A Short Asymmetric Synthesis of (+)-Nonactic Acid and (−)-8-*epi*-Nonactic Acid Induced by a Chiral Sulfoxide Group†

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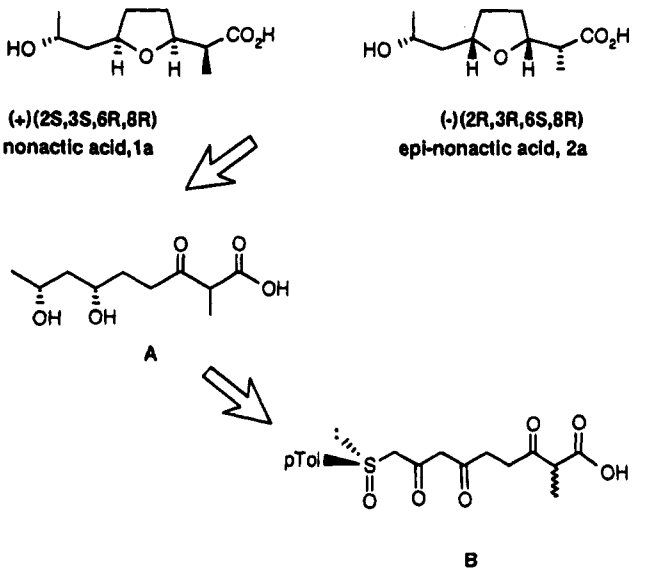
A short enantioselective synthesis of (+)-(2*S*,3*S*,6*R*,8*R*)-nonactic acid and (−)-(2*R*,3*R*,6*S*,8*R*)-*epi*-nonactic acid is described. The key step was the stepwise stereoselective reduction of the triketo sulfoxide B without any protective group on the different carbonyls.

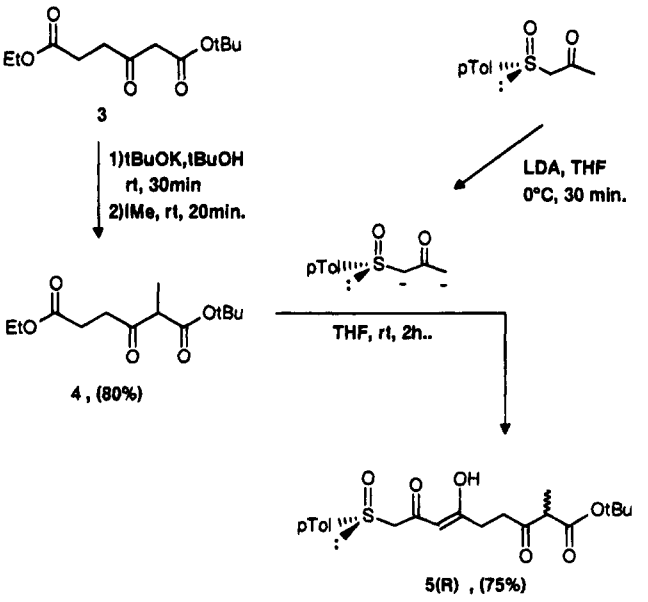
The ionophoric macrolide antibiotic nonactin, isolated from a variety of *Streptomyces* cultures,[1] consists of two subunits of (+)-nonactic acid (**1a**) and two subunits of (−)-nonactic acid arranged in an alternating order. Many syntheses of nonactic acid in both optically active and racemic form have been reported in recent years with varying success with respect to the degree of stereoselectivity.[2] We now report the enantioselective synthesis of both (+)-(2*S*,3*S*,6*R*,8*R*)-nonactic acid and (−)-(2*R*,3*R*,6*S*,8*R*)-*epi*-nonactic acid. As shown in the retrosynthetic Scheme 1, this new approach is based on the asymmetric reduction of the (*R*)-β,δ-diketo sulfoxide B using our recently reported methodology,[3] which, when applied to the complex molecule B, does not require protection of any functional groups.

The synthesis of the *tert*-butyl ester **5** of the β,δ-diketo sulfoxide B was carried out, following our methodology[3] from the diester **4** (prepared by methylation of the diester **3** of 3-oxoadipic acid,[4] in 80% yield) and the dianion of (*R*)-(+)-1-(*p*-tolylsulfinyl)-2-propanone[3a] in 75% yield (Scheme 2).

Scheme 1



Scheme 2



As expected from our previous results,[3] the δ-carbonyl in **5** was totally enolized and the reduction required 2

† This paper is dedicated to Professor Harry M. Walborsky on the occasion of his 70th birthday.

‡ On leave from the University Complutense, Madrid.

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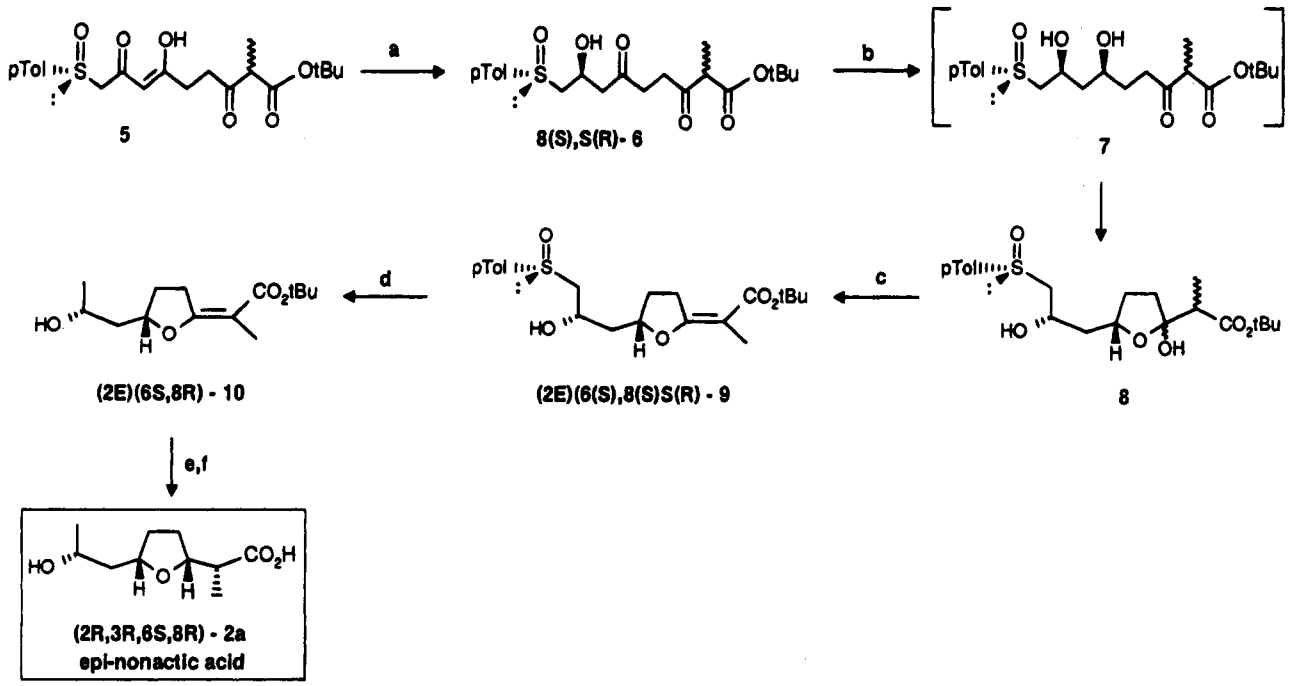
Scheme 3[a]



[a] (a) DIBAL, THF, −78 °C, 15 min, 60%; (b) Et_2BOMe, $NaBH_4$, THF, MeOH, −78 °C, 2.5 h, 80%; (c) PPTS, CH_2Cl_2, rt, 1 h, 95%; (d) Raney Ni, MeOH, rt, 30 min, 98%; (e) Rh/Al_2O_3, H_2, MeOH, 3 days, 98%; (f) 2 N KOH, H_2O, rt, 48%.

equiv of Dibal: one to quench the δ-enolate and one to reduce the β-carbonyl. As shown before,[3c] this reduction involves an intramolecular hydride transfer from an intermediate in which Dibal is chelated by the sulfoxide oxygen. Therefore it was expected that, by using the right number of equivalents, we should be able to reduce the β-carbonyl only and that the protection of the carbonyl β to the ester should not be necessary. Dibal reduction of compound **5** gave, as expected, the [S(*R*),8(*S*)]-hydroxy sulfoxide **6** in 60% yield. The absence of over-reduction products was confirmed by the ^1H NMR spectrum of the crude product. The diastereoselectivity (de > 98%) was determined by ^1H NMR analysis from the characteristic AB pattern displayed by the methylene protons α to the sulfoxide (only one diastereomer was indeed detected). The absolute configuration of the hydroxylic center was deduced from our previous results[3] and will be confirmed by the final correlation with nonactic acid. The 60% isolated yield is due to the formation of a secondary product resulting from a desulfurization reaction which is at the present time difficult to explain. However, this 60% yield is still acceptable because of the absence of any additional step to protect the other reducible groups (Scheme 3).

In the next step the 6-keto group was reduced to the *syn*-diol using diethylmethoxyborane/sodium borohydride.[5] However, the resulting *syn*-diol **7** could not be isolated. It spontaneously cyclized to the lactol **8** by reaction with the carbonyl β to the ester group. The lactol **8** was easily identified on the basis of its ^{13}C NMR spectrum (a signal at 110 ppm coresponding to the hemiketal-C) and by subsequent transformation to the next product **9**. The preference for the cyclic hemiketal over the open diol may be due to the stabilization of the hemiketal via hydrogen-bonding with the ester carbonyl as it has been already observed in similar structures.[6]

Pyridinium *p*-toluenesulfonate catalyzed dehydration of the lactol **8** gave the (+)-enantiomer of [6(*S*),8(*S*),S-(*R*)]-(2*E*)-2,3-dehydro-*epi*-nonactate **9**, in 95% yield, easily identified from the related work of Bartlett.[2n] Desulfurization with Raney nickel afforded the dehydro-*epi*-nonactate[2n] **10** as a single diastereomer as determined by its ^1H-NMR spectrum (mainly from the terminal methyl group signal) and by its ^{13}C-NMR spectrum (from the signal at 82.37 ppm, corresponding to the asymmetric carbon on the cycle). Subsequent $Rh-Al_2O_3$-catalyzed hydrogenation[2n] afforded the (−)-*tert*-butyl-*epi*-nonactate **2b** which results from hydrogenation on the least-hindered face of the double bond. The (−)-ester **2b** was finally hydrolyzed to (−)-(2*R*,3*R*,6*S*,8*R*)-*epi*-nonactic acid (**2a**) in basic medium (2 N KOH) which showed spectral data identical to literature.[2i] It has been already proved that the hydrolysis of the ester proceeds without epimerization at C-2[2n] (Scheme 3).

For the synthesis of (+)-*tert*-butyl nonactate (**1b**), we used an approach based on the obtention of the *anti*-diol **11** from the intermediate **6**. The compound **6** was thus reduced by Evan's reagent,[7] tetramethylammonium triacetoxyborohydride, in modified experimental conditions, into the corresponding *anti*-diol **11**, which cyclized spontaneously into the bicyclic acetal **12**, identified by ^1H- and ^{13}C-NMR and by further transformations (Scheme 4).

As expected, acidic treatment (catalytic amount of a 1 N HCl solution in THF) of the bicyclic acetal **12** yielded [6(*R*),8(*S*),S(*R*)]-(2*E*)-2,3-dehydrononactate **13**, via a carbocationic opening of the seven membered ring, in a moderate and nonoptimized yield. Compound **13** was easily identified by comparison with the diastereomer **9**. Desulfurization with Raney nickel afforded **14** as a single diastereomer (determined mainly from the signal of the

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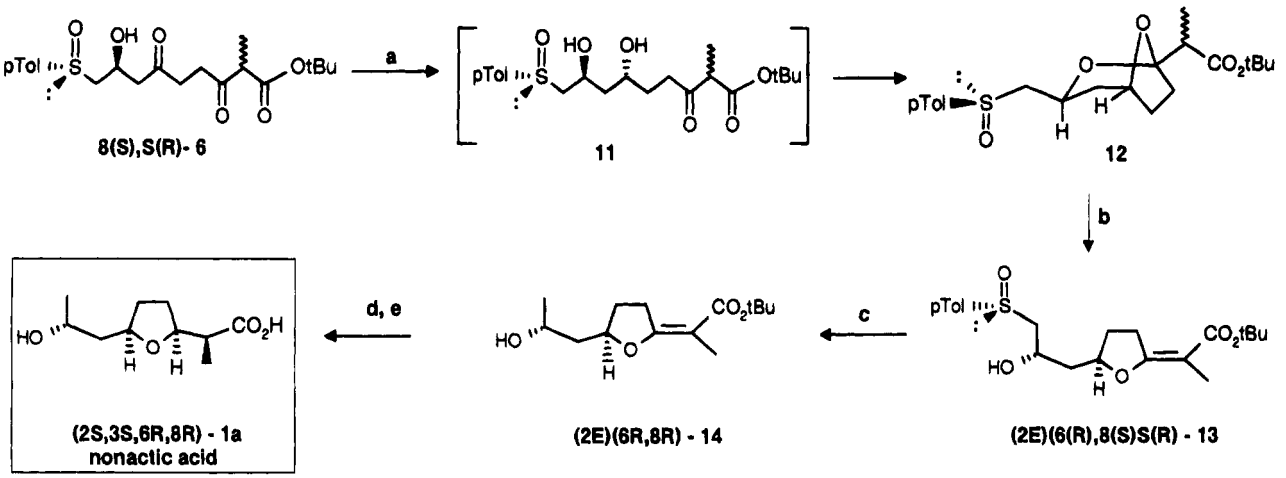
Scheme 4[a]



[a] (a) $(Me_4N)BH(OAc)_3$, AcOH, rt, 2.5 h, 78%; (b) HCL, rt, 3 h, 50%; (c) Raney Ni, MeOH, rt, 30 min, 97%; (d) Rh/Al_2O_3, H_2, 3 days, 97%; (d) 2 N KOH, H_2O, rt, 58%.

terminal methyl group in the ^{1}H-NMR spectrum and the signal of C-6 in the ^{13}C NMR spectrum). Finally, Rh–Al_2O_3-catalyzed reduction[2n] of **14** gave the desired (+)-(2*S*,3*S*,6*R*,8*R*)-*tert*-butyl-nonactate (**1b**), which was converted by saponification to (+)-(2*S*,3*S*,6*R*,8*R*)-nonactic acid (**1a**).[2i]

In conclusion, we have reported a short asymmetric synthesis of both subunits of the antibiotic nonactin, (−)-(2*R*,3*R*,6*S*,8*R*)-*epi*-nonactic acid and (+)-(2*S*,3*S*,6*R*,8*R*)-nonactic acid, in only six steps with an overall yield of 35 and 20%, respectively (yields were not optimized). The formation of the exocyclic asymmetric center at C-8 of the nonactic esters frame has been induced by a chiral sulfoxide group, and no protecting groups were used in any step of the synthesis.

Experimental Section

***tert*-Butyl ethyl 3-oxo-2-methyladipate (4).** To a stirred solution of potassium *tert*-butoxide (1.43 g, 11.4 mmol) in *tert*-butyl alcohol (30 mL) was added a solution of **3**[4] in *tert*-butyl alcohol (10 mL). The solution was stirred at 25 °C for 30 min and then an excess of iodomethane (2 mL) was added. The mixture was stirred for 20 min, hydrolyzed with H_2O, and extracted with CH_2Cl_2 (3 × 20 mL). The organic phases were dried and evaporated, and the crude product was purified by column chromatography (silica gel, AcOEt/hexane: 1/2) to give 1.96 g (80%) of the keto ester **4** as a colorless liquid: IR 1730 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.22 (t, 3H, J = 7 Hz), 1.30 (d, 3H, J = 7 Hz), 1.46 (s, 9H), 2.54-2.89 (m, 4H), 3.47 (q, 1H, J = 7 Hz), 4.10 (q, 2H, J = 7 Hz); ^{13}C-NMR δ 204.48, 172.42, 169.5, 81.78, 60.58, 53.75, 35.90, 29.10, 14.09, 12.61.

***tert*-Butyl (+)-(*R*)-2-Methyl-3,6,8-trioxo-9-(*p*-toluenesulfinyl)nonanoate (5).** To a stirred solution of diisopropylamine (4.6 mL, 33 mmol) in THF (38 mL) under argon at −15 °C was dropwise added a 1.5 M solution of *n*-butyllithium in hexane (21 mL, 32.1 mmol). After stirring for 30 min, the mixture was allowed to reach 0 °C and a solution of (+)-(*R*)-1-(*p*-toluenesulfinyl)propanone-2[3a] (3.2 g, 16.3 mmol) in THF (30 mL) was added and stirred for 30 min. The resulting solution was added to a solution of ester **4** (1.35 g, 5.26 mmol) in THF (33 mL) at 0 °C. The reaction mixture was allowed to reach room temperature and was stirred for 2 h. The solution was finally hydrolyzed with saturated ammonium chloride (150 mL) and a 5% sulfuric acid solution till pH = 2, extracted with ethyl acetate (3 × 35 mL), dried (Na_2SO_4), and evaporated. The crude product was purified by chromatography on metal-free silica gel[8] to obtain **5** as a yellow oil (1.6 g, 75%): $[\alpha]_D$ = +149 (c = 0.7, $CHCl_3$); ^{1}H NMR (200 MHz) δ 1.29 (d, 3H, J = 7 Hz), 1.46 (s, 9H), 2.42 (s, 3H), 2.60−2.90 (m, 4H), 3.47 (q, 1H, J = 7 Hz), 3.58 (AB, 2H, J_{AB} = 11.8Hz), 5.56 (s, 1H), 7.31−7.55 (4H). Anal. Calcd for $C_{21}H_{28}O_6S$: C, 61.74; H, 6.91. Found: C, 61.80; H, 6.89.

***tert*-Butyl [8(*S*),S(*R*)]-8-Hydroxy-2-methyl-3,6-dioxo-9-(*p*-toluenesulfinyl)nonanoate (6).** To a solution of compound **5** (300 mg, 0.73 mmol) in anhydrous THF (15 mL) under argon at −78 °C was added dropwise a solution 1 M in toluene of DIBAL (1.5 mL, 1.5 mmol). After stirring for 15 min at −78 °C the mixture was quenched with a saturated ammonium chloride solution (50 mL) and the pH was adjusted to 4−5 with a 5% H_2SO_4 solution. The solution was extracted with ethyl acetate (3 × 20 mL), dried, and evaporated. The crude product was purified by chromatography on metal-free silica gel[8] to give **6** (180 mg, 60%): $[\alpha]_D$ = +135 (c = 1.01, $CHCl_3$); ^{1}H NMR (200 MHz) δ 1.27 (d, 3H, J = 7 Hz), 1.44 (s, 9H), 2.40 (s, 3H), 2.60−2.84 (m, overlap of the AB pattern of CH_2SO and the m of CH_2CH_2), 2.60−3.05 (AB part of ABX partially overlapped with a m, J_{AX} = 9.5 Hz, J_{AB} = 13.4 Hz), 3.44 (q, 1H, J = 7 Hz), 4.29 (bs, 1H), 4.60 (X part of ABX, 1H), 7.30−7.53 (m, 4H); ^{13}C NMR δ 207.81, 205.09, 170.20, 141.75, 130.19, 124.08, 82.03, 63.77, 61.27, 53.78, 48.87, 36.91, 35.01, 27.97, 21.50, 12.81. Anal. Calcd for $C_{21}H_{30}O_6S$: C, 61.44; H, 7.37. Found: C, 61.20; H, 7.41.

(2*E*)-[6(*S*),8(*S*),S(*R*)]-*tert*-Butyl 2,3-Dehydro-*epi*-nonactate (9). (1) Formation of the lactol 8. to a solution of **6** (80 mg, 0.19 mmol) in a 3/1 mixture of anhydrous THF and methanol (2 mL), under argon at −78 °C, was added dropwise a 1 M solution in THF of diethylmethoxyborane (0.2 mL, 0.2 mmol), producing a white precipitate. After the slurry was stirred for 15 min, sodium borohydride (8 mg, 0.21 mmol) was introduced. H_2 evolution was immediate, giving a clear, effervescent solution. The reaction was stirred for 2.5 h at −78 °C, quenched with 1 mL of a 1 N aqueous acetic acid, and warmed to room temperature. After it was stirred for an additional 20 min, the mixture was diluted with 5 mL of saturated $NaHCO_3$ and extracted with ethyl acetate (3 × 10 mL). The organic layers were dried, filtered, and evaporated. The residue thus obtained was azeotroped five times with methanol until the hydrolysis of the boronate was complete and then percolated on silica gel using ethyl acetate as eluent to give 62 mg of lactol **8** (80%) as a colorless oil: ^{1}H NMR (200 MHz) δ 1.07, 1.01 (two d), 1.43 (s, 9H), 1.65−2.19 (m, 6H), 2.41 (s, 3H), 2.69−2.95 (AB part of a ABX and m overlapped), 4.17−4.44 (m, 3H), 7.27−7.55 (m, 4H); ^{13}C NMR δ 172.82, 141.57, 130.11, 123.99, 110.4, 81.02, 78.29, 66.00, 63.55, 48.48, 28.03, 21.48, 13.18.

(2) Dehydration of Lactol 8. The lactol **8** (62 mg, 0.15 mmol) was dissolved in dichloromethane (5 mL), a catalytic

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amount of pyridinium *p*-toluenesulfonate was added, and the mixture was stirred at room temperature for 1 h. The resulting solution was partitioned between saturated $NaHCO_3$ (10 mL) and AcOEt (10 mL). The organic layer was dried and evaporated, and the crude product was purified by column chromatography on silica gel with AcOEt as eluent to give **9** (56 mg, 95%) as a colorless oil: $[\alpha]_D = +120$ ($c = 0.4$, $CHCl_3$); ^1H NMR (200 MHz) δ 1.45 (s, 9H), 1.6–1.8 (m, partially overlapped with a d), 1.70 (t, $J = 1.5$ Hz) 2.20 (m, 1H), 2.43 (s, 3H), 2.6–3.26 (m, 4H), 4.10 (bs, 1H), 4.50 (m, 2H), 7.3–7.5 (m, 4H); ^{13}C NMR δ 168.12, 147.7, 130.2, 124.05, 139.31, 99.61, 80.14, 79.38, 65.17, 60.88, 41.68, 30.72, 30.46, 28.51, 21.51, 11.79. Anal. Calcd for $C_{21}H_{30}O_5S$: C, 63.93; H, 7.67. Found: C, 63.84; H, 7.73.

***tert*-Butyl (2*R*,3*R*,6*S*,8*R*)-*epi*-nonactate (2b). (1) Desulfurization of Compound 9.** To a solution of **9** (100 mg, 0.25 mmol) in methanol (10 mL) a catalytic amount of Raney nickel was added. The mixture was vigorously stirred for 30 min at room temperature. The solution was filtered through Celite to remove the remaining nickel and the Celite washed with methanol. The solution was evaporated and the crude product purified by column chromatography (silica gel, AcOEt/Hexane: 1/1) to give 63 mg of (2*E*)-(6*S*,8*R*)-*tert*-butyl 2,3-dehydro-*epi*-nonactate (**10**) (98%) as a colorless oil: ^1H NMR (200 MHz) δ 1.24 (d, 3H, $J = 6$ Hz), 1.42 (S, 9H), 1.62–1.80 (m, 6H), 1.75 (t, $J = 1.5$Hz), 2.25 (m, 1H), 2.74–3.00 (m, 1H), 3.12–3.26 (m, 1H), 4.10 (m, 1H), 4.50 (m, 1H); ^{13}C RMN δ 168.72, 168.18, 99.65, 82.37 (C-6), 79.36, 67.07, 44.52, 30.83, 30.66, 28.51, 23.55 11.83.

(2) Double Bond Reduction of Compund 10. A mixture of **10** (25 mg, 0.1 mmol) and 5% rhodium on alumina (60 mg) in methanol (10 mL) was shaken under a hydrogen atmosphere of 4 bars for 3 days. The mixture was filtered through Celite and evaporated to give 25 mg of **2b** pure (98%) as a colorless oil: $[\alpha]_D = -19$ ($c = 0.5$, $CHCl_3$); ^1H NMR (200 MHz) δ 1.08 (d, 3H, $J = 7$ Hz), 1.16 (d, 3H, $J = 6$ Hz), 1.44 (s 9H), 1.47–1.63 (m, 4H), 1.94–2.0 (m, 2H), 2.37–2.5 (m, 1H), 3.60 (bs, 1H), 3.96–4.10 (m, 3H); ^{13}C NMR δ 174.26, 81.86, 80.30, 80.4, 68.00, 46.28, 44.69, 31.86, 28.27, 28.12, 23.49, 13.54.

(−)-(2*R*,3*R*,6*S*,8*R*)-*epi*-Nonactic Acid (2a). The saponification of the ester **2b** was carried out following the known procedure[2i] with a 2 N aqueous KOH solution: yield 48%; $[\alpha]_D = -48$ ($c = 0.2$, $CHCl_3$), lit.[2i] −50 ($c = 1$, $CHCl_3$). All the spectral characteristics were identical to the reported values.[2i] Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.50; H, 8.88.

(2*E*)-[6(*R*),8(*S*),S(*R*)]-*tert*-Butyl 2,3-Dehydrononactate (13). (1) Formation of the Bicyclic Acetal 12. Tetramethylammonium triacetoxyborohydride (355 mg, 1.35 mmol, 5 equiv) was dissolved in anhydrous acetic acid (3 mL) and stirred for 30 min at room temperature. The mixture was then cooled with an ice bath till solidification and a solution of **6** (110 mg, 0.27 mmol, 1 equiv) in acetic acid (6 mL) was added dropwise. The solution was stirred at room temperature for 2.5 h. A saturated sodium tartrate solution (10 mL) was then added and the resulting mixture poured on ice and neutralized with $NaHCO_3$. After extraction with CH_2Cl_2, the organic phases were washed with brine (15 mL), dried (Na_2SO_4), and evaporated to give the crude product which was filtered through silica gel (AcOEt/hexane: 20/3) to give 80 mg (78%) of the bicyclic acetal **12**: ^1H NMR (200 MHz) δ 1.20, 1.30 (2 × d, $J = 7$ Hz, two isomers), 1.42 (s, 9H), 1.70–2.40 (m, 6H), 2.4 (s, 3H,), 2.7–3.0 (m, 3H), 4.6 (m, 2H), 7.3–7.5 (m, 4H); ^{13}C NMR δ 171.9, 141.7, 141.6, 130.3, 123.96, 107.56, 80.79, 75.2, 63.3, 65.6, 36.5, 31.7, 28.0, 47.7, 28.3, 21.6, 12.6.

(2) Acetal Opening. Compound **12** (60 mg, 0.15 mmol) was dissolved in THF (5 mL) and a catalytic amount of a 1 N HCl solution was added. The mixture was stirred for 3 h at room temperature. The solution was then neutralized with a saturated solution of $NaHCO_3$, extracted with CH_2Cl_2, dried, and evaporated. The resulting oil (mixture of starting material and compound **13**) was chromatographed on silica gel (AcOEt) to give 30 mg (50%) of **13**: $[\alpha]_D = -150$ ($c = 0.3$, $CHCl_3$); ^1H NMR (200 MHz) δ 1.47 (s, 9H), 1.6–1.95 (m, partially overlapped with the signal at 1.70), 1.70 (t, $J = 1.5$ Hz, 3H), 2.2 (m, 1H), 2.4 (s, 3H), 2.7–3.2 (m, 4H), 4.1 (d, 1H), 4.5 (m, 2H), 7.3–7.5 (m, 4H). Anal. Calcd for $C_{21}H_{30}O_5S$: C, 63.93; H, 7.67. Found: C, 63.79; H, 7.54.

(2*S*,3*S*,6*R*,8*R*)-*tert*-Butyl Nonactate (1b). (1) Desulfurization of compound 13. To a solution of **13** (30 mg, 0.07 mmol) in methanol (6 mL) was added a catalytic amount of Raney nickel. The mixture was vigorously stirred for 30 min at room temperature. Remaining nickel was filtered on Celite and the Celite washed with methanol. The solution was evaporated and the crude product purified by column chromatography (AcOEt/hexane: 1/1) to obtain 17 mg of (2*E*)-(6*R*,8*R*)-*tert*-butyl 2,3-dehydrononactate (**14**) (97%) as a colorless oil: ^1H NMR (200 MHz) δ 1.26 (d, 3H, $J = 6$ Hz), 1.47 (s, 9H), 1.69–1.79 (m, 6H), 1.76 (t, 3H, $J = 1.5$Hz), 2.2 (m, 1H), 2.83–3.00 (m, 1H), 3.11–3.26 (m, 1H), 4.1 (m, 1H), 4.61 (m, 1H); ^{13}C NMR δ 168.87, 168.53, 99.33, 79.99, 79.19, 65.37, 44.04, 31.05, 30.56, 28.53, 24.08, 11.78.

(2) Double Bond Reduction of Compound 14. A mixture of **14** (17 mg, 0.07 mmol) and 5% rhodium on alumina (30 mg) in methanol (6 mL) was shaken under hydrogen atmosphere at 4 bars for 3 days. The mixture was filtered through Celite and evaporated to give 16 mg of pure **1b** (97%) as a colorless oil: $[\alpha]_D = +15$ ($c = 0.3$, $CHCl_3$); ^1H NMR (200 MHz) δ 1.11 (d, 3H, $J = 7$ Hz), 1.20 (d, 3H, $J = 6$ Hz), 1.4 (s, 9H), 1.53–1.76 (m, 4H), 1.92–2.10 (m, 2H), 2.39–2.50 (m, 1H), 3.6 (bs, 1H), 3.97–4.13 (m, 3H).

(+)-(2*S*,3*S*,6*R*,8*R*)-Nonactic Acid (1a). The saponification of the ester 1b was carried out following the known procedure[2i] with a 2 N aqueous KOH solution: yield 58%; $[\alpha]_D = +9$ ($c = 0.15$, $CHCl_3$), lit.[2i] +10 ($c = 1.69$, $CHCl_3$). Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.14; H, 9.10.

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Supplementary Material Available: The full listing of NMR data, complete with peak assignments (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.