# Enantiodivergent Syntheses of (+)- and (−)-Nonactic Acid and the Total Synthesis of Nonactin

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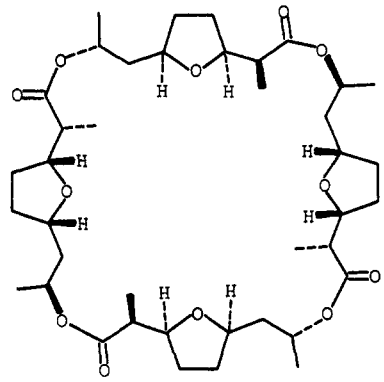
**Abstract:** The crystalline (*S*)-(−)-epoxy tosylate **16** is prepared in 76% overall yield from dimethyl (*S*)-(−)-malate. Reaction of this material with lithium dimethylcyanocuprate affords (*S*)-(−)-1,7-octadien-4-ol ((−)-**17**). Iodocyclization of the *tert*-butyl carbonate (−)-**6** and deiodination of the cis product lead to the cyclic carbonate (−)-**18**, which is transformed in a straightforward series of reactions to the β-keto ester (−)-**21**. This compound is a pivotal intermediate in the synthesis, because it can be converted into nonactic acid derivatives of either the (+) or the (−) series. Methanolysis of the cyclic carbonate moiety of (−)-**21**, acid-catalyzed dehydration, and hydrogenation of the resultant (6*S*,8*R*)-(*E*)-2,3-dehydrononactate (+)-**8** provide (−)-methyl 8-*epi*-nonactate ((−)-**9**). In contrast, direct cyclization of the potassium enolate of (−)-**21** affords the diastereomeric (6*R*,8*R*)-(*E*)-2,3-dehydrononactate (−)-**25** and, after hydrogenation, (+)-methyl nonactate ((+)-**2b**). The two subunits are coupled with inversion of configuration at C-8 of the (−)-nonactate moiety to afford methyl (+)-nonactyl (−)-nonactate **35a**. After methyl ester cleavage, the dimeric acid **35b** is activated and simultaneously dimerized and cyclized to provide the natural product nonactin (**1**).

Nonactin (**1**) has proven to be a molecule of enduring interest since its characterization in 1955.[2] It is the lowest homologue

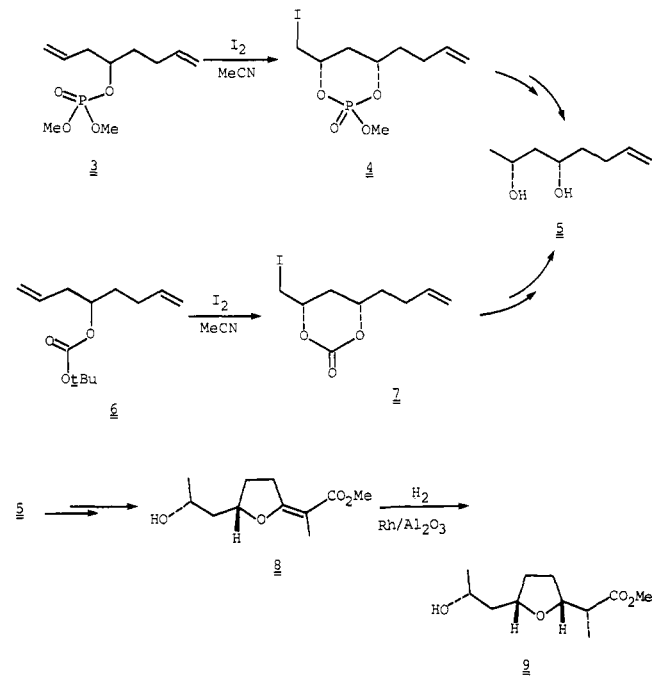


nonactin, 1

and most symmetrical member of the actin family of antibiotics, which have been isolated from a variety of *Streptomyces* cultures.[3] It was the first naturally occurring compound to be identified as a crown ether, and one of the earliest whose antibiotic activity could be traced to its ionophoric properties. In a classic application of stereochemical logic and chemical analysis, both the *meso* nature of the macrotetrolide ring and the relative stereochemistry of the nonactic acid subunits were determined by Prelog and Gerlach and their collaborators 20 years ago.[4] Their assignment was later confirmed by a crystallographic study of the nonactin–potassium thiocyanate complex.[5]

As a target for total synthesis, there are a number of stereochemical challenges embodied in the structure of nonactin. Within the nonactic acid subunit itself, there are 1,2- and 1,3-acyclic relationships to be controlled, as well as the cis stereochemistry around the tetrahydrofuran ring. In the assembly of the macrotetrolide, a higher level of stereocontrol must be exercised, in that optically active nonactic acid subunits must be incorporated in the correct sequence of alternating chirality. One is therefore confronted with the unusual requirement for *both* enantiomers of an intermediate target.

**Scheme I**



No fewer than nine syntheses of nonactic acid have been described, with various strategies and varying success with respect to diastereomeric and enantiomeric control.[6-9] The first synthesis which afforded the two enantiomers of nonactic acid in optically active form was that of Schmidt et al.[8a] Starting with (*S*)-propene

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oxide, a mixture of all four 3,6-cis-8*S*-methyl esters was generated; manipulation of this mixture provided the (−) enantiomer (−)-**2a**

(−)-**2** **a**: R = H **b**: R = Me (+)-**2**

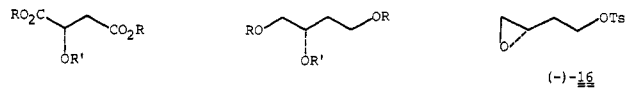
(2*R*,3*R*,6*S*,8*S*) and the tosylate of the (+)-C-8 epimer (2*S*,3*S*,6*R*,8*S*). The latter isomer led to (+)-nonactate (+)-**2b** on inversion at C-8. Subsequent syntheses of optically active material have utilized carbohydrate precursors, necessitating duplicate parallel sequences to produce the two enantiomers. Interestingly, no resolution of racemic nonactic acid has been reported.[10]

Two syntheses of the macrocyclic natural product itself have been described. Gerlach and co-workers assembled the linear tetramer from racemic nonactic acid monomers; macrocyclization of the 2-pyridinethiol ester then furnished a mixture of three (out of a possible four) stereoisomeric macrotetrolides, from which nonactin could be isolated in ca. 10% yield.[11] The Schmidt group constructed the same cyclization substrate in a stereocontrolled fashion; that is, with nonactic acid subunits of alternating chirality. Cyclization in this instance afforded a 20% yield of nonactin.[8a]

In our approach to nonactic acid (Scheme I), we first addressed the 1,3-relationship between C-6 and C-8.[6c] This relationship was introduced in a diastereoselective manner by iodocyclization of the phosphate ester **3**.[12] Subsequent elaboration of the iodo phosphate **4** provided the *syn*-7-octene-2,4-diol (**5a**). More recently, we have developed an analogous carbonate cyclization process (**6** → **7** → **5**) which affords the same intermediate.[13] After elaboration of **5** to the conjugated enol ether **8**, the remaining chiral centers are introduced with the correct configuration relative to C-6 by hydrogenation. The major product of this reduction is 8-*epi*-nonactate **9**, and inversion at C-8 is necessary to produce the natural diastereomer.

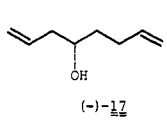
In this report, we describe a more direct route to the natural diastereomer of nonactic acid, application of this route to the enantiospecific synthesis of both optical antipodes from a common optically active intermediate (an "enantiodivergent" strategy[14]) and the total synthesis of the natural nonactin.

**Synthesis of (*S*)-(−)-1,7-Octadien-4-ol ((−)-17).** In the preparation of optically active dienol **17**, epoxy tosylate **16** is the key



**10**: R = R' = H
**11**: R = Me, R' = H
**12**: R = Me, R' = $CH(OEt)CH_3$
**13**: R = H, R' = $CH(OEt)CH_3$
**14**: R = Tosyl, R' = $CH(OEt)CH_3$
**15**: R = Tosyl, R' = H

(−)-**16**



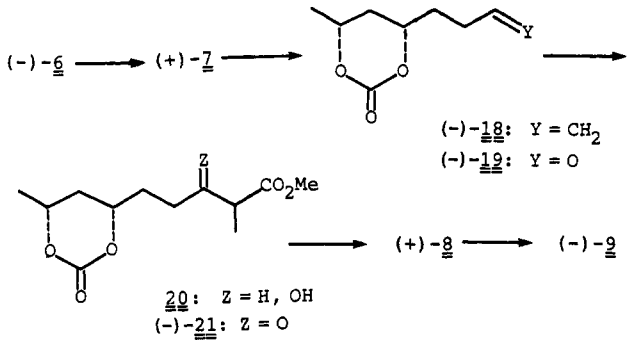
(−)-**17**

intermediate. This crystalline material is prepared in a straightforward manner as follows. (*S*)-(−)-Malic acid (**10**) is esterified and protected as the ethoxyethyl ether **12**; lithium aluminum hydride reduction and tosylation of the resulting diol provides bis(tosylate) **14**; finally, deprotection and potassium carbonate induced cyclization lead to the crystalline epoxy tosylate (−)-**16**. Although the sequence to this synthon involves a number of transformations, the overall yield of 75% compares favorably to those leading to the related optically active halides and mesylate.[15]

Reaction of the bifunctional intermediate **16** with an excess of a divinylcuprate reagent affords the optically active octadienol (−)-**17** directly. We explored both the conventional Gilman reagent (lithium divinylcuprate,[16] prepared from CuBr/dimethyl sulfide in 20% dimethyl sulfide/ether[16c]), and the Lipschutz version (prepared from cuprous cyanide).[17] The latter reagent gave consistently better results, affording dienol **17** in >80% yield on a 10-g scale.

A critical element in this transformation is the purity of the vinyllithium, particularly with respect to contamination by butyllithium. The preparation of vinyllithium by the reaction of butyllithium with tetravinylstannane[18] in our hands produces material that is contaminated with ca. 3–5% of butyllithium, even with careful washing of the precipitated vinyllithium with hexane. Although lithium methylvinylcuprate selectively transfers the vinyl group in conjugate addition reactions,[19] the reverse selectivity appears to hold in substitution reactions with $sp^3$-hybridized substrates.[19b] In our experience, if the vinyllithium is not freed of contaminating butyllithium prior to formation of the cuprate, a significant amount of a butyl-containing side product is produced in the conversion of epoxy tosylate **16** to dienol **17**. Since at least 4 equiv of vinyllithium are required by the stoichiometry of the reaction between a divinylcuprate and **16**, 3–5% contamination by a butyl-containing cuprate results in approximately 15–20% of the side product. We were able to free the vinyllithium from butyllithium contaminant by taking advantage of their differing stabilities in tetrahydrofuran:[18b,20] on standing in THF solution at room temperature for several days, the butyllithium is selectively destroyed, and the vinyllithium (reisolated by evaporation) affords divinylcuprate reagents that lead cleanly to the dienol **17**.

**Synthesis of (−)-Methyl 8-*epi*-Nonactate ((−)-9).** Although the diol **5** (in racemic form) figured in our previously reported synthesis of methyl nonactate,[6c] use of the carbonate cyclization (**6** → **7**) allows the route to be streamlined as shown below. Iodocyclization of the (*S*)-(−)-carbonate (−)-**6** gives a 6.5:1 ratio of cis and trans iodocarbonates, from which the desired cis isomer (+)-**7** can be isolated by chromatography in 55% yield on a 15-g scale.[13a] Tributylstannane reduction of this intermediate gives 2*R*,4*S*-(−) carbonate (−)-**18**, a protected derivative of diol **5**. The



(−)-**6** (+)-**7** (−)-**18**: Y = $CH_2$ (−)-**19**: Y = O (+)-**8** (−)-**9**

**20**: Z = H, OH (−)-**21**: Z = O

overall yield in this sequence is 53%, including chromatographic separation of the iodocarbonate diastereomers. The efficiency of this transformation is comparable to that involving the more stereoselective phosphate cyclization (**3** → **5**),[6c] but it is more reproducible and easier to carry out on a multigram scale.

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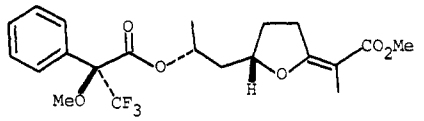
Ozonolysis of **18**, condensation of the aldehyde (−)-**19** with the trimethylsilyl enol ether of methyl propionate according to Mukaiyama,[21] and Jones oxidation of the resulting β-hydroxy ketone **20** proceed in strict analogy to our earlier route[6c] and afford the β-keto ester (−)-**21** in ca. 75% overall yield. This material proved to be a crucial intermediate in a route to the two enantiomeric forms of the nonactic acid moiety, as described in the following section. Methanolysis of the carbonate protecting group and oxalic acid catalyzed dehydration of the hydroxy ketone provide the (+)-enantiomer of **8** ((6*S*,8*R*)-(*E*)-2,3-dehydrononactate) in 76% yield, intersecting our previous synthesis.

The optical purity of (+)-**8** was demonstrated by formation of the Mosher ester with (*S*)-(−)-2-methoxy-2-phenyl-3,3,3-trifluoropropanoyl chloride.[21] The product **22** was obtained in 88%



**22**

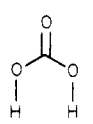
yield and appeared to be a single isomer (>98%) by both 250-MHz $^1$H and 84.7-MHz $^{19}$F NMR.

The remaining two chiral centers are introduced by hydrogenation of (+)-**8** with 5% rhodium on alumina catalyst. The chemical yield in this step is quantitative, and the desired product, methyl (2*R*,3*R*,6*S*,8*R*)-nonactate (8-*epi*) (−)-**9**, is the major product. The stereochemical aspects of the reaction will be discussed more fully below.

**Synthesis of (+)-Methyl Nonactate ((+)-2b).** To synthesize the enantiomeric nonactate esters, an obvious approach would be to invert the configuration of the optically active octadienol precursor (**17**). A more efficient approach, however, would be to invert the configuration at this center at a later stage in the synthesis. The stereochemical rotationale behind such a strategy is illustrated in Scheme II. In the synthesis just described, the tetrahydrofuran ring is formed by acid-catalyzed dehydration of keto diol **23**. This process involves closure of the hydroxyl oxygen on the carbonyl carbon, along path a, and furnishes derivatives of the (−)-nonactic acid series. In contrast, if ring closure could be induced along the alternative path b, by attack of the carbonyl oxygen on C-6 *with inversion*, a diastereomeric enol ether **25** would be produced, and direct access to the enantiomeric (+)-nonactate derivatives would be possible.

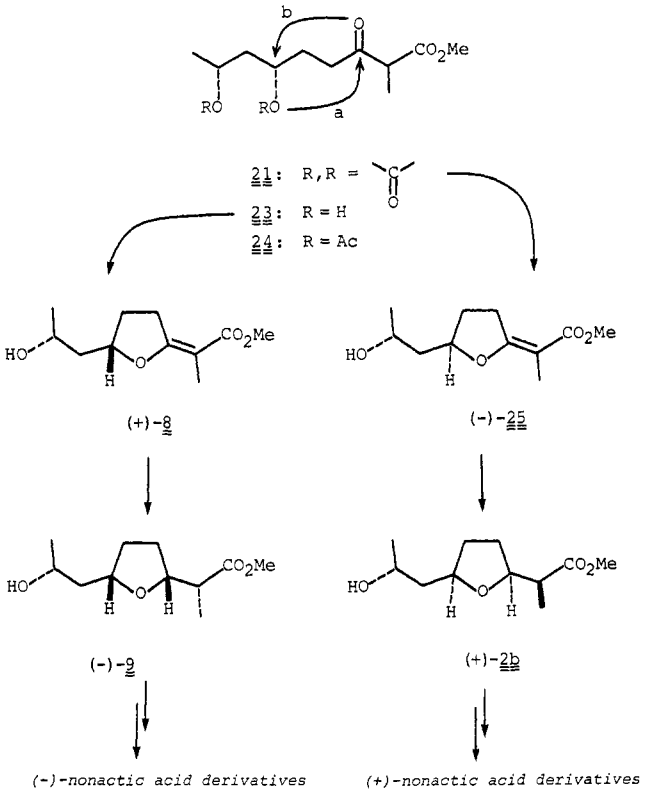
In fact, formation of the enolate of β-keto ester **21** results in facile cyclization along path b, with the carbonate ion functioning as the leaving group in an intramolecular O-alkylation process. Under the optimal cyclization conditions, involving potassium hydride in 5% hexamethylphosphoramide (HMPA)/THF at room temperature, this reaction provides (−)-**25** in >90% yield. That cyclization occurs exclusively on oxygen was not unexpected, there being ample theoretical[23] and experimental[24] precedent. We were not prepared for the ease with which this cyclization takes place, however. In contrast, the enolate of the analogous diacetate **24** shows only slow degradation in $Me_2SO$ at 150 °C, with no evidence for the formation of cyclic enol ether.

The greater reactivity of the cyclic carbonate can be understood when one recognizes that it is constrained in the doubly unfavorable syn–syn conformation. It has in fact been estimated on the basis of ab initio studies that the analogous conformation of carbonic acid (**26**) is more than 12 kcal mol$^{-1}$ less stable than the



syn–anti or anti–anti forms.[25] Since there is only a single bi-

**Scheme II**




carbonate anion, the instability of the syn–syn conformer of carbonic acid would be released on ionization. Clearly, only a part of this instability must be released in the transition state for cyclization of **21** to explain the extraordinary reactivity of the carbonate anion as a leaving group. The enhanced reactivity of cyclic carbonates toward nucleophilic displacement has been described previously for ethylene carbonate and cyclic carbonates in the carbohydrate field.[26]

Inversion of C-6 during the cyclization of **21** to **25** not only provides access to the enantiomeric series, it also obviates the necessity for inversion at C-8 in order to obtain the correct relative configuration of nonactic acid: hydrogenation of **25** provides (+)-methyl nonactate ((1+)-**2b**) directly.

**Stereochemistry of Reduction of (+)-8 and (−)-25.** We envisaged that the chiral centers at C-2 and C-3 could be introduced with the correct relative configuration with respect to that at C-6 if (1) the *E* geometry of the enol ether moiety could be established either thermodynamically or kinetically, and (2) hydrogenation of the double bond could be directed sterically to the face that is cis to the hydrogen at C-6. The desired *E* stereochemistry is in fact the overwhelmingly preferred configuration of the double bond, and the hydrogenation with rhodium on alumina does proceed predominantly in the desired sense, as we reported for (±)-**8**[6c] and as Barrett and Sheth subsequently confirmed for a protected derivative of its diastereomer (±)-**25**.[6f]

In our original communication, we reported that hydrogenation of (±)-**8** results in an 85:15 ratio of the desired product (±)-8-*epi*-nonactate (±)-**9** and the trans tetrahydrofuran **27** ("8-*epi*-trans"), which results from catalyst approach from the opposite face of the double bond. In subsequent experiments, the observed ratios of desired to undesired isomers varied and appeared to correlate with the condition of the catalyst; freshly obtained 5% $Rh/Al_2O_3$, for example, gave apparent ratios up to 20:1. When optically active substrate was hydrogenated, however, the specific rotation of the product was considerably lower than expected, on

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**Table I.** $^1$H NMR Chemical Shifts of Methyl Nonactate Diastereomers[a]

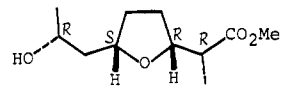
| stereoisomer | δ MeO | δ 2-Me ($J$ = 7.0 Hz) | δ 9-Me ($J$ = 6.2 Hz) |
|---|---|---|---|
| From Hydrogenation of (+)-Methyl 8-*epi*-(*E*)-2,3-Dehydrononactate ((+)-**8**) | | | |
| *R,R,S,R*, (−)-**9** (8-*epi*) | 3.700 (3.644) | 1.125 (1.093) | 1.169 (1.074) |
| *S,S,S,R*, **27** (8-*epi*-trans) | 3.693 (*b*) | 1.125 (*b*) | 1.168 (*b*) |
| *S,R,S,R*, **28** (2,8-bis-*epi*) | 3.681 (3.629) | 1.221 (1.204) | 1.177 (1.083) |
| *R,S,S,R*, **29** (2,8-bis-*epi*-trans) | 3.678 (3.629) | 1.226 (1.223) | 1.178[c] (1.082)[c] |
| From Hydrogenation of (−)-Methyl (*E*)-2,3-Dehydrononactate ((−)-**25**) | | | |
| *S,S,R,R*, (+)-**2b** (natural) | 3.696 (3.639) | 1.132 (1.089) | 1.206 (1.124) |
| *R,R,R,R*, **30**, (trans) | 3.698 (3.642) | 1.117 (1.078) | 1.202[c] (1.124)[c] |
| *R,S,R,R*, **31** (2-*epi*) | 3.683 (3.623) | 1.222 (1.190) | 1.214 (1.130) |
| *S,R,R,R*, **32** (2-*epi*-trans) | (*b*) (*b*) | 1.227 (1.197) | 1.216 (1.137) |

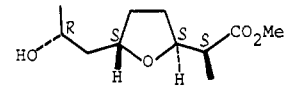
[a] Chemical shifts given for dilute solution in $CDCl_3$ and ($CCl_4$) solvent, relative to internal tetramethylsilane. Spectra were recorded on a 250-MHz FT instrument. [b] Resonance not observed. [c] Assignment tentative (peak overlapped with that of another isomer).

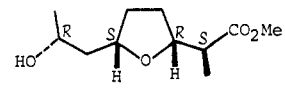
the basis of this apparent ratio.[27] Moreover, examination of the hydrogenation products by 250-MHz $^1$H NMR revealed additional diastereomers. These more recent results indicated that the hydrogenation process is more complicated than initially anticipated and required reassignment of the stereochemistry of the minor isomers and an alternative explanation for their formation.

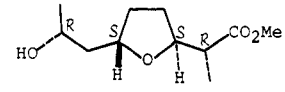
The 250-MHz $^1$H NMR spectrum in $CDCl_3$ solvent of the crude product resulting from hydrogenation of (+)-**8** showed methoxyl resonances for the major isomer (−)-**9** at δ 3.700 and for minor isomers at δ 3.693 and 3.681. As will be discussed below, the minor isomers were shown to be the *S,S,S,R* (8-*epi*-trans, **27**) and *S,R,S,R* (2,8-bis-*epi*, **28**) diastereomers, respectively. The selectivity of the hydrogenation process depends upon the catalyst sample (see below), but a typical product contained (−)-**9** and the two isomers **27** and **28** in the ratio 88:9:3, respectively. Careful column chromatography provided a sample of the less polar *S,R,S,R* isomer **28**, free of (−)-**9** (*R,R,S,R*). The NMR spectrum of this column fraction (<4% of the purified product) revealed a peak at δ 3.678 for a *fourth* compound, which proved to be the other trans isomer, **29** (*R,S,S,R*, 2,8-bis-*epi*-trans). The stereorelationship between the various isomers was revealed by subjecting the two chromatographic fractions to DBU in refluxing benzene. As Schmidt has reported,[8a] these conditions result in epimerization of the C-2 methyl group without ring opening and cis/trans isomerization. The interconversion of (−)-**9** and **28** indicated that they are C-2 epimers and allowed the structure of the latter to be assigned. The trans isomers **27** and **29** were also interconverted under these conditions; which was the *S,S,S,R* isomer and which was the *R,S,S,R* was revealed by the methyl doublet regions of their $^1$H NMR spectra (Table I). First, the doublets for the C-2 methyl substituent and the C-9 methyl can be distinguished by their coupling constants: $J$ = 7.0 Hz for the former and 6.2 Hz for the latter.[8a] Second, as noted prevously,[4b,6b] in isomers with the natural relative configuration between C-2 and C-3 (2*R*,3*R* or 2*S*,3*S*), the C-2 methyl group resonates approximately 0.1 ppm upfield of its position in the 2-*epi* diastereomers. This relationship appears to be valid for the trans isomers as well.

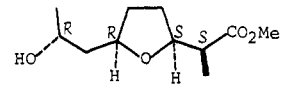
Analogous results were obtained on reduction of (−)-**25**: the product showed methoxyl resonances in the 250-MHz $^1$H NMR spectrum ($CDCl_3$ solvent) at δ 3.696, 3.698, and 3.683 for (+)-methyl nonactate ((+)-**2b**, *S,S,R,R*) and the trans (**30**, *R,R,R*) and 2-*epi* (**31**, *R,S,R,R*) isomers, respectively. The ratios varied but were again typically 88:9:3. Although a fourth methoxyl resonance could not be discerned unambiguously, the methyl doublets of the remaining diastereomer **32** (*S,R,R,R*) could be found in spectra of early chromatographic fractions. Again, epimerization studies indicated that the four isomers comprised two sets of C-2 epimers. High-field $^1$H NMR information is therefore available for all eight diastereomers of methyl nonactate, and is summarized in Table I.

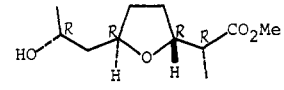

(−)-**9**

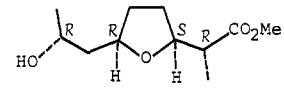

**27**

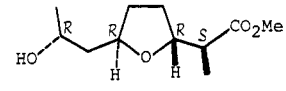

**28**


**29**


(+)-**2b**


**30**


**31**

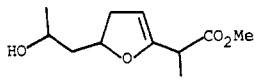

**32**

A gratifying consistency extends throughout this table. As indicated above, the chemical shift of the C-2 methyl substituent has been correlated previously with the stereochemical relationship between C-2 and C-3.[4b,6b] Table I indicates that this correlation extends to the trans tetrahydrofuran isomers as well and that the natural and 2-*epi* isomers can be distinguished unambiguously (2*R**,3*R**, δ <1.14 in $CDCl_3$ (<1.10 in $CCl_4$); 2*R**,3*S**, δ >1.22 (≥1.19)). A correspondence is likewise noted for the methyl ester resonances, although the separation is much less: δ >3.69 for 2*R**,3*R** isomers in $CDCl_3$ (≥3.64 in $CCl_4$), <3.69 for the 2*R**,3*S** diastereomers (<3.63). A similar correlation is also noted for the configuration at C-8 relative to that at C-6: for the 6*R**,8*R** isomers (natural relative configuration), the doublet for the terminal methyl appears at δ >1.20 in $CDCl_3$ (>1.12 in $CCl_4$); for the 6*R**,8*S** diastereomers, this resonance appears at δ <1.18 (<1.09).

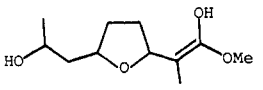
Formation of the trans isomers **27** and **30** is readily explained by syn addition of hydrogen to the enol ether precursors from the more sterically hindered direction, as initially anticipated.[6c,6f] The origin of the 2-*epi* diastereomers **28** and **31** is less clear. It is unlikely that these compounds are formed as a result of acid- or base-catalyzed epimerization of the reduced product, since the hydrogenation is carried out under neutral conditions and the workup only involves simple filtration and evaporation. Contamination of the hydrogenation is carried out under neutral conditions and the workup only involves simple filtration and

(27) Note: the specific rotation of the 6-*epi*-nonactate isomer is not known, hence a quantitative estimate of the isomeric purity of the reduction product could not be obtained from the observed rotation.

evaporation. Contamination of the hydrogenation substrates by the (*Z*)-enol ethers cannot account for the C-2 isomers either, since the samples of (+)-**8** and (−)-**25** were at least 99% pure. Conceivably, in the presence of the catalyst the substrate undergoes either $E \rightleftharpoons Z$ isomerization or (more likely) deconjugation to the 3,4-dehydrononactate diastereomers **33**. A final possibility,



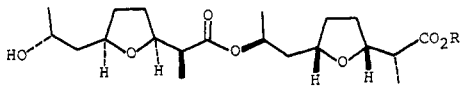
**33**



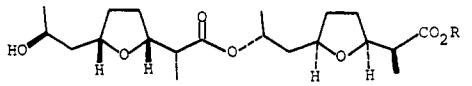
**34**

1,4-reduction via enol **34**, cannot be ruled out at this point either.

**Assembly of Nonactin.** With the methyl esters of (+)-nonactic acid ((+)-**2b**) and (−)-8-*epi*-nonactic acid ((−)-**9**) in hand, we investigated methods for linking them to produce the dimer (+)-nonactyl-(−)-nonactate **35b**. The most logical esterification



**35**

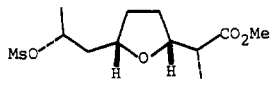


**36**

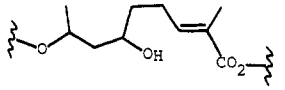
a: R = Me b: R = H c: R = $PhCH_2$ d: R = $PO_3Ph_2$

process was one that would simultaneously invert the configuration at C-8 of the (−) subunit. White et al. demonstrated previously that Mitsunobu esterification[28] of (±)-methyl 8-*epi*-nonactate ((±)-**9**) with benzoic acid affords methyl 8-benzoylnonactate in high yield.[6b] Acetic and formic acids are similarly effective in this reaction. Unfortunately, 8-(*tert*-butyldimethylsilyl)nonactic acid is not; even with a large excess of ethyl azodicarboxylate and triphenyl phosphine and prolonged reaction times, only low yields (<30%) of the desired coupling product can be obtained. The major side product appears to be the acid anhydride. Steric congestion due to the α-methyl group in the acid component is apparently severe enough to hinder the desired $S_N2$ displacement reaction.

Schmidt et al. accomplished what is essentially the enantiomeric coupling reaction by displacement of the tosylate of (+)-benzyl 8-*epi*-nonactate with the potassium salt of (−)-nonactic acid, to produce dimer **36c** in 75% yield.[8a] An analogous process works very efficiently in our system as well. The (−)-8-*epi* ester (−)-**9** and (+) ester (+)-**2b** can be converted into the mesylate **37** and



**37**



**38**

free acid (+)-**2a**, respectively, in better than 90% yields. Reesterification of a sample of the acid (+)-**2a** with diazomethane and examination by NMR indicated that hydrolysis of the ester (2 N NaOH) proceeds without epimerization at C-2. Treatment of the mesylate **37** with 1.5 equiv of the potassium salt of (−)-**2a** (formed in situ with KH) in DMF at 75 °C for 18 h affords the dimeric ester **35a** in 86% yield (78% based on unrecovered (+)-**2a**).

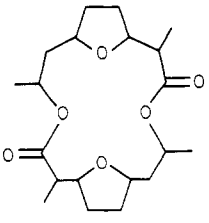
For further elaboration to nonactin (**1**), manipulation of the dimer **35a** and its conversion to a linear tetramer could be envisaged. However, this route has been used in previously reported total syntheses of nonactin,[7,8a] and it therefore seemed more worthwhile to investigate an alternative strategy. Most appealing to us was the possibility that the dimeric acid **35b** could itself be dimerized directly to the tetrameric product. Schmidt and coworkers have in fact reported this transformation with the 2-pyridinethiol ester of the enantiomer **36b**,[29] indicating without detail that nonactin was formed in low yield.

We explored a variety of conditions for selective cleavage of the methyl ester in **35a**, including simple alkaline hydrolysis, lithium iodide in refluxing DMF or collidine (with or without lithium cyanide),[30] aluminum halide/alkanethiol reagents,[31] and lithium methyl mercaptide[32] and lithium *n*-propyl mercaptide in HMPA.[33] The only reagents that proved to be sufficiently reactive as well as selective for cleavage of the methyl ester were the lithium thiolates in HMPA. The methyl mercaptide reagent is more convenient to use, although it results in up to 20% of material with the ring-opened part structure **38**. This contaminant was identified by the appearance of $^1H$ NMR signals indicative of the vinyl hydrogen and vinyl methyl groups at δ 6.75 (t) and 1.80 (br s), respectively. However, none of this material is produced in ester cleavage reactions with the *n*-propyl mercaptide reagent, and the desired cleavage product can be isolated in up to 80% yield.

The difference in behavior of these related reagents suggests that the latter is less basic, apparently as a result of the method of preparation. According to Kelly's procedure,[32] lithium methyl mercaptide is generated with butyllithium and methanethiol in hexane, isolated as the dry salt, and subsequently dissolved in HMPA. The *n*-propyl derivative in contrast is generated in situ from lithium hydride and excess thiol in HMPA and used directly.[33] The latter reagent is in effect buffered by the excess thiol remaining in solution. In support of this conjecture, addition of excess methanethiol to the methyl mercaptide reagent prevents formation of the ring-opened material.

Reesterification of the dimeric acid **35b** with diazomethane revealed that even the *n*-propyl mercaptide reagent results in up to 25% epimerization, presumably at one or both of the C-2 positions. Attempts to minimize this process by conducting the reaction for short times or with a stoichiometric amount of the reagent were not successful. The solution to this irksome question would clearly be a straightforward one: to replace the methyl moiety with one that can be cleaved under different conditions, as has already been accomplished by Schmidt et al., with the enantiomeric benzyl ester series **36c**.[8a] In the present case, since the epimeric mixture is not resolved on TLC, we employed it directly for conversion to nonactin.

Following Masamune's macrolactonization procedure,[34] the dimeric acid **35b** was converted to the mixed anhydride **35d** with diphenyl phosphorochloridate and dimerized/cyclized in refluxing benzene in the presence of 4-(dimethylamino)pyridine. A mixture of products was isolated, including polymeric material, the desired tetramer nonactin **1**, and cyclic dimer **39**. Chromatography and



39

crystallization afforded nonactin in 15–20% yield, which compares

(28) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679.

(29) Gombos, J.; Häslinger, E.; Nikiforov, A.; Zak, H.; Schmidt, U. *Monatsh. Chem.* **1975**, *106*, 1043.

(30) McMurry, J. *Org. React.* **1976**, *24*, 187. Elsinger, F.; Schreiber, J.; Eschenmoser, A. *Helv. Chim. Acta* **1960**, *43*, 113. Dean, P. D. G. *J. Chem. Soc.* **1965**, 6655.

(31) Node, M.; Nishide, K.; Sai, M.; Fujita, E. *Tetrahedron Lett.* **1978**, 5211.

(32) Kelly, T. R.; Dali, H. M.; Tsang, W.-G. *Tetrahedron Lett.* **1977**, 3859.

(33) Bartlett, P. A.; Johnson, W. S. *Tetrahedron Lett.* **1970**, 4459.

(34) Kaiho, T.; Masamune, S.; Toyoda, T. *J. Org. Chem.* **1982**, *47*, 1612.

favorably with the yields reported for direct cyclization of the linear tetramer.[7,8a] The cyclic dimer **39** was not obtained in pure form but was identified on the basis of its spectral similarities with the tetramer and from its mass spectrum. Interestingly, this dimer appeared to be the major product formed in a dimerization/cyclization attempt using the Mukaiyama lactonization reagent, 2-chloro-*N*-methylpyridinium tetrafluoroborate.[35]

Since the unimolecular lactonization reaction must be preceded by an intermolecular esterification, we expected to find a concentration dependence on the yield of nonactin, with cyclic dimer predominating when the reaction is conducted in dilute solution and higher oligomers and polymers under concentrated conditions. However, the relative amount of nonactin formed its relatively invariant over the concentration range 0.1–0.001 M. We were not able to demonstrate a template effect in the cyclization either: the inclusion of an equivalent of silver tetrafluoroborate[7,8a] had no effect on the yield of cyclic tetramer.

In conclusion, the total synthesis of the macrotetrolide nonactin has been accomplished by a route that is stereochemically economical and synthetically convergent. Nonactin acid subunits in both enantiomeric series are prepared from a single optically active starting material with a minimum amount of manipulation. Moreover, after formation of the epoxy tosylate **16**, no protecting groups are introduced per se and, with the exception of the methyl ester, no group serves solely a protective role. Finally, the macrotetrolide itself is produced in relatively few steps by a convergent dimerization sequence.

## Experimental Section

**General.** NMR spectra were obtained on 180-, 200-, or 250-MHz FT instruments. Unless otherwise indicated, all reaction procedures culminated in washing the organic layer with brine, drying over $MgSO_4$, filtering, and concentrating under reduced pressure on a rotary evaporator and at 0.1 torr to constant weight.

**Nonactin (1).** To a stirred solution of 135 mg (0.35 mmol) of dimeric acid **35b** (see below) in 14 mL of THF under nitrogen at 0 °C was added 54 μL (0.39 mmol) of triethylamine and 85 μL (0.39 mmol) of diphenyl phosphorochloridate. After 40 min, the mixture was filtered, the precipitate was washed with 2 mL of THF, and the combined filtrate was diluted with 24 mL of dry benzene. 4-(Dimethylamino)pyridine (64 mg, 0.52 mmol) was added and the solution was heated at reflux for 16 h. The mixture was cooled, the solvent was evaporated at reduced pressure, and the residue was purified by column chromatography (66:33 EtOAc/$CHCl_3$) to give 68 mg of crude product. From this material 21 mg (16% yield) of nonactin **1** was obtained by recrystallization from 80:20 ether/hexane: mp 147 °C (lit.[8a] 149–150 °C); $^1H$ NMR δ 1.08 (d, 12, $J$ = 7.0 Hz), 1.22 (d, 12, $J$ = 6.2 Hz), 1.4–1.7, (m, 8), 1.7–1.8 (m, 8), 1.9–2.0 (m, 8), 2.50 (d q, 4, $J$ = 6, 7), 3.84 (apparent quintet, 4, $J$ = 6 Hz, H-6), 4.00 (apparent quartet, 4, $J$ = 7 Hz, H-3), 4.96 (ddq, 4, $J$ = 6 Hz, H-8); MS, $m/z$ 736 ($M^+$), 708, 626, 571, 553, 534, 479, 443, 437, 387, 369, 321, 327, 295, 258, 253, 185, 167, 143, 125, 111. These spectra were identical with those of an authentic sample provided by Dr. Barry Hesp of ICI, Inc.

**Methyl (2*S*,3*S*,6*R*,8*R*)-Nonactate ((+)-2b).** A mixture of 1.48 g (6.9 mmol) of the 6*R*,8*R* enol ether (−)-**25** (see below) and 3.0 g of 5% rhodium on alumina in 20 mL of MeOH was shaken under a hydrogen atmosphere at 60 psi for 5 days. The mixture was filtered through Celite and evaporated, and the residue was dissolved in ether, filtered again through Celite, and reevaporated to give 1.50 g (100% yield) of analytically pure (+)-methyl nonactate (+)-**2b**. This material proved on NMR analysis to contain ~9% of the 2*R*,3*R*,6*R*,8*R* (trans) and 3% of the 2*R*,3*S*,6*R*,8*R* (2-*epi*) isomers **30** and **31**, respectively: $[\alpha]^{25}_D$ +13.1° (*c* 0.708, $CHCl_3$) (lit.[6d] for (+) isomer, $[\alpha]^{25}_D$ +22.1° (*c* 0.7, $CHCl_3$), for (−) isomer,[8a] $[\alpha]_D$ −17.8° (*c* 3.6, $CHCl_3$)); IR 1740, 2960, 3100–3700 (br) $cm^{-1}$; $^1H$ NMR δ 1.13 (d, 3, $J$ = 7.0 Hz), 1.20 (d, 3, $J$ = 6.3 Hz), 1.5–2.1 (m, 6), 2.54 (m, 1), 3.695 (s, 3), 3.9–4.2 (m, 3). Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.41; H, 9.31.

**1,1-Dimethylethyl (*S*)-1-(2-Propenyl)-4-pentenyl Carbonate, (−)-6.** *n*-Butyllithium (65 mL of 1.52 M solution in hexane, 98.8 mmol) was added to a solution of 12.35 g (98.0 mmol) of (*S*)-1,7-octadien-4-ol (**17**) in 250 mL of ether. The resulting solution was added to a solution of 24.4 g (99.2 mmol) of 2-[((*tert*-butoxycarbonyl)oxy)imino]-2-phenylacetonitrile in 100 mL of THF. After 4 h, the solution was washed with 2 N NaOH and worked up to give 21.70 g (98% crude yield) of carbonate (−)-**6** of sufficient purity to be used in the subsequent step. A portion was purified for analytical purposes by preparative VPC: $[\alpha]^{25}_D$ −25.5° (*c* 2.71, acetone); IR 1650, 1740, 3020 $cm^{-1}$; $^1H$ NMR δ 1.48 (s, 9), 1.6–1.8 (m, 2), 2.12 (m, 2), 2.35 (dd, 2, $J$ = 6.2, 7.0 Hz), 4.71 (q, 1, $J$ = 6.2, 7.0 Hz), 4.71 (q, 1, $J$ = 6.3 Hz), 4.9–5.2 (m, 4), 5.7–5.9 (m, 2). Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.93; H, 9.60.

**(4*S*,6*S*)-4-(3-Butenyl)-6-(iodomethyl)-1,3-dioxan-2-one ((+)-7) and the 4*S*,6*R* Isomer.** A mixture of 20.0 g (88 mmol) of the *tert*-butyl (*S*)-1,7-octadien-4-yl carbonate (prepared as described above) and 70 g (276 mmol) of iodine in 800 mL of dry acetonitrile was stirred mechanically under nitrogen at −20 °C for 10 h. The mixture was partitioned between 1 L of 20% $Na_2S_2O_3$/5% $NaHCO_3$ and 1.5 L of ether, and the organic layer was worked up to give 30 g of a yellow oil. After initial purification by open-column chromatography (2:3 EtOAc/hexanes), the isomers were separated on a Waters Prep 500 HPLC instrument (2:1 hexane/EtOAc) to give 2.37 g (9% overall yield from **17**) of the trans 4*S*,6*R* iodo carbonate, 1.37 g (5% yield) of a mixed fraction, and 14.69 g (55% overall yield) of the 4*S*,6*R* isomer (−)-**7**.

Trans (4*S*,6*R*) isomer: $[\alpha]^{25}_D$ −46.3° (*c* 3.48, acetone); IR 1640, 1740, 2925 $cm^{-1}$; $^1H$ NMR δ 1.6–2.4 (m, 6), 3.29 ($H_A$ of ABX, 1, $J_{AB}$ = 10.5, $J_{AX}$ = 8.6 Hz), 3.46 ($H_B$ of ABX, 1, $J_{AB}$ = 10.5, $J_{BX}$ = 4.7 Hz), 4.4–4.7 (m, 2), 5.0–5.2 (m, 2), 5.7–5.9 (m, 1); MS, $m/e$ 297 ($M^+$ + 1), 296 ($M^+$). HRMS calcd for $C_9H_{13}IO_3$ 295.9911, found 295.9902.

Cis (4*S*,6*S*) isomer, (+)-7: $[\alpha]^{25}_D$ +7.25° (*c* 3.02, acetone); IR 1640, 1740, 2925 $cm^{-1}$; $^1H$ NMR δ 1.6–2.5 (m, 6), 3.29 ($H_A$ of ABX, 1, $J_{AB}$ = 10.6, $J_{AX}$ = 7.1 Hz), 3.41 ($H_B$ of ABX, 1, $J_{AB}$ = 10.6, $J_{BX}$ = 4.4 Hz), 4.3–4.6 (m, 2), 5.0–5.2 (m, 2), 5.7–5.9 (m, 1); MS, $m/e$ 297 ($M^+$ + 1), 296 ($M^+$). Anal. Calcd for $C_9H_{13}IO_3$: C, 36.50; H, 4.43; I, 42.86. Found: C, 36.38; H, 4.38; I, 42.94.

**Methyl (6*S*,8*R*)-(*E*)-2,3-Dehydrononactate ((+)-8).** A mixture of 2.14 g (8.29 mmol) of β-keto ester (−)-**21** (see below) and 1.78 g (12.9 mmol) of $K_2CO_3$ in 100 mL of methanol was stirred at 21 °C for 9 h. The solution was neutralized with 4.2 mL of 3 M HCl, filtered, and evaporated, and the residue was triturated with ether and $CH_2Cl_2$. Evaporation of the solvent gave a total of 1.87 g of crude lactol. This material was dissolved in 150 mL of dichloromethane, 2.0 g of oxalic acid dihydrate was added, and the mixture was heated at reflux for 4 h. The reaction mixture was partitioned between saturated $NaHCO_3$ and EtOAc, the organic layer was worked up, and the crude product was purified by column chromatography (1:9 hexane/ether) to give 1.34 g (76% yield) of the enol ether (+)-**8**: $[\alpha]^{25}_D$ +45.1° (*c* 1.165, acetone). IR 1630, 1685, 2940, 3100–3700 (br) $cm^{-1}$; $^1H$ NMR δ 1.26 (d, 3), 1.6–1.9 (m, 6), 1.80 (t, $J$ = 1.5 Hz), 2.25 (m, 1), 2.8–3.0 (m, 1), 3.26 (m, 1), 3.69 (s, 3), 4.08 (m, 1), 4.53 (m, 1). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.48; H, 8.39.

**Methyl (2*R*,3*R*,6*S*,8*R*)-Nonactate ((−)-9).** A mixture of 1.27 g (5.93 mmol) of methyl 8-*epi*-dehydrononactate (+)-**8** and 2.2 g of 5% rhodium on alumina catalyst in 20 mL of methanol was shaken under a hydrogen atmosphere at 60 psi for 5 days. The mixture was filtered through Celite and evaporated and the residue was dissolved in ether, filtered again through Celite, and reevaporated to give 1.28 g (100% yield) of analytically pure (−)-methyl 8-*epi*-nonactate ((−)-**9**). This material proved on NMR analysis to contain ~9% of the 2*S*,3*S*,6*S*,8*R* (8-*epi*-trans) and 3% of the 2*S*,3*R*,6*S*,8*R* (2,8-bis-*epi*) isomers **27** and **28**, respectively: $[\alpha^{25}_D$ −23.1° (*c* 1.07, $CHCl_3$) (lit.[6d] for (+)-isomer $[\alpha]_D$ +32.9° (*c* 1.07, $CHCl_3$)); IR 1735, 2960, 3100–3700 (br) $cm^{-1}$; $^1H$ NMR δ 1.13 (d, 3, $J$ = 7.0 Hz), 1.17 (d, 3, $J$ = 6.2 Hz), 1.5–2.1 (m, 6), 2.55 (m, 1), 3.700 (s, 3), 3.9–4.2 (m, 3). Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.09; H, 9.31.

**(*S*)-(−)-Dimethyl 2-*O*-(1-ethoxyethyl)malate (12).** Ethyl vinyl ether (51 mL, 534 mmol) and 500 mg (2 mmol) of pyridinium *p*-toluenesulfonate were added to a stirred solution of 58.0 g (358 mmol) of dimethyl (S)-(−)-malate[15] in 500 mL of $CH_2Cl_2$. After 36 h, 3.0 g of $K_2CO_3$ was added, and after 30 min, the solution was filtered through Celite. Solvent evaporation in vacuo gave 84.1 g (100% yield) of the ethoxyethyl ether **12**, which was carried on directly: $[\alpha]^{25}_D$ −52.4° (*c* 6.900, acetone); IR 1735, 2970 $cm^{-1}$; $^1H$ NMR δ 1.16, 1.18 (two t, 3 H, $J$ = 7.0 Hz), 1.31, 1.35 (two d, 3 H, $J$ = 5.4 Hz), 2.78 (m, 2 H), 3.4–3.7 (m, 2 H), 3.71 (s, 3 H), 3.76 (s, 3 H), 4.51, 4.65 (two t, 1 H), 4.82, 4.86 (two q, 1 H); MS, $m/e$ $M^+$ (absent), 219 ($M^+ - CH_3$), 189 ($M^+ - CH_3CH_2O$); HRMS (for $M^+ - CH_3$) calcd for $C_9H_{15}O_6$ 219.0868, found 219.0866.

**(*S*)-(−)-2-(1-Ethoxyethoxy)-1,4-butanediol (13).** A solution of 78.7 g (336 mmol) of the ether **12** described above in 200 mL of THF was added to a mechanically stirred suspension of 25.0 g (660 mmol) of $LiAlH_4$ in 1 L of THF at 0 °C. The mixture was then allowed to warm to 21 °C. After 12 h, 200 g of $Na_2SO_4 \cdot (H_2O)_{10}$ was added. After it was stirred for several hours, the mixture was filtered, and the solid material was washed with 1.5 L of THF. Evaporation of the filtrate furnished 50.30 g of the diol **13**. The solid residue was collected and stirred vig-

(35) Narasaka, K.; Masui, T.; Mukaiyama, T. *Chem. Lett.* **1977**, 763.

orously in 600 mL of MeOH for 30 min, and the mixture was filtered. The methanol solution was evaporated and the residue was triturated with 500 mL of THF. Filtration and evaporation provided an additional 4.79 g of product (total yield 55.1 g, 92%): $[\alpha]^{25}_D$ −21.7° (*c* 2.670, MeOH); IR 2930, 3000–3700 (br) cm$^{-1}$; $^1$H NMR δ 1.24 (t, 3 H, *J* = 7.0 Hz), 1.36 (d, 3 H, *J* = 5.2 Hz), 1.74 (m, 2 H), 2.3, 2.7, 3.0, 3.3 (br s, 2 H), 3.5–4.0 (m, 7 H), 4.72, 4.83 (two q, 1 H); MS, *m/e* $M^+$ (absent), 147 ($M^+ - CH_3O$), 133 ($M^+ - CH_3CH_2O$).

**(*S*)-(−)-2-(1-Ethoxyethoxy)-1,4-butanediol (14).** A solution of 54.2 g (304 mmol) of the diol **13** described above in 100 mL of pyridine at 0 °C was added to a solution of 128.0 g (672 mmol) of *p*-toluenesulfonyl chloride in 200 mL of pyridine at 0 °C. After 10 h, 100 g of ice was added, followed after 10 min by 1.5 L of ether. The solution was washed with 30% aqueous copper sulfate (3 × 2 L), water (1 L), and brine (1 L), and the combined aqueous layers were extracted with 1 L of ethyl acetate. The combined organic layers were dried and evaporated to give 135.7 g (92% yield) of the ditosylate 14: $[\alpha]^{25}_D$ −16.3° (*c* 3.245, acetone); IR 1580, 2970 cm$^{-1}$; $^1$H NMR δ 1.07, 1.11 (two t, 3 H, *J* = 7.1 Hz), 1.14, 1.18 (two d, 3 H, *J* = 5.2 Hz), 1.4–2.0 (m, 2 H), 2.45 (s, 6 H), 3.3–3.6 (m, 2 H), 3.7–4.2 (m, 5 H), 4.54, 4.66 (two q, 1 H, *J* = 5.2 Hz), 7.35 (d, 2 H, *J* = 8.2), 7.77 (d, 2 H, *J* = 8.2 Hz); MS, *m/e* $M^+$ (absent), 471 ($M^+ - CH_3$), 441 ($M^+ - CH_3CH_2O$); HRMS (for $M^+ - CH_3CH_2O$) calcd for $C_{20}H_{25}O_7S_2$ 441.1041, found 441.1028.

**(*S*)-(−)-2-(Oxiran-2-yl)ethyl Tosylate (16).** Pyridinium *p*-toluenesulfonate (5.2 g, 21 mmol) was added to a stirred solution of 135.3 g (278 mmol) of the ditosylate **14** described above in 500 mL of methanol at 21 °C. After 14 h, 50.0 g (362 mmol) of $K_2CO_3$ was added, followed after 7 h by 500 mL of water and 1.5 L of ether. The organic layer was washed with 500 mL of brine, and the combined aqueous washings were back-extracted with 600 mL of ether. Evaporation of the combined organic layer and purification of the residue by column chromatography (600 g silica, 20% hexane/ether) afforded 60.4 g (76% yield from dimethyl (*S*)-(−)-malate) of the epoxy tosylate **16** as a white solid: mp 28–32 °C; $[\alpha]^{25}_D$ −14.6° (*c* 4.725, acetone); IR 1580, 2920 cm$^{-1}$; $^1$H NMR δ 1.7–2.1 (m, 2 H), 2.45 (s, 3 H), 2.47 (dd, 1 H, *J* = 2.7, 4.9 Hz), 2.76 (t, 1 H, *J* = 4.9 Hz), 2.97 (m, 1 H), 4.17 (dd, 2 H, J = 4.9, 5.6 Hz), 7.36 (d, 2 H, *J* = 8.2 Hz), 7.80 (d, 2 H); HRMS calcd for $C_{11}H_{14}O_4S$ 242.0610, found 242.0611. Anal. Calcd for $C_{11}H_{14}O_4S$: C, 54.54; H, 5.83; S, 13.21. Found: C, 54.72; H, 5.74; S, 12.99.

**Preparation of Vinyllithium:**[18b] *n*-Butyllithium (1.71 mol) in 1 L of hexane was added to 196 g (864 mmol) of tetravinyltin[18a] in a 2-L three-neck flask equipped with mechanical stirrer, nitrogen inlet, and fritted side arm. After stirring at 21 °C for 2 h, the precipitated vinyllithium was filtered under nitrogen pressure, washed with four 500-mL portions of hexane, and dissolved in 400 mL of THF. After 3 days at 21 °C, the THF was evaporated (initially under reduced pressure, with the last 20–30 mL being evaporated under a fast stream of dry nitrogen). Ether was added and the solution was filtered through a glass frit to give 570 mL of a clear brown solution of butyllithium-free vinyllithium (2.51 M, 84% yield based on *n*-butyllithium).

**(*S*)-(−)-1,7-Octadien-4-ol (17).** In a flame-dried 1-L round-bottom flask, 30 g (330 mmol) of cuprous cyanide was dried azeotropically by distilling off two 25-mL portions of toluene. Dry THF (150 mL) was added, the stirred slurry was cooled to −78 °C, and 500 mL of a 1.2 M solution (600 mmol) of a vinyllithium solution, prepared as described above, was added slowly. The resulting pale yellow solution was stirred for 30 min at −78 °C then brought to −40 °C. A solution of 25 g (103 mmol) of the epoxy tosylate **16** in 150 mL of THF was added slowly, the reaction mixture was allowed to warm gradually to 0 °C and was kept at this temperature for 6 h. The brown solution was poured into 1.5 L of a mixture of 1.35 L of saturated aqueous $NH_4Cl$ and 150 mL of concentrated $NH_4OH$. After stirring for 30 min, the organic layer was separated and washed with brine. The aqueous phases were extracted with ether (3 × 500 mL), and the combined organic layers were worked up (evaporation performed at reduced pressure, with water bath <0 °C) to give 11.9 g (92% yield) of the octadienol **17**. A sample was purified for analysis by distillation: bp 80–83 °C (7 mmHg); $[\alpha]^{25}_D$ −6.02° (*c* 4.900, MeOH); IR 1650, 2950, 3100–3700 cm$^{-1}$; $^1$H NMR δ 1.58 (m, 2 H), 2.1–2.4 (m, 4 H), 3.68 (m, 1 H), 4.9–5.2 (m, 4 H), 5.7–6.0 (m, 2 H). Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 75.83; H, 10.95.

**(4*S*,6*R*)-4-(3-Butenyl)-6-methyl-1,3-dioxan-2-one ((−)-18).** Tri-*n*-butyltin hydride (18.4 mL, 69.7 mmol) was added to a stirred solution of 13.74 g (46.4 mmol) of iodo carbonate (−)-**7** in 200 mL of THF under nitrogen at 40 °C. After 24 h, an additional 10.0 g (37.9 mmol) of hydride reagent was added, followed after another 12 h by 40 mL of $CCl_4$. After 36 h, the reaction mixture was worked up by adding 200 mL of aqueous $KF\cdot(H_2O)_2$, filtering, and stirring vigorously for 3 h. The mixture was extracted with ether, the organic layer was worked up, and the crude product was purified by column chromatography (1:1 EtOAc/hexane) to afford 8.04 g (98% yield) of carbonate (−)-**18**, >98% pure by $^1$H NMR analysis. An analytical sample was purified by preparative VPC: $[\alpha]^{25}_D$ −23.0° (*c* 2.79, acetone); IR 1645, 1750, 2960 cm$^{-1}$; $^1$H NMR δ 1.42 (d, 3, *J* = 3.6 Hz), 1.6–2.0 (m, 3), 2.06 (d t, 1, J = 14.2, 3.0 Hz), 2.25 (m, 2), 4.4–4.6 (m, 2), 5.0–5.2 (m, 2), 5.7–5.9 (m, 1). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.24; H, 8.24.

**(4*S*,6*S*)-6-Methyl-2-oxo-1,3-dioxane-4-propanal ((−)-19).** Ozone was bubbled through a solution of 7.4 g (42.8 mmol) of the cyclic carbonate (−)-**18** in 300 mL of MeOH at −78 °C. When the solution became blue, it was purged with nitrogen and 20 mL of dimethyl sulfide was added, the solution being maintained at −78 °C throughout. Warming to room temperature and solvent evaporation (first at water pump pressure then at 0.03 mmHg for 2 days) gave 8.35 g of aldehyde (−)-**19** of sufficient purity for use in the subsequent step ($^1$H NMR showed 0.3 molar equiv of dimethyl sulfoxide): $[\alpha]^{25}_D$ −36.7° (*c* 2.43, $CHCl_3$); IR 1760, 2920 cm$^{-1}$; $^1$H NMR δ 1.42 (d, 3, *J* = 6.3 Hz), 1.5–2.2 (m, 4), 2.76 (t, 2, *J* = 6.9 Hz), 4.4–4.7 (m, 2), 9.83 (s, 1); MS, *m/e* 173 ($M^+ + 1$); HRMS (for $M^+ + 1$) calcd for $C_8H_{12}O_4$ 173.0813, found 173.0804.

**Methyl (4*S*,6*R*)-β-Hydroxy-α,6-dimethyl-2-oxo-1,3-dioxane-4-pentanoate (20).** A solution of 5.3 g (30.8 mmol) of (−)-aldehyde (−)-**19** prepared as described above in 400 mL of $CH_2Cl_2$ under a nitrogen atmosphere was cooled to −78 °C and 13 mL (117 mmol) of $TiCl_4$ was added slowly. The resulting yellow slurry was stirred at −78 °C for 15 min before 14.7 mL of the trimethylsilyl enol ether of methyl propanoate[36] was added. The reaction mixture was stirred for 2 h at −78 °C, brought to −20 °C over a period of 4 h, and kept overnight at −15 °C. $NaHCO_3$ (78 g) and 17 mL of water were added, and the suspension was stirred for 2.5 h at 21 °C. The mixture was filtered through Celite and evaporated, and the crude product was purified by column chromatography (ethyl acetate) to give 6.8 g (85% yield) of the β-hydroxy ester **20** as a mixture of diastereomers: IR ($CHCl_3$) 1740, 3020, 3300–3650 (br) cm$^{-1}$; $^1$H NMR δ 1.12, 1.22 (two d, 3, *J* = 6.2 Hz), 1.42 (d, 3, *J* = 6.3 Hz), 1.5–2.2 (m, 6), 2.46–2.6 (m, 1), 2.9–3.1 (br, 1), 3.6–3.8 (m, 0.5), 3.72 (s, 3), 3.7–4.0 (m, 0.5), 4.4–4.7 (m, 2); $^{13}$C NMR δ 10.96, 13.65, 20.89, 28.46, 28.80, 29.15, 29.44, 31.08, 31.55, 31.66, 32.02, 34.59, 34.76, 44.65, 45.30, 51.38, 71.07, 71.44, 72.20, 72.72, 75.00, 77.17, 78.22, 78.92, 149.12, 175.55. Anal. Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.75. Found: C, 54.82; H, 7.64.

**Methyl (4*S*,6*R*)-α,6-Dimethyl-β,2-dioxo-1,3-dioxane-4-pentanoate ((−)-21).** Jones reagent (10.8 mL, 2.67 M) was added dropwise to a stirred solution of 5.04 g (19.4 mmol) of the β-hydroxy ester **20** in 150 mL of acetone at 0 °C. After 10 min, 20 mL of isopropyl alcohol was added, and after an additional 5 min, the mixture was partitioned between EtOAc and water. The organic layer was washed with saturated $NaHCO_3$, the aqueous layer was extracted twice with EtOAc, and the combined organic layer was worked up to give a crude product, which was purified by chromatography (1:4 hexane/EtOAc) to give 4.54 g (91% yield) of β-keto ester (−)-**21**: $[\alpha]^{25}_D$ −24.8° (*c* 2.70, acetone); IR 1740, 2940 cm$^{-1}$; $^1$H NMR δ 1.36 (d, 3, *J* = 7.1 Hz), 1.42 (d, 3, *J* = 6.2 Hz), 1.5–2.2 (m, 4), 2.7–3.0 (m, 2 H), 3.60, 3.57 (two q, 1, *J* = 7.2 Hz), 3.75 (s, 3), 4.4–4.7 (n, 2); MS, *m/e* 258 ($M^+$), 227 ($M^+ - CH_3O$); HRMS calcd for $C_{12}H_{18}O_6$ 258.1097, found 258.1100. Anal. Calcd: C, 55.80; H, 7.03. Found: C, 55.48; H, 6.79.

**Methyl (6*R*,8*S*)-(*E*)-2,3-Dehydrononactate (*S*)-(−)-2-Methoxy-2-phenyl-3,3,3-trifluoropropanoate Ester (22).** To a stirred solution of 85 mg (0.397 mmol) of (+)-methyl 8-*epi*-2,3-dehydrononactate ((+)-**8**) and 98 mg (0.8 mmol) of 4-(dimethylamino)pyridine in 5 mL of THF at 0 °C was added 151 mg (0.596 mmol) of (*S*)-(−)-2-metoxy-2-phenyl-3,3,3-trifluoropropanoyl chloride.[21] The mixture was stirred for 4 h, 20 mL of saturated $NaHCO_3$ was added, and the mixture was extracted 3 times with 20 mL of $CH_2Cl_2$. After the usual workup, the crude product was purified by chromatography (30:70 hexane/ether) to give 7 mg (8% yield) of recovered starting material and 150 mg (88% yield) of the ester **22**: $[\alpha]^{22}_D$ −54.86° (*c* 1.05, acetone); IR ($CHCl_3$) 1640, 1705, 1745 cm$^{-1}$; $^1$H NMR δ 1.44 (d, 3, J = 6.4 Hz), 1.5–1.85 (m, 2), 1.77 (t, 3, *J* = 1.4 Hz), 2.0–2.2 (m, 2), 2.82 (m, 1), 3.22 (m, 1), 3.57 (br q, 3), 3.69 (s, 3), 4.2 (m, 1), 5.3 (m, 1), 7.35–7.55 (m, 5); MS, *m/e* 430 ($M^+$), 398, 368, 196, 189, 181, 165, 155. Anal. Calcd for $C_{21}H_{25}O_6F_3$: C, 58.60; H, 5.85. Found: C, 58.45; H, 5.91.

**Methyl (6*R*,8*R*)-(*E*)-2,3-dehydrononactate ((−)-25).** A suspension of 400 mg (10.0 mmol) of KH in 10 mL of THF was added to a stirred solution of 2.13 g (8.26 mmol) of β-keto ester (−)-**21** in 400 mL of 5% hexamethylphosphoramide/THF. After 40 h, the mixture was partitioned between saturated $NH_4Cl$ and ether, the organic layer was washed with water, the aqueous layers were back-extracted with ether, and the combined organic fraction was worked up to give the crude enol ether.

(36) Ainsworth, C.; Chen, F.; Kuo, Y.-N. *J. Organomet. Chem.* **1972**, *46*, 59.

Purification by column chromatography (1:9 hexane/ether) gave 1.62 g (92% yield) of the 6*R*,8*R* enol ether (−)-**25**: $[\alpha]^{25}_D$ −184° (*c* 1.87, acetone). IR 1630, 1685, 2940, 3100–3700 (br) $cm^{-1}$; $^1H$ NMR δ 1.27 (d, 3, *J* = 6.3 Hz), 1.6–1.9 (m, 6), 1.80 (t, *J* = 1.4 Hz), 2.22 (m, 1), 2.8–3.0 (m, 1), 3.26 (m, 1), 3.69 (s, 3), 4.10 (m, 1), 4.61 (m, 1); MS, *m/e* 214 ($M^+$), 183 ($M^+ - CH_3O$); HRMS calcd for $C_{11}H_{18}O_4$ 214.1205, found 214.1200.

**Methyl (+)-Nonactyl-(−)-nonactate (35a).** A mixture of 545 mg (2.52 mmol) of (+)-methyl nonactate ((+)-**2b**) and mL of 2 N NaOH was stirred vigorously at 21 °C for 30 min. After acidification to pH 1 with 2 N HCl, the mixture was extracted with five 50-mL portions of $CHCl_3$ and the combined organic layer was dried and evaporated to give 463 mg (91% yield) of oily (+)-nonactic acid ((+)-**2a**). A potassium hydride/oil suspension (2.76 mmol, 1.2 equiv) was washed with dry hexane, a solution of the (+)-nonactic acid (463 mg, 2.29 mmol) in 15 mL of dry DMF was added, and the mixture was stirred for 20 min at 21 °C. To this solution of potassium (+)-nonacetate was added a solution of 450 mg (1.53 mmol) of mesylate **37** (see below) in 15 mL of dry DMF, and the reaction mixture was stirred at 70 °C for 18 h. The solution was cooled, 20 mL of saturated $NaHCO_3$ and 25 mL of saturated NaCl were added, and the mixture was stirred for 20 min. The aqueous layer was extracted with $CHCl_3$, and the combined organic layers were dried and evaporated to give fraction I of the dimeric ester **35a**. The aqueous phase was acidified to pH 1 with 2 N HCl and extracted with five 50-mL portions of $CHCl_3$. The combined organic layers were dried and evaporated to give fraction II, containing a mixture of dimer and recovered (+)-nonactic acid. Fraction II was partitioned again between aqueous $NaHCO_3$ and $CHCl_3$ to give complete separation of the neutral diester and (+)-nonactic acid. In this manner, 126 mg (82% yield) of the excess (+)-nonactic acid was recovered. The fractions containing the dimeric ester were combined and purified by column chromatography (90:10 ether/hexane) to give 523 mg (86% yield based on mesylate **37**, 78% based on (+)-nonactic acid consumed) of **35a** as an oil: $[\alpha]^{22}_D$ 5.75° (*c* 2.0, $CHCl_3$); IR ($CHCl_3$) 1730, 3500 $cm^{-1}$; $^1H$ NMR δ 1.11 (d, 6, *J* = 7 Hz), 1.19 (d, 3, *J* = 6 Hz), 1.23 (d, 3, *J* = 6 Hz), 1.4–2.15 (m, 12), 2.5 (m, 2), 2.9 (s, 1), 3.69 (s, 3), 3.8–4.2 (m, 5), 4.9–5.1 (m, 1); $^{13}C$ NMR δ 13.2, 20.4, 23.2, 28.4, 28.5, 30.6, 31.2, 42.4, 43.1, 45.3, 45.4, 51.5, 64.9, 69.3, 76.3, 76.8, 76.9, 80.3, 80.7, 174.1, 175.2. Anal. Calcd for $C_{21}H_{36}O_7$: C, 62.98; H, 9.06. Found: C, 62.96; H, 9.05.

**(+)-Nonactyl-(−)-nonactic Acid (35b).** To 707 mg (1.77 mmol) of dimeric ester **35a** under an argon atmosphere at 21 °C was added 7.4 mL (3.55 mmol, 2 equiv) of a 0.48 M solution of lithium *n*-propyl mercaptide in HMPA.[33] After 2 h the mixture was diluted with 40 mL of saturated $NaHCO_3$ and 30 mL of water and extracted with six 25-mL portions of $CHCl_3$. The aqueous phase was acidified to pH 1 with 2 N HCl and extracted with eight 50-mL portions of $CHCl_3$. The combined organic layer was worked up in the usual manner and the crude product was purified by chromatography (8:92 ethanol/$CHCl_3$) to give 547 mg (80% yield) of the dimeric acid **35b**: IR 3500–3000, 1730 $cm^{-1}$; $^1H$ NMR δ 1.11 (d, 3, *J* = 7 Hz), 1.15 (d, 3, *J* = 7 Hz), 1.20 (d, 3, *J* = 6 Hz), 1.235 (d, 3, *J* = 6.4 Hz), 1.5–2.15 (m, 12), 2.4–2.6 (m, 2), 3.9–4.3 (m, 5), 4.95–5.15 (m, 2), 5.6 (br s, 2); $^{13}C$ NMR δ 12.83, 20.0, 20.0, 27.7, 28.1, 30.4, 31.0, 36.2, 42.0, 43.2, 44.4, 45.0, 64.6, 68.9, 75.9, 76.5, 79.7, 80.2, 173.7, 176.9; MS, *m/e* 387 ($M^+ + 1$), 368, 342, 341, 313, 258, 240, 203, 186, 185, 184, 183, 169, 167; HRMS calcd for $C_{20}H_{15}O_7$ ($M^+ + 1$) 387.2383, found 387.2380. Reesterification of a sample of this material with diazomethane and NMR comparison with the starting diester showed an additional methyl ester resonance in the $^1H$ NMR at δ 3.67 and resonances in the $^{13}C$ NMR at δ 28.9, 30.7, 31.3, 43.0, 51.4, 76.1, 79.9, and 80.4, consistent with the presence of 20% of an epimeric compound.

**Methyl (2*R*,3*R*,6*S*,8*R*)-Nonactate Mesylate Ester ((−)-37).** To a stirred solution of 50 mg (0.231 mmol) of (−)-methyl 8-*epi*-nonactate ((−)-**9**) in 5 mL of $CH_2Cl_2$ at 0 °C was added 76 mg (3.25 equiv) of triethylamine, 5 mg of 4-(dimethylamino)pyridine, and 90 mg (3 equiv) of mesyl chloride. After 2 h, the mixture was diluted with saturated $NaHCO_3$ and extracted 3 times with $CH_2Cl_2$. The combined organic layer were worked up in the usual manner and the crude product was purified by column chromatography (60:40 ether/hexane) to give 65 mg (91% yield) of the desired mesylate **37** and 4 mg (5.6% yield) of an isomer. For **37**: $[\alpha]^{22}_D$ −16.18° (*c* 2.62 $CHCl_3$); IR ($CDCl_3$) 1190, 1360, 1730 $cm^{-1}$; $^1H$ NMR δ 1.12 (d, 3, *J* = 7 Hz), 1.45 (d, 3, *J* = 6 Hz), 1.5–2.2 (m, 6), 2.5 (m, 1), 3.0 (s, 3), 3.7 (s, 3), 3.9–4.1 (m, 2), 4.9 (m, 1); MS, *m/e* 293 ($M^+ - 1$), 279, 263, 234, 207, 199, 198, 183, 167, 157. Anal. Calcd for $C_{12}H_{22}O_6S$: C, 48.96; H, 7.53; S, 10.89. Found: C, 48.59; H, 7.55; S, 10.72.

**(+)-Nonactyl-(−)-nonactate Cyclic Dimer (39).** A solution of 70 mg (0.18 mmol) of the linear dimer **35a**, 156 mg (0.75 mmol) of 2-chloro-*N*-methylpyridinium tetrafluoroborate, 0.2 mL of triethylamine, and 5 mg of 4-(dimethylamino)pyridine in 18 mL of $CH_2Cl_2$ was kept at 21 °C for 14 h and then at reflux for 58 h. The mixture was washed with saturated $NaHCO_3$ and 2 N HCl, dried, and evaporated, and the crude product was purified by chromatography (33:66 $CHCl_3$/EtOAc) to give 25 mg of cyclization product. Although a trace of nonactin could be discerned by TLC analysis, the major product appeared to be cyclic dimer: $^1NMR$ δ 1.10 (d, 6, *J* = 7.0 Hz), 1.23 (d, 6, *J* = 6.4 Hz), 1.6–2.0 (m, 12), 2.4 (m, 2), 3.6–4.1 (m, 4), 5.1 (m, 2); MS, *m/e* 368 ($M^+$), 353, 340, 311, 295, 269, 258, 253, 241, 214, 185, 167, 143, 125, 111.

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**Registry No. 1**, 6833-84-7; (+)-**2a**, 16221-10-6; (+)-**2b**, 54594-23-9; (−)-**6**, 91111-11-4; *cis*-(+)-**7**, 91177-74-1; *trans*-(−)-**7**, 91177-73-0; (+)-**8**, 91199-05-2; (−)-**9**, 74957-68-9; **11**, 617-55-0; **12**, 72229-30-2; **13**, 72229-31-3; **14**, 76494-96-7; (−)-**16**, 91111-12-5; (−)-**17**, 91111-13-6; (−)-**18**, 91111-14-7; (−)-**19**, 91111-15-8; **20**, 91111-16-9; (−)-**21**, 91111-17-0; **22**, 91111-18-1; (−)-**25**, 91199-06-3; **27**, 91177-75-2; **28**, 91177-76-3; **30**, 91177-77-4; **31**, 91177-78-5; **35a**, 91111-19-2; **35b**, 91177-79-6; **37**, 91111-20-5; **39**, 91129-65-6; 2-[((*tert*-butoxycarbonyl)oxy)imino]-2-phenylacetonitrile, 58632-95-4; vinyllithium, 917-57-7; methyl propanoate trimethylsilyl enol ether, 34880-70-1; (*R*)-(−)-2-methoxy-2-phenyl-3,3,3-trifluoropropanoyl chloride, 39037-99-5.