene oxide, 286-20-4; 2-methylcyclohexanol, 7429-40-5; 2,3-oxidogeraniol, 50727-94-1.

A Facile Synthesis of (+)- and (-)-Shikimic Acid with Asymmetric Deuterium Labeling, Using Tricarbonyliron as a Lateral Control Group

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(-)-Methyl shikimate has been prepared from tricarbonyliron complexes of methyl dihydrobenzoate. Reaction of optically pure (+)-tricarbonyl(1-carbomethoxycyclohexa-1,3-dienyl)iron hexafluorophosphate with hydroxide ion and then *tert*-butyldimethylsilyl chloride (TBDMSCl) followed by metal removal with Me_3NO gave (+)-1-carbomethoxy-5-hydroxycyclohexa-1,3-diene as its TBDMS ether. Osmium tetraoxide oxidation and then desilylation gave optically pure (-)-methyl shikimate. Also, fully resolved (-)-tricarbonyl(1-carbomethoxycyclohexa-1,3-dienyl)iron hexafluorophosphate was hydroxylated and then treated with CrO_3 followed successively by $ZnBH_4$ and TBDMS triflate. Demetalation gave the same TBDMS-protected (+)-1-carbomethoxy-5-hydroxycyclohexa-1,3-diene as that obtained above by direct reaction. Thus, although resolution is necessary, both enantiomers of tricarbonyl(1-carbomethoxycyclohexa-1,3-dienyl)iron hexafluorophosphate are convertible into natural (-)-methyl shikimate. Deuterium was incorporated enantiospecifically to give (6*R*)- or (6*S*)-methyl 6-deuterioshikimate.

The lateral control of synthesis exercised by a complexed transition-metal atom can often mimic the control exercised by enzymes but with a wider range of reaction mechanisms and substrates.[1,2] In particular, optically active complexes provide unique synthetic opportunities for asymmetric bond formation[3] at new chiral centers of known absolute configuration, if that of the complex is known. This capability results from the normal complete stereospecificity of the bond formations, and the resulting asymmetry is equivalent to that of the complex. We have provided one example[1] in the total enantiospecific synthesis of the enzyme-inhibitor gabaculine and its derivative containing also a chiral center of known absolute configuration in which asymmetry is due to ^2H vs H.

The key intermediate in that enantiospecific synthesis was the resolved complex **2b** (R = H or ^2H) obtained[1] from benzoic acid via 1,4-dihydrobenzoic acid. The derived cation **3** (R = H or ^2H) had previously been shown to react with nucleophiles solely at the 5-exo position.[4] We have now employed these complexes in the form of *both antipodes* to synthesize the one natural enantiomer (-)-shikimic acid as its Me ester (**1a**).

Shikimic acid has been synthesized in racemic and optically active forms.[5] The synthesis of Campbell et al. attracted our attention because we envisaged enantiospecific synthesis of their key precursor **6** (R = R′ = H) by a method analogous to the processes used for gabaculine.[1] The related deuterio labeled derivatives **1b** (R = ^2H, R′ = H) and **1c** (R = H, R′ = ^2H) can be also prepared from the resolved cation salts **3a** (R = ^2H) and **3b** (R = ^2H), already described,[1] as shown for salt **3a** (R = H or ^2H) in

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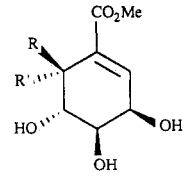
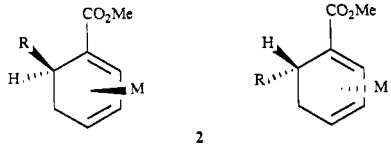
(2) Birch, A. J. *Progress in Bio-organic Chemistry and Molecular Biology*; Ovchinnikov, Yu. A., Ed.; Elsevier: New York, 1984; p 471.
(3) Birch, A. J.; Bandara, B. M. R.; Chamberlain, K.; Chauncy, B.; Dahler, P.; Day, A. I.; Jenkins, I. D.; Kelly, L. F.; Khor, T. C.; Kretschmer, G.; Liepa, A. J.; Narula, A. S.; Raverty, W. D.; Rizzardo, E.; Sell, C.; Stephenson, G. R.; Thompson, D. J.; Williamson, D. H. *Tetrahedron* **1981**, *37* (Woodward Special Issue), 289.
(4) Birch, A. J.; Williamson, D. H. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1892.
(5) Campbell, M. M.; Kaye, A. D.; Sainsbury, M.; Yavarzadeh, R. *Tetrahedron* **1984**, *40*, 2461. For recent references in this area, see: Pawlak, J. L.; Berchtold, G. A. *J. Org. Chem.* **1987**, *52*, 1765.

0022-3263/88/1953-0278$01.50/0



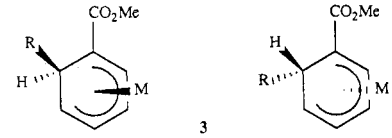
1

(a) Methyl shikimate (R=R'=H)
(b) (R=D, R'=H)
(c) (R=H, R'=D)



2

(a) (b)



3

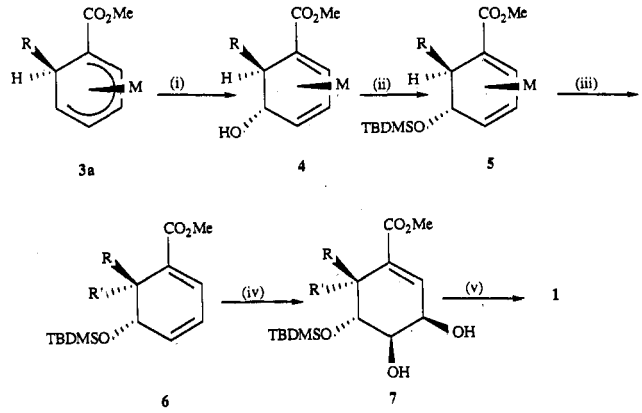
(a) (b)

Scheme I. Reaction of the unlabeled (+)-**3a** (R = H) in acetonitrile solution with aqueous sodium hydrogen carbonate yielded the alcohol complex (+)-**4** (R = H), after chromatographic removal of a little bis ether also formed.[4] Protection of its OH by reaction with *tert*-butyldimethylsilyl chloride (TBDMSCl) and diisopropylethylamine followed by decomplexation with anhydrous Me_3NO, provided the free diene (+)-**6** (R = R′ = H) in 78% yield from (+)-**3a** (R = H). The conversion of this diene into (−)-methyl shikimate (**1a** R = R′ = H) was achieved in 67% yield by a slight modification to the procedure of Campbell et al.[5] via the cis-diol **7** (R = R′ = H) using osmium tetraoxide, followed by fluoride ion to remove the silyl-protecting group. The product was identical in properties with (−)-methyl shikimate.

The presence of the readily removable lateral control group $Fe(CO)_3$ permits in this series the use of both of the enantiomeric complexes **2a** (R = H) and **2b** (R = H) to produce either (−)- or (+)-shikimic acid. The former can be derived not only directly as shown from **3a** (R = H) but also indirectly starting from **3b** (R = H), which reacts with hydroxide ion as described earlier to produce alcohol **8** (R = H) with the "wrong" absolute configuration of the 5-OH. This center could be inverted to the required absolute configuration as shown in Scheme II. *Therefore, although resolution of the initial complex is necessary, both enantiomers can be made to give the same fully resolved product of either absolute configuration.*

Inversion of the 5-OH of **8** (R = H) was accomplished first by abolishing the asymmetry at that center by oxidation to carbonyl in **9** (R = H). The molecular asymmetry due to complexation is still retained, and using the complexing group to direct stereospecific (and therefore enantiospecific) reduction of the carbonyl led to the 5-OH of the desired configuration in **10** (R = H). This complex is a diastereomer of **4** (R = H), and formation of the silyl ether with TBDMSCl proved difficult, presumably for steric reasons. However, the more reactive triflate formed the required **11** (R = H) in good yield. Removal of the $Fe(CO)_3$ with Me_3NO gave **6** (R = R′ = H) identical in properties, including optical rotation, with that obtained directly from **2a** (R = H).

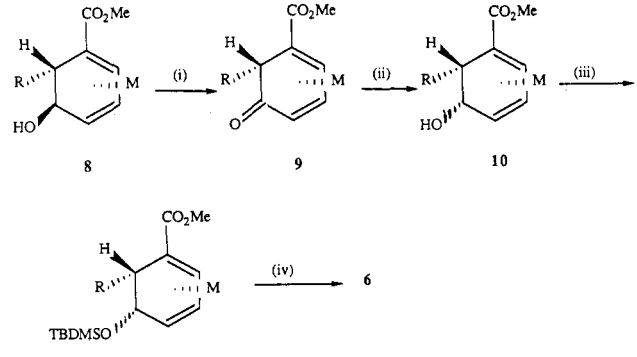
Scheme I[a]



R = H, D ; R'=H, D ; M = $Fe(CO)_3$

[a] (i) $NaHCO_3$/aqueous CH_3CN (95%); (ii) TBDMSCl/DMF/(i-Pr)$_2$NEt (98%); (iii) Me_3NO/C_6H_6 (84%); (iv) OsO_4/acetone (67%); (v) (n-Bu)$_4$NF/THF (85%).

Scheme II[a]



R = H, D M = $Fe(CO)_3$

[a] (i) CrO_3/pyridine/CH_2Cl_2 (85%); (ii) $NaBH_4/ZnCl_2/Et_2O$ (98%); (iii) TBDMS triflate/DMF/(i-Pr)$_2$NEt (83%); (iv) Me_3NO/C_6H_6 (82%).

Completely stereospecific reduction of the carbonyl in **9** (R = H) proved more experimentally difficult than was anticipated. As we have already noted,[6] complex–hydride reductions of cations in this series are the only clearly kinetically controlled processes so far observed to lead to mixed steric results, and this was also found to be true of reductions of **9** (R = H) by the standard procedures. Possibly hydride is transferred to some extent via the metal. Noting[7] that $Zn(BH_4)_2$ directs the stereospecific reductions of keto esters, apparently by complexation with a carbonyl, although the situation here is different, we examined the reduction of **9** (R = H) with $ZnCl_2$–$NaBH_4$ and obtained only the one desired isomer **10** (R = H). The Zn^{2+} can be shown to form a complex with the nuclear carbonyl, probably yielding the readily reducible derivative of an hydroxycarbenium complex. Complexation of this carbonyl is attested by the 200-MHz ^1H NMR spectrum, which shows significant chemical shifts of protons around it on the addition of zinc chloride, the ester Me being unchanged.

Shikimic acid is a very important biosynthetic intermediate. The present approach seems to be uniquely

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(7) Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338.

simple for the total synthesis of some analogues for biochemical studies, starting from benzoic acids, including homologues and derivatives incorporating isotopes of hydrogen which previously have been only available by biochemical methods.[8] We report, as examples, the total synthesis of several enantiospecifically labeled 6-^{2}H derivatives.

The 1-carbomethoxy isomer **2** (R = H) was deuteriated in the 6-endo position by heating in $^2H_2SO_4$–MeO^{2}H solution.[1] Theory indicates[3,4] that such 6-deuteriation should be preceded by equilibration of this isomer with our initial experimental precursor,[1] the 2-carbomethoxy isomer, which was found conveniently to incorporate deuterium directly, by this process, to yield the 6-endo-^{2}H ester already reported. Prolonged heating of the deuteriomethanol solution (5 days) causes some incorporation into the 5-endo position of **2** (about 20%), but under the described conditions[1] the major product is the (±)-6-endo-monodeuterio derivative, which on resolution[1] yields the asymmetric esters **2a** (R = ^{2}H) and **2b** (R = ^{2}H), convertible by reaction with trityl cation[4] into **3a** (R = ^{2}H) and **3b** (R = ^{2}H). By means of the sequences detailed (Schemes I and II), the cations **3a** (R = ^{2}H) and **3b** (R = ^{2}H) were converted into the methyl esters of shikimic-d_1 acid: the 6*S* enantiomer (**1b**) and the 6*R* isomer (**1c**), respectively.

Experimental Section

Details are mostly included in the previous paper[1] and in the references cited.

(1*R*,5*R*)-Tricarbonyl(1-carbomethoxy-5-hydroxycyclohexa-1,3-diene)iron (4, R = H). The 1-CO_2Me salt **3a** (R = H) (2 g, 4.7 mmol) was dissolved in acid-free acetonitrile (25 mL) and a saturated aqueous solution of $KHCO_3$ (25 mL) added. The resulting mixture was stirred for 30 min and the product extracted into diethyl ether (2 × 25 mL). The combined extracts were washed with water, dried, and evaporated under reduced pressure. The resulting yellow oil was chromatographed (Kieselgel 60, 70–230 mesh, 30% ethyl acetate in hexane) to remove a trace of the bis ether. The pure oil upon standing crystallized as yellow needles; mp 78 °C; 1.32 g (95%). Anal. Calcd for $C_{11}H_{10}FeO_6$: C, 44.9; H, 3.4. Found: C, 45.1; H, 3.4. ^{1}H NMR ($CDCl_3$) δ 6.28 (d, *J* = 5 Hz, 1 H), 5.50 (t, *J* = 5 Hz, 1 H), 4.45 (br m, 1 H), 3.70 (s, 3 H), 3.20 (m, 4 H), 2.80 (dd, *J* = 19, 12 Hz, 1 H), 2.03 (br s, OH), 1.35 (dd, *J* = 19, 3 Hz, 1 H); IR ($CHCl_3$) 3440, 2070, 2000, 1990, 1710 cm^{-1}; MS, *m/e* (relative intensity) 294 (M^+) (0.2), 266 (0.2), 238 (0.3), 210 (0.3), 136 (36), 105 (100); $[\alpha]_D$ +94° (*c* 0.8, $CHCl_3$). Enantiomeric **8** (R = H) was prepared from **3b** (R = H) by a procedure similar to above: $[\alpha]_D$ −94° (*c* 0.7, $CHCl_3$). The spectra of this compound were identical with those of its enantiomorph.

(1*S*)-Tricarbonyl(1-carbomethoxycyclohexa-1,3-dien-5-one)iron (9, R = H). The alcohol **8** (R = H) (2.5 g, 8.5 mmol) was dissolved in dry dichloromethane (100 mL) and reacted with CrO_3 (5.1 g, 51 mmol) in pyridine (4.0 g, 51 mmol) at room temperature for 48 h. The resulting black solution was filtered through Celite, diluted with diethyl ether, washed successively with water, dilute aqueous acid, and water. The dried organic extract upon concentration gave a yellow solid, which was purified by chromatography under the same conditions as for the previous compound, to yield yellow needles: mp 126 °C, 2.11 g (85%). Anal. Calcd for $C_{11}H_8FeO_6$: C, 45.2; H, 2.8. Found: C, 45.1; H, 2.9. ^{1}H NMR ($CDCl_3$) δ 6.35 (d, *J* = 6 Hz, 1 H), 6.00 (t, *J* = 6 Hz, 1 H), 3.76 (s, 3 H), 3.40 (d, *J* = 6 Hz, 1 H), 2.95 (d, *J* = 21 Hz, 1 H), 2.10 (d, *J* = 21 Hz, 1 H); IR ($CHCl_3$) 2090, 2025, 2015 cm^{-1}; MS, *m/e* (relative intensity) 292 (M^+) (15), 264 (6), 236 (30), 208 (26), 152 (50), 121 (100); $[\alpha]_D$ +382° (*c* 0.3, $CHCl_3$).

(1*S*,5*R*)-Tricarbonyl(1-carbomethoxy-5-hydroxycyclohexa-1,3-diene)iron (10, R = H). To a well-stirred suspension of $NaBH_4$ (0.38 g, 10 mmol) and anhydrous $ZnCl_2$ (1.36 g, 10 mmol) in diethyl ether (50 mL) was added the keto complex **9** (R = H) (2 g, 6.85 mmol) in small portions. The resulting mixture was stirred at room temperature overnight, water (2 mL) was added, and stirring was continued until the gas evolution stopped. Anhydrous $MgSO_4$ was added, the solution decanted, and the residue washed with diethyl ether (2 × 10 mL). The combined ether extract was dried ($MgSO_4$) once more and filtered and the filtrate evaporated to dryness under reduced pressure to obtain a viscous yellow oil. This oil upon standing in vacuo solidified and was recrystallized from ethyl acetate–hexane as yellow needles: mp 80–81 °C; 1.97 g (98%). Anal. Calcd for $C_{11}H_{10}FeO_6$: C, 44.9; 3.4. Found: C, 45.0; H, 3.3. ^{1}H NMR ($CDCl_3$) δ 6.05 (d, *J* = 4 Hz, 1 H), 5.34 (t, *J* = 4 Hz, 1 H), 3.97 (br m, 1 H), 3.72 (s, 3 H), 3.36 (m, 1 H), 1.92 (m, 2 H), 1.75 (br s, OH); IR ($CHCl_3$) 3500, 2060, 2000, 1980, 1710 cm^{-1}; MS, *m/e* (relative intensity) 266 (M^+ − CO) (2), 238 (13), 210 (10), 192 (25), 105 (100); $[\alpha]_D$ −45° (*c* 0.5, $CHCl_3$).

(1*R*,5*R*)-Tricarbonyl(1-carbomethoxy-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]cyclohexa-1,3-diene)iron (5, R = H). To a mixture of the alcohol **4** (R = H) (1.55 g, 5.27 mmol) and diisopropylethylamine (6.81 g, 52 mmol) was added *tert*-butyldimethylsilyl chloride (0.95 g, 6.33 mmol) with stirring for 5 min. Dry dimethylformamide was added to this mixture until a clear solution resulted and stirring was continued for a further 30 min. Water (50 mL) and $KHCO_3$ (5 g) were added and the product extracted into light petroleum. The extract was washed with water, dried ($MgSO_4$), filtered, and evaporated. The crude product was purified by chromatography (Kieselgel 60, 70–230 mesh, 25% ethyl acetate in *n*-hexane) as a yellow oil (2.1 g, 98%). Anal. Calcd for $C_{17}H_{24}FeO_6Si$: C, 50.0; H, 5.9. Found: C, 49.8; H, 5.8. ^{1}H NMR ($CDCl_3$) δ 6.22 (d, *J* = 4 Hz, 1 H), 5.47 (t, *J* = 6 Hz, 1 H), 4.38 (m, 1 H), 3.69 (s, 3 H), 3.10 (m, 1 H), 2.69 (dd, *J* = 19, 12 Hz, 1 H), 1.30 (dd, *J* = 19, 3 Hz, 1 H), 0.85 (s, 9 H), 0.05 (s, 3 H), 0.02 (s, 3 H); IR ($CDCl_3$) 2060, 2000, 1990, 1710 cm^{-1}; MS, *m/e* (relative intensity) 352 (M^+ − CMe_3) (2), 324 (7), 268 (8), 209 (100); $[\alpha]_D$ +37° (*c* 0.5, $CHCl_3$).

(1*S*,5*R*)-Tricarbonyl(1-carbomethoxy-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]cyclohexa-1,3-diene)iron (11, R = H). This compound was obtained as an oil in 83% yield from **10** (R = H) and *tert*-butyldimethylsilyl triflate by a method similar to that above. Anal. Calcd for $C_{17}H_{24}FeO_6Si$: C, 50.0; H, 5.9. Found: C, 50.1; H, 5.8. ^{1}H NMR ($CDCl_3$) δ 6.00 (d, *J* = 4 Hz, 1 H), 1.86 (m, 2 H), 0.90 (s, 9 H), 0.06 (s, 3 H), 0.03 (s, 3 H); IR ($CDCl_3$) 2060, 2020, 1980, 1710 cm^{-1}; MS, *m/e* (relative intensity) 408 (M^+) (1), 380 (45), 352 (24), 324 (100), 105 (93); $[\alpha]_D$ −2°, $[\alpha]_{486}$ +97° (*c* 0.5, $CHCl_3$).

(5*R*)-Carbomethoxy-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]cyclohexa-1,3-diene (6, R = R′ = H). $Me_3NO{\cdot}2H_2O$ (10 g, 90 mmol) was heated at reflux for 40 h in benzene (50 mL) with azeotropic removal of water. To this mixture at room temperature was added a solution of **5** (R = H) (2 g, 4.9 mmol) in benzene (15 mL). After being stirred for 3 h, the solution was filtered through a pad of Celite and the filtrate washed with water (3 × 100 mL). The dried ($MgSO_4$) filtrate was evaporated and the residue further purified by chromatography on Kieselgel 60 (70–230 mesh) in 25% ethyl acetate in *n*-hexane to yield **6** (R = R′ = H) as a colorless oil (1.10 g, 84%): $[\alpha]_D$ +177° (*c* 0.9, $CHCl_3$). Alternatively, treatment of the other diastereomer, **11** (R = H), with $Me_3NO{\cdot}2H_2O$ in benzene in a similar manner also gave **6** (R = R′ = H) in 82% yield: $[\alpha]_D$ +177° (*c* 0.9, $CHCl_3$). The spectral data were identical with those previously reported by Campbell et al. for the racemic material.[5]

(5*R*)-5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl Shikimate (7, R = R′ = H). Osmium tetraoxide oxidation was performed on **6** (R = R′ = H) as previously described but by using a stoichiometric quantity of oxidant.[5] The resulting black residue was dissolved in dichloromethane and washed with 10% NaOH followed by water. The dried organic extract was evaporated to dryness, and the residue was purified by chromatography (Kieselgel 60, 70–230 mesh, 75% ethyl acetate in *n*-hexane). The spectral data were identical with literature values reported[5] for **6** (R = R′ = H) except for the ^{1}H NMR resonances of the *tert*-butyldimethylsilyl group; we found δ 0.88 (s, 9 H) and 0.2 (s, 6 H) [lit. δ 1.88 and 0.4, respectively]: $[\alpha]_D$ −76° (*c* 0.5, $CHCl_3$).

(−)-Methyl Shikimate (1a, R = R′ = H). Deprotection of the hydroxy group of **7** (R = R′ = H) following the published procedure[5] yielded (−)-methyl shikimate: $[\alpha]_D$ −128° (*c* 0.5,

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ethanol) [lit. $[\alpha]_D$ −128° (c 1.79, ethanol)].

Deuteriated Compounds. The ^1H NMR of some of the deuteriated intermediates have already been discussed.[1] Key differences in ^1H NMR signals from the undeuteriated to the deuteriated compounds are as follows: **1b** (R = ^2H, R′ = H), δ 2.20 (dd, J = 16, 7 Hz) has disappeared, and δ 2.80 (dd J = 16, 8 Hz) is a broad doublet (J = 8 Hz); **1c** (R = H, R′ = ^2H), δ 2.80 (dd, J = 16, 8 Hz) has disappeared, and δ 2.20 (dd, J = 16, 7 Hz) is a broad singlet; **4** (R = ^2H), δ 2.80 (dd J = 19, 12 Hz) has disappeared, and δ 1.35 (dd J = 19, 3 Hz) has become a broad singlet; **5** (R = ^2H), δ 2.69 (dd, J = 19, 12 Hz) has disappeared and δ 1.30 (dd, J = 19, 3 Hz) is a broad singlet; **6** (R = ^2H, R′ = H) and **6** (R = H, R′ = ^2H), δ 2.62 (m) has reduced intensity and is a broad singlet; **7** (R = ^2H, R′ = H) and **7** (R = H, R′ = ^2H), δ 2.15 (dd J = 9, 3 Hz) has disappeared, and δ 2.75 (dd, J = 9, 3 Hz) is a broad singlet; **11** (R = ^2H), δ 1.86 (m) has become reduced and converted into a broad doublet (J = 8 Hz).

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An Alternative Total Synthetic Approach toward Octosyl Acid A

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The naturally occurring nucleoside octosyl acid A (1) has been synthesized as its dimethyl ester, 2. Nitrooctose 5, prepared by a Henry reaction of the 5-nitro-D-ribose 3 with 2,3-*O*-isopropylidene-D-glyceraldehyde (4), has been converted to octosyl acid A dimethyl ester (2) by the following sequence: deoxygenation at C-6, interconversion of the 5-nitro group into an oxygen function, glycosylation with a uracil base, intramolecular cyclization to a bicyclic 3′,7′-anhydride, oxidation to obtain a carboxyl function at C-8′, and epimerization to the natural configuration at C-7′. Since 2 has already appeared in a total synthesis of octosyl acid A by the Danishefsky group, a formal total synthesis of the acid has been accomplished.

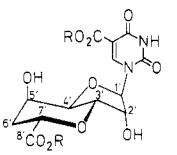
The octosyl acids were isolated from the culture filtrates of *Streptomyces cacaoi* var. *asoensis*. Although octosyl acid A itself does not possess any biological activity, its adenine analogue, readily obtained by transglycosylation, was shown to be an inhibitor of cyclic-AMP phosphodiesterase.[1] The structures were clarified as shown in Chart I by Isono et al.[2] A 3,7-anhydrooctofuranose skelton, a furanose to which a pyrane ring is trans-fused, is also found in the antifungal ezomycins.[3] Because of their unique structures, various synthetic approaches have been carried out and total synthesis of octosyl acid A has been reported by two groups.[4,5]

In our laboratory, a general synthesis of higher carbon carbohydrates has been developed by use of a fluoride anion catalyzed Henry reaction between a nitro sugar and a sugar aldehyde. We have reported syntheses of tunicamycins[6] and ezomycines[7] using this methodology. The present article describes a synthesis of octosyl acid A.

Results and Discussion

Octose construction was carried out by condensation of a C_5-nitrosugar and a C_3-aldehyde. A Henry reaction between 5-deoxy-1,2-*O*-isopropylidene-3-*O*-[(methylthio)-methyl]-5-nitro-α-D-ribofuranose (**3**)[7a,8] and 2,3-*O*-isopropylidene-D-glyceraldehyde (**4**) gave a diastereoisomeric mixture of 5-deoxy-5-nitrooctofuranose **5** in the presence of potassium fluoride–tetrabutylammonium iodide in toluene (Scheme I). Acetylation of **5** with acetic anhydride and pyridine, in the presence of 4-(dimethylamino)-pyridine, and successive treatment with sodium borohydride resulted in elimination of acetic acid to afford 45% (based on **3**) of the 6-deoxygenated compounds **6a** and **6b** as a diastereomeric mixture. The nitro group of the

Chart I



1: R = H
2: R = CH_3

mixture was hydrogenated with Raney nickel to give a single amino sugar **7** in 70% yield. Conversion of the amino group to a keto function was performed by Corey's method.[9] Thus, condensation of **7** with 3,5-di-*tert*-butyl-1,2-benzoquinone and subsequent hydrolysis of the resultant imine with oxalic acid afforded the ketone **8** in 65% yield. Other methods[10] for transforming **7** to **8** failed.

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