diffractometer (graphite-monochromated Cu Kα radiation, W-2θ scans). The size of the crystal used for data collection was approximately 0.11 × 0.13 × 0.83 mm; the data were not corrected for absorption. Of the 1406 independent reflections for $\theta < 60°$, 1406 were considered to be observed [$I > 3.0\sigma(I)$]. The structure was solved by a multiple-solution procedure[21] and was refined by full-matrix least squares. In the final refinement, anisotropic thermal parameters were used for the nonhydrogen atoms and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations, but their parameters were not refined. The final discrepancy indices are $R = 0.054$ and $wR = 0.073$ for the 1406 observed reflections. The final difference map has no peaks greater than 0.3 e Å^{-3}.

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Acknowledgment. We express our gratitude to the members of the Physical Chemistry Department of Hoffmann-La Roche Inc. for determination of spectra and analytical data. We thank L. J. Todaro and A.-M. Chiu for carrying out the X-ray analysis.

Registry No. **1a**, 86677-62-5; **2a**, 97-67-6; **2b**, 636-61-3; **3**, 59025-03-5; **4**, 52485-05-9; **5**, 76224-59-4; **6**, 52079-23-9; **7a**, 86677-74-9; **7b**, 86677-82-9; **8a**, 86677-75-0; **8b**, 86677-83-0; **9**, 86677-76-1; **10**, 107900-37-8; **11**, 107900-38-9; **12**, 107900-39-0; **13**, 107900-40-3; **14a**, 112138-90-6; **14b**, 112138-91-7; **15a**, 112138-92-8; **15b**, 112138-93-9; **16**, 93489-57-7; **17**, 112138-94-0; **18**, 112138-95-1; **19**, 112138-96-2; **20**, 112138-97-3; **21**, 112138-98-4; **22**, 112138-99-5; **23**, 112139-00-1; **24**, 112139-01-2; **25**, 112139-02-3; **26**, 112151-59-4; **27**, 112139-03-4; **28**, 81522-68-1; **29**, 112139-04-5; MeOC(Ph)(CF$_3$)COCl, 20445-33-4; EtOCH=CH$_2$, 109-92-2; (EtO)$_2$POCH$_2$CO$_2$Et, 867-13-0; (*R*)-(+)-methylbenzylamine, 3886-69-9; dihydropyran, 110-87-2.

A Highly Stereocontrolled Route to the Monensin Spiroketal Ring System

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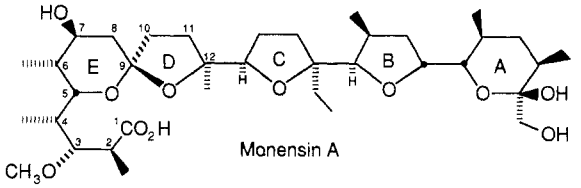
A highly stereoselective approach to the construction of the monensin A spiroketal ring system is illustrated by a total synthesis of enantiomerically pure spiroketal **35**. Key steps include cyclization of the diketo diol deriving from deprotection of dione **33** to the spiroketal ketone **34**, followed by reduction of ketone **34** to afford the target hydroxy spiroketal **35** containing all of the important structural elements of the monensin A DE ring system. The structure of compound **35** is established by single-crystal X-ray analysis. The key intermediate ketone **31** is prepared in enantiomerically pure form by using Evans' asymmetric aldol chemistry.

Introduction

The polyether antibiotics (ionophores) represent especially attractive targets for total synthesis due to their novel and interesting biological activity, physicochemical properties, and structural complexity.[1] Monensin A (hereafter simply referred to as monensin), in particular, has received a large amount of attention from the synthetic community[2] in part due to its historical and commercial importance.



Monensin A

In addition, monensin possesses a moderately complex structure with many of the most interesting features representative of this class of natural products and has been perhaps the most well studied ionophore with respect to physical properties[3] and biosynthesis.[4] Monensin gains additional attractiveness as a target due to its novel Na^+ selectivity: methods developed for construction of monensin may in principle find utility for preparation of more highly Na^+ selective analogues,[3b,d] which could prove useful as biochemical probes, and even as cardiovascular drugs.

Any strategy for the total synthesis of monensin must confront the interesting spiroketal DE ring system. Development of methods for preparation of this structural fragment gain added importance due to the occurrence of similar ring systems in a variety of other natural products, such as phyllanthocin[5] and calyculin.[6] In considering the problem in the context of monensin, the availability of

† University of Colorado Chemistry X-ray facility.

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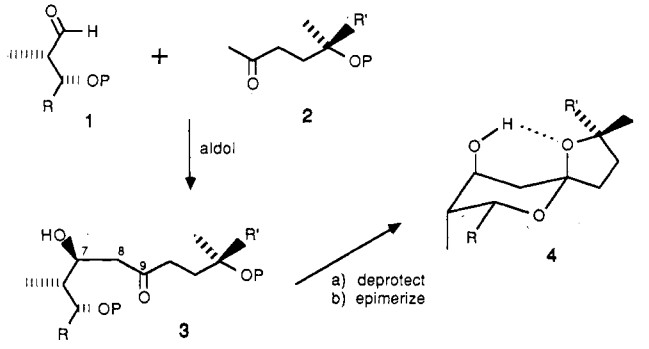
Scheme I. Kishi's Spiroketal Synthesis



tetracyclic compounds possessing the elements of the ABCD rings by degradation of the natural product suggests a route involving coupling of an ABCD fragment with a fragment containing carbons 1–7 of the molecule. As discussed below, this type of strategy has been utilized in several published studies,[2a,b] though Ireland has developed an elegant alternative approach.[2e] In this paper we describe some details of our own work on the preparation of the monensin DE ring system resulting in an efficient and highly stereocontrolled solution to the problem.

In 1979, Kishi first demonstrated the route to the monensin DE system illustrated in Scheme I.[2a] Aldol coupling of an aldehyde of type **1** with a ketone of type **2** gives the aldol **3** with formation of the C7–C8 bond. Compound **3** is produced as the major diastereomer, though significant amounts of the epimer at C7 are produced. Deprotection of keto triol **3** then gives spiroketal **4** with the correct stereochemistry at C9 after a separate acid catalyzed epimerization step. This same route was used by Still in his monensin total synthesis.[2b]

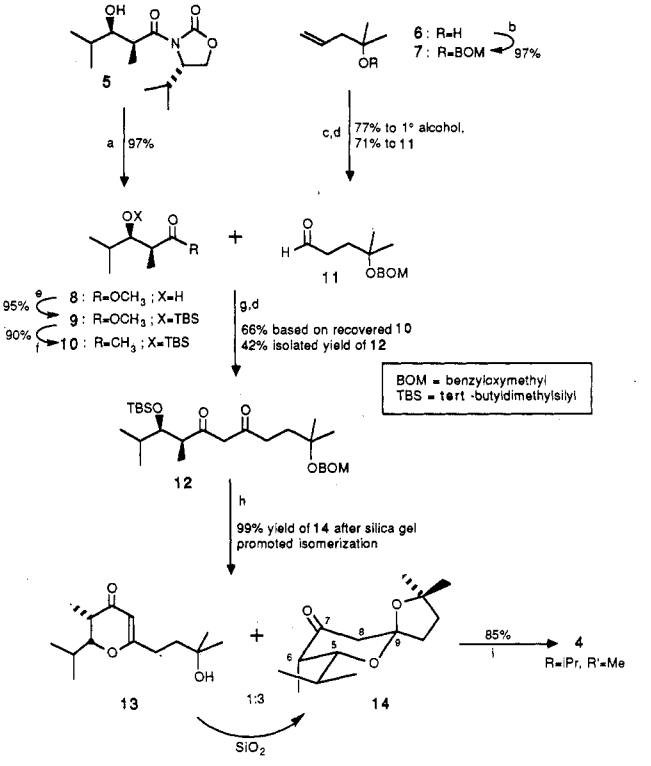
This approach, involving formation of the C7 stereochemistry concomitant with the coupling reaction, is attractive, but the lack of stereocontrol in the aldol and the difficulty of the spiroketalization–epimerization process are problematical. While Sih has recently reported a very elegant solution to the problem of aldol stereoselection in this sequence,[2h] we felt that an alternative strategy utilizing the well-defined conformational and configurational preferences of spiroketals for control of both C7 and C9 stereochemistry offered advantages as described herein.

Results and Discussion

Our monensin DE ring synthesis is illustrated by the reaction sequence shown in Scheme II. The target is spiroketal **4** (R = *i*-Pr, R′ = Me), where R and R′ are chosen to mimic the monensin system in the simplest possible structure.

In general, the approach was envisioned to proceed via acylation of an enolate derived from a methyl ketone of type **10** with formation of the C8–C9 (the monensin numbering scheme is used throughout this paper) bond, to give a β-diketone diol of type **12**, postponing formation of the stereocenter at C7 until after spirocyclization. Deprotection of the hydroxyl moieties of diketone **12** was then expected to give rise to the spirocycle **14** with the required stereochemistry, due to the expected equatorial preference

Scheme II.[a] Synthesis of Spiroketal 4 (R = *i*-Pr, R′ = Me)



[a] (a) NaOMe, MeOH, 0 °C; (b) $PhCH_2OCH_2Cl$, *i*-Pr_2EtN, CH_2Cl_2; (c) (1) BH_3·SMe_2, THF; (2) 30% aqueous H_2O_2; (d) $(COCl)_2$, DMSO, CH_2Cl_2, −70 °C, Et_3N; (e) TBSOTf, lutidine, CH_2Cl_2; (f) (1) $TMSCH_2Li$, THF, −60 °C; (2) MeOH, 0 °C; (g) (1) LDA, THF, −45 °C; (2) add **11**; (h) HF, aqueous CH_3CN; (i) K-Selectride, THF, −78 °C→−15 °C.

of the large C5 substituent and the axial (anomerically stabilized) preference of the five-membered-ring oxygen. This forces the methyl group at C6 into the axial conformation. Finally, hydride reduction of the carbonyl grouping of compound **14** was expected to proceed from the less hindered equatorial face to produce the target compound with the monensin stereochemistry at C5 and C7.

Several questions regarding this scenario needed to be addressed. Specifically, the stereocontrol at C9 is thermodynamic in nature and requires equilibration to the *presumed* most stable configuration at C9. The configuration at C6, however, is expected to be thermodynamically disfavored. That is, equilibration α to the C7 carbonyl would give rise to the wrong stereochemistry at C6. In order for this strategy to succeed, deprotection of the hydroxyl functions of a protected diketo diol of type **12** and equilibration of configuration at the spiroketal carbon must proceed under mild conditions such that the configuration at C6 remains intact.

Synthesis of Spiroketal 4 (R = *i*-Pr, R′ = Me). In fact, all of these requirements can be met as shown in Scheme II. Thus, ketone **10** is readily prepared from the known *N*-acyloxazolidone **5**[7] (enantiomerically enriched) by methanolysis to give the methyl ester **8**, followed by protection of the hydroxyl grouping as the *tert*-butyldimethylsilyl (TBS) ether[8] to give ester **9**. It should be mentioned that changing the order of the protection and

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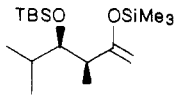
methanolysis steps is unsatisfactory. Thus, the TBS ether of oxazolidone **5** can be prepared in high yield. However, the methanolysis reaction run on the TBS ether gives a low yield of protected ester **9**. Apparently, the TBS ether grouping increases the steric hindrance at the acyl carbonyl carbon of the *N*-acyloxazolidone, and considerable nucleophilic attack occurs at the ring carbonyl, leading to a very stable but undesired amide. Finally, treatment of ester **9** with 2.1 equiv of (lithiomethyl)trimethylsilane,[9] followed by quenching of the reaction mixture with methanol, gives the desired methyl ketone **10** in 83% overall yield from oxazolidone **5**.

Unfortunately, no conditions for direct acylation of the kinetic enolate derived from ketone **10** to give a β-diketone of type **12** could be found. For example, attempted coupling of lactone **16**[10] with the enolate derived by treatment of ketone **10** with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) gave starting materials as the only identifiable products. Silylation of this enolate gave enol ether **15**. But, attempted C-acylation[11] of the amine free enolate of ketone **10** (from **15**: methyllithium, THF) with acid chloride **17** (derived from 4-hydroxy-4-methylpentene (**6**):[12] (a) TBSOTf, lutidine; (b) borane–methyl sulfide, then H_2O_2; (c) $RuCl_3/NaIO_4$;[13] (d) NaH, oxalyl chloride[14]) under a variety of conditions gave a complex mixture of unidentified products.



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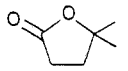

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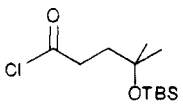

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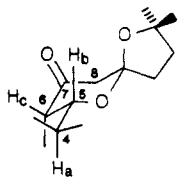
The required coupling was finally achieved by an aldol–oxidation sequence[15] as shown in Scheme II. Thus, aldehyde **11** was prepared by protection of allylic alcohol[12] **6** as the (benzyloxy)methyl (BOM) ether[16] to give alkene **7**, followed by hydroboration–oxidation of this alkene, and then oxidation of the resulting primary alcohol under the conditions of Swern.[17] Aldol coupling of the lithium enolate of ketone **10** with aldehyde **11**, followed directly by Swern oxidation, gives the β-diketone **12**.

Deprotection of the hydroxyl functions of compound **12** using aqueous hydrofluoric acid in acetonitrile was very clean, resulting in formation of the desired spiroketal **14** and a much more polar product with spectra consistent with the partially cyclized pyranone **13** in a ratio of about 3:1. As expected, treatment of spiroketal **14** with potassium carbonate in refluxing methanol gave the epimeric spiroketal **18** as the major product. None of diastereomer **18** could be detected in the deprotection reaction mixture.

The structure of the desired spiroketal **14** was deduced on the basis of the COSY 2D ^1H NMR spectrum. Compound **14** shows the expected 3-Hz coupling constant between H_b and H_c and a small *W* coupling between H_c and the equatorial proton at C8. Compound **18**, on the other hand, showed a 13-Hz coupling constant between H_b and H_c and no *W* coupling.



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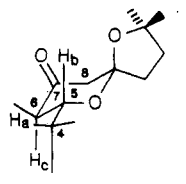

18

Interestingly, structural determination of compounds **14** and **18** was not possible by examination of the 250-MHz 1D ^1H NMR spectra alone, since H_b showed a qualitatively similar pattern for both isomers. Given the COSY results, this implies that the configuration at C6 is controlling the conformation at the C4–C5 bond! Thus, for compound **14**, $J_{a,b}$ = 10 Hz, while for compound **18**, $J_{a,b}$ = 3 Hz. For both isomers, H_b shows one large and one small coupling, implying the preferred conformations indicated in the drawings. It seems likely that, for monensin itself, the axial methyl group at C6 exerts an important influence on the side-chain conformation.

Experiments directed toward increasing the conversion of diketone **12** to spiroketal **14** were then undertaken. It was discovered that silica gel is capable of catalyzing the isomerization of enone **13** to spiroketal **14**. This reaction is exactly analogous to an alumina-catalyzed spirocyclization reported by Danishefsky.[18] In that case, the enone of type **13** was prepared by a Lewis acid catalyzed hetero-Diels–Alder reaction.

The pyranone **13** is polar enough that it remains close to the origin of a flash column using a solvent system that elutes the spiroketal. Thus, loading the crude reaction mixture on a silica gel column set up for flash chromatography, then eluting with 10% ethyl acetate/hexanes, gives spiroketal **14**, while the enone remains on the column. After 24 h, a second elution with the same solvent affords additional spiroketal, and repetition of this process twice more finally gives a very satisfactory 99% isolated yield spiroketal **14** in pure form! No trace of stereoisomeric material is observed.

We feel that the success of this approach is a consequence of the presumed extremely facile equilibration between pyranone **13** and spiroketal **14**. Thus, it seems highly likely that the kinetic product mixture formed in the spirocyclization step from the diketo diol is a mixture at C9, as is found for the spiroketalization of the C7-hydroxy compound.[2a] In our case, however, equilibration of the C9 stereocenter to the thermodynamically preferred configuration via pyranone **13** proceeds under the conditions of the deprotection reaction. Thus, no C9 epimer is isolated.

Completion of the synthesis of the target spiroketal **4** (R = *i*-Pr, R′ = Me) now requires stereoselective reduction of the carbonyl grouping from the equatorial face.[5] The reduction was easily accomplished by treatment of the spiroketal **14** with K-Selectride[20] (Aldrich), affording the target **4** (R = *i*-Pr, R′ = Me) as the only observable stereoisomer (ratio of equatorial to axial attack >30:1 on the basis of the NMR spectrum).

Spectra of compound **4** (R = *i*-Pr, R′ = Me) are consistent with the presence of intramolecular hydrogen

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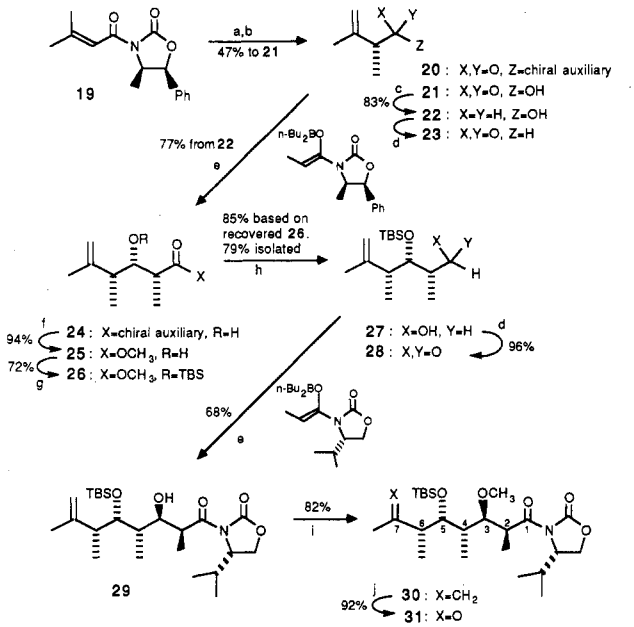
Scheme III.[a] Synthesis of Ketone 31



[a] (a) (1) LDA, THF, −50 °C; (2) MeI, 12 h; (b) KOH, MeOH, 0 °C; (c) LAH, ether, 0 °C; (d) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, *i*-Pr_2EtN; (e) Evans aldol; (f) NaOMe, MeOH, 0 °C; (g) TBSOTf, lutidine, CH_2Cl_2; (h) DIBAH, ether, 0 °C; (i) 30 equiv of MeOTf, di-*tert*-butylpyridine, $CHCl_3$, ↑↓; (j) (1) O_3, CH_2Cl_2, MeOH, $NaHCO_3$, −78 °C; (2) Me_2S, 0 °C→room temperature, 10 h.

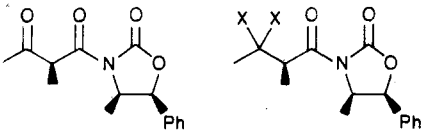
bonding. As expected, in the ^1H NMR spectrum, the hydroxyl proton is split into a doublet with a coupling constant of 9.8 Hz due to coupling with the C7 proton. The concentration dependence of the infrared spectrum of this alcohol is also consistent with intramolecular hydrogen bonding. In this system, these data are consistent only with the structure proposed. As described below, the stereochemical assignments at C7 and C9 of spiroketal **4** (R = *i*-Pr, R′ = Me) are fully corroborated by single-crystal X-ray analysis of the more complex derivative **35**.

Synthesis of Ketone 31. Use of the approach outlined in Scheme II in a total synthesis of monensin requires preparation of a ketone similar to compound **10**, but possessing the stereocenters at carbons 2–4 of monensin, with the carboxylic acid grouping suitably protected. In order to more fully test the utility of the strategy, we prepared a ketone applicable to the actual total synthesis, and the spiroketalization protocol was tested by using aldehyde **11** as a model for the "tetracyclic" ABCD fragment.

The structure of the required ketone fragment **31**, possessing carbons 1–8 of monensin, is shown in Scheme III. Since the monensin side chain fragment has two syn aldol connections (bonds C2–C3 and C5–C6), preparation of a compound of type **31** in enantiomerically enriched form seemed a perfect test of recently developed asymmetric aldol chemistry. We chose to apply the elegant *N*-acyloxazolidone strategy of Evans to this problem.[21] Given this approach, it seemed reasonable to propose use of the oxazolidone ring as a protecting group for the C1 carboxylic acid group of monensin, thereby defining target structure **31**. Since completion of this work, Evans has reported an alternative approach to a similar target—the aldehyde corresponding to ketone **31** wherein the hydroxyl groupings are protected as an acetonide—using novel variants of his aldol chemistry.[2k]

(21) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23–32.

Stereochemistry at carbons 2–5 of ketone **31** would be introduced during aldol condensations. We initially envisioned the stereochemistry at C6 to derive from an asymmetric acylation reaction, on the basis of the results of Evans showing that β-diketones of type **36** are stable with respect to epimerization.[22,2k] In this scenario, the

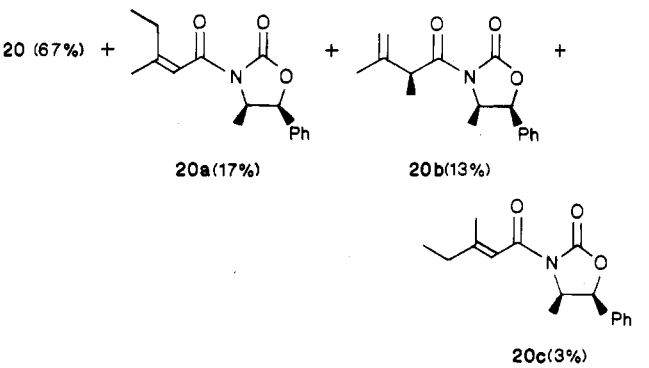


36 **37a**: X=OCH_3 **b**: X, X=OCH_2CH_2O

ketone carbonyl grouping of compound **36** becomes the C6 carbonyl of key intermediate **31** and must be suitably protected. To test the approach, we protected compound **36**, prepared according to Evans,[20] as either the dimethyl ketal **37a** or the ethylene ketal **37b** (actually the *R* configuration at the C6 stereocenter is required for monensin, but compound **36** was available in connection with other work and was used to test the protection scheme). The strategy now required removal of the chiral auxiliary and further elaboration.

Unfortunately, all attempts at removal of the auxiliary from compounds **37** led to very low yields of the desired product. In our hands, all nucleophiles tested, including hydride, hydroxide, and alkoxide, preferentially attack the ring carbonyl in these cases. Clearly, this is due to steric hindrance at the *N*-acyl carbonyl grouping due to the quaternary nature of the β carbon. In this case, of course, removal of the auxiliary before protection of the ketone carbonyl grouping is not possible without racemization at the stereocenter. We therefore chose to investigate use of the sterically undemanding methylene grouping as a protected C6 carbonyl. This led to the synthetic route shown in Scheme III.

The α,β-unsaturated *N*-acyloxazolidone **19** was obtained in near quantitative yield by sequential lithiation of the norephedrine-derived oxazolidone and then acylation with β-methylcrotonoyl chloride. Treatment of imide **19** with LDA and then alkylation of the resultant enolate with methyl iodide gave a mixture of stereo- and regioisomers, with the major product being the desired β,γ-unsaturated *R*-methylated compound **20** (67%, by HPLC analysis). Attempts to increase the relative yield of this compound by altering the reaction temperature, changing to dimethoxyethane solvent, or using dimethyl sulfate or methyl triflate as alkylating agent failed.



Efficient purification of this mixture on a preparative scale by crystallization or chromatography proved im-

(22) Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984**, *106*, 1154–1156.

possible in our hands. However, it was found that the α,β-unsaturated isomers **20a** and **20c** react much more slowly with hydroxide than the β,γ-unsaturated isomers and could be readily removed in the next step. Separation of diastereomers **20** and **20b** proved much more difficult, and the C6 *S* material deriving from **20b** was carried through the sequence until it could be efficiently removed by crystallization after the second aldol reaction.

Thus, treatment of the mixture of compounds **20** with potassium hydroxide in methanol at 0 °C gave the known acid **21**,[23] which was easily separated from other components of the reaction mixture, including unreacted conjugated imides, by alkaline extraction. The yield of acid, based on *N*-acyloxazolidone **19**, was 47%. The measured optical rotation of acid **21** ($[\alpha]^{25}_D$ −27° (*c* 0.73, $CHCl_3$)) corresponds to a 71% enantiomeric excess of the desired *R* enantiomer based on comparison with the literature value.[21]

Reduction of the acid **21** to primary alcohol **22** was straightforward. Oxidation of the alcohol to the required aldehyde **23**, however, proved problematical due to the acidic nature of the allylic proton α to the carbonyl. Thus, under standard Swern oxidation conditions, the sole product of oxidation was conjugated aldehyde, wherein the stereocenter is lost. This problem could be solved by replacement of triethylamine with a more hindered base. Swern oxidation using diisopropylethylamine, followed by a cold acidic workup and buffered wash (acid can also lead to conjugation of the product), gives a good yield of the very sensitive aldehyde **23**. Due to the instability of this aldehyde, the compound was freshly prepared and used immediately in the next reaction.

Application of the Evans aldol protocol to aldehyde **23** was straightforward. Thus, reaction of the aldehyde with the dibutylboryl enolate of the *N*-propionyl norephedrine-derived oxazolidone gave, after standard workup, a good yield of the desired erythro aldol product **24**. The C6 *S* diastereomer could be detected by TLC and separated from the mixture by careful flash chromatography. However, for preparative purposes it was found expedient to carry this diastereomer through until after the second aldol.

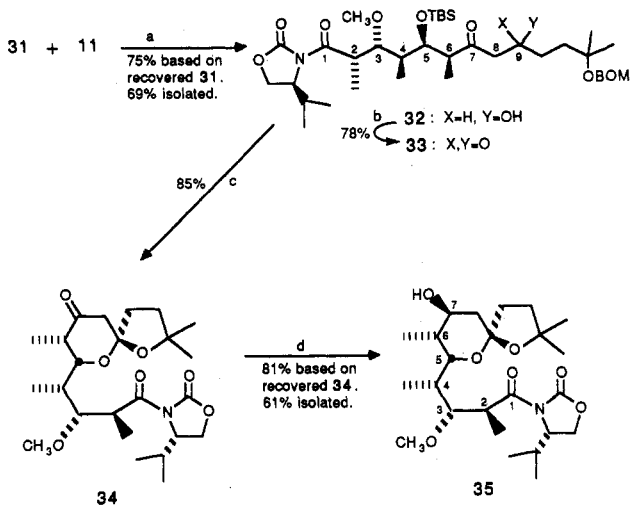
Treatment of the imide **24** with sodium methoxide in cold methanol gave ester **25** and the norephedrin-derived oxazolidone, which were easily separated by taking advantage of the low solubility of the oxazolidone in 20% ethyl acetate/hexane. Protection of the hydroxyl grouping of ester **25** as the TBS ether then gave ester **26**.

It was found that treatment of ester **26** with lithium aluminum hydride (LAH), in addition to reducing the ester, also removed the silyl protecting group. Reduction of ester **26** with diisobutylaluminum hydride, however, proved effective and gave a good yield of the desired alcohol **27**. Oxidation of alcohol **27** using the Swern conditions with diisopropylethylamine gave aldehyde **28**. This aldehyde could be purified by flash chromatography or recrystallized from hexanes at −15 °C (the compound melts below room temperature). However, this material was generally carried on to the next reaction without purification.

Application of Evans' protocol to aldehyde **28**, now by using the valinol-derived chiral auxiliary, afforded aldol **29** as the major product. Recrystallization of this compound from hexanes gave the pure aldol as find needles: chromatography of the residue from the mother liquor and subsequent recrystallization finally gave a 68% yield of

(23) Sato, F.; Iijima, S.; Sato, M. *J. Chem. Soc., Chem. Commun.* **1981**, 180–181.

Scheme IV.[a] **Synthesis of Spiroketal 35**



[a] (a) (1) LDA, THF on **31**; (2) add **11**; $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, *i*-Pr_2EtN; (c) (1) HF, aqueous CH_3CN; (2) silica gel; (d) K-Selectride, THF, −78 °C.

diastereomerically pure aldol product **29**. It should be noted that although this yield seems low, this is partly due to efficient removal of the C6 *S* diastereomer at this stage.

The hindered nature of the hydroxyl function of aldol **29** makes the necessary conversion to the methyl ether somewhat problematical. Treatment of compound **29** with 30 equiv of methyl triflate and 60 equiv of di-*tert*-butylpyridine[24] in refluxing chloroform did, however, produce an 81% yield of the methyl ether **30**. Deprotection of the C7 ketone carbonyl was readily achieved by ozonolysis in dichloromethane followed by reduction of the ozonide with dimethyl sulfide. The yield, however, was low (50%). Attempted cleavage using ruthenium tetraoxide (Sharpless conditions),[13] or *m*-chloroperbenzoic acid epoxidation followed by perchloric acid promoted opening of the epoxide and periodate cleavage, all gave similarly poor yields. The problem was easily solved, however, by ozonolysis of the alkene in 1:1 methanol/dichloromethane with sodium bicarbonate at −78 °C.[25] The resulting ozonide was quite stable, but could be efficiently reduced by treatment with dimethyl sulfide at room temperature for 10 h, resulting in an acceptable yield of the required ketone **31**.

Synthesis of Spiroketal 35. Ketone **31** was tested in the spiroketalization protocol as shown in Scheme IV. Thus, aldol coupling of ketone **31** with the (benzyloxy)-methyl-protected hydroxy aldehyde **11** gave aldol **32**. This material was oxidized directly with Swern reagent to the β-diketone **33** in an overall yield from **31** of 58%. Considerable effort was expended in optimizing this transformation. The oxidation step, in particular, is problematical. It was found that *slow addition* of the aldol to the Swern reagent was essential for obtaining a good yield in the oxidation step.

As expected, treatment of the β-diketone **33** with aqueous hydrofluoric acid in acetonitrile led to a mixture of partially cyclized enone and the desired spiroketal ketone **34**. Once again, the enone was easily transformed to the spiroketal by equilibration on a silica gel flash column, finally affording spiroketal **34** in acceptable yield. The ^1H NMR spectrum of ketone **34** was similar to that observed for ketone **14**. Thus, the coupling constant between the

(24) Arnap, J.; Kenne, L.; Lindberg, B.; Lönngren, J. *J. Carbohydr. Res.* **1975**, *44*, C5–C7.

(25) Danishefsky, S.; Chackalamannil, S.; Harrison, P.; Silvestri, M.; Cole, P. *J. Am. Chem. Soc.* **1985**, *107*, 2474–2484.

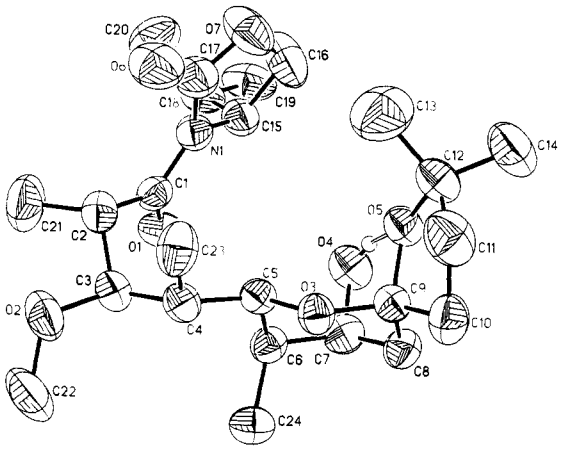


Figure 1. Perspective view of spiroketal **35** ($C_{24}H_{41}NO_7$) showing the numbering scheme adopted. Thermal ellipsoids are shown at the 50% probability level. Hydrogen atoms, except for H1, are omitted for clarity.

protons at C5 and C6 was 3 Hz, and the C6 proton also showed *W* coupling to the β proton at C8. No trace of diastereomeric material could be observed.

Again, highly stereoselective reduction of the ketone was accomplished by using K-Selectride. It was found that when the reduction was carried out at −30 °C, an assortment of products was formed. When the reaction was executed at −70 °C, however, the predominant product was the desired axial alcohol **35**. Although this reaction was quite slow, after 22 h a 60% isolated yield of spiroketal **35** was realized (80% based on recovered starting material). Again, the structure of the spiroketal could be deduced by spectroscopic means. The ^{1}H NMR spectrum shows a doublet for the hydroxyl proton with a 9.1-Hz splitting. The IR spectrum shows a broad peak at 3500–3200 cm^{-1}, with no sharp peak at 3600 cm^{-1}, and no change upon dilution. All spectroscopic evidence is consistent with structure **35**.

Crystal Structure of Spiroketal 35. The structure of the target spiroketal was established unequivocally by single-crystal X-ray analysis. Crystals of compound **35** suitable for X-ray analysis were grown from hexane. These exhibited a sharp melting point at 124–125 °C. Crystal data and details of the structure determination and refinement are given in the Experimental Section. Figure 1 shows a perspective view of the molecule showing the numbering scheme adopted in the crystallography work. As can be seen in the figure, the compound has the desired constitution and stereochemistry.

Some interesting structural features of this molecule deserve comment. First, the distance between the axial alcohol oxygen on the pyran ring (O4) and the pyran ring oxygen (O5) is 2.793 A. This value is consistent with the expected intramolecular hydrogen bond.

Secondly, the *N*-acyloxazolidone system behaves in a manner consistent with the expected amide resonance and with the proposal that the preferred arrangement of the two carbonyls minimizes the overall dipole moment of the structure. Thus, the dihedral angle between the planes of the ketonic moiety C1, C2, O1 and the oxazolidone ring carbonyl grouping N1, C17, O6 is 6.8° (a near-planar arrangement), and the carbonyl groups are "anti" disposed. The shortening of the C1–N1, 1.393 (3) Å, and C17–N1, 1.380 (3) Å, bonds relative to the C15–N1, 1.457 (3) Å, bond is also consistent with the amide resonance. The oxazolidone ring is essentially planar with C15 0.2 Å below and C16 0.1 Å above the plane defined by N1, C17, O6, and O7. The tetrahydrofuran ring moiety of the spiroketal is in an envelope conformation, while the tetrahydropyran moiety is in a nice chair conformation as expected.

Conclusion

A procedure for coupling of an ABCD fragment of monensin with an E ring side chain fragment, with highly stereoselective formation of the stereocenters at C7 and C9, has been developed. Using Evans' asymmetric aldol chemistry, we have achieved a useful synthesis of the E ring side chain fragment **31**, affording gram quantities of ketone **31** in enantiomerically pure form. The coupling–spiroketalization protocol has been tested by using ketone **31** with the model aldehyde **7**, to give the desired spiroketal **35**. The crystal structure of ketal **35** is reported.

Experimental Section

Unless otherwise stated, all reactions were run under positive argon pressure. An argon atmosphere in the reaction vessel was maintained by use of a Firestone valve with a silicon oil bubbler. Chromatographic purifications were performed by using the flash chromatography[26] technique of Still with E. Merck 40–60-μm normal-phase silica gel. All solvents were distilled before use. Analytical thin-layer chromatography was performed on 2 × 10 cm cut glass plates (0.2-mm-thick E. Merck silica gel 60 F254).

Proton and carbon NMR spectra were run on a JEOL FX-90Q, Bruker WM-250, or Chem Magnetics A-200 spectrometer. Spectra were run in $CDCl_3$, which in carbon spectra was used as the internal chemical shift standard (≡ δ 77); in proton spectra, residual $CHCl_3$ was used as the standard (≡ δ 7.24). Mass spectra were run on either a Varian MAT CH5 or a VG 7070 EQ mass spectrometer. In cases where the CI spectrum is reported, the reagent gas is isobutane. In cases where the FAB spectrum is reported, the matrix compound is PEG 600. High-performance liquid chromatography analyses were run on a Waters chromatographic system using an M45 pump and a μ-Porasil column.

Most reagents were obtained from commercial sources and used without purification. Starting materials that were not commercially available were synthesized by using the literature procedures. Ether and tetrahydrofuran (THF) were distilled from benzophenone ketyl; diisopropylamine, dimethylformamide (DMF), methanol, and *N,N*-diisopropylethylamine (Hünig's base) were distilled from calcium hydride; dichloromethane was distilled from phosphorus pentoxide; chloroform was dried over 3-Å molecular sieves.

Elemental analyses were performed by either Galbraith Laboratories, Knoxville, TN, or Spang Laboratories, Eagle Harbor, MI. Infrared spectra were taken on a Perkin-Elmer 727B instrument.

Proton spectra are reported by giving the number of the carbon to which the protons in question are attached in italics. The crystal structure numbering scheme is used throughout. Carbons 25, 26, and 27 refer to the methyleneoxy, benzyloxy, and the C7 methylene groups respectively.

Methyl (2*S*,3*R*)-2,4-Dimethyl-3-hydroxypentanoate (8). To a stirred solution of 0.2 g (0.78 mmol) of imide **5**[7] in 3 mL of dry, cold (0 °C) methanol was added 46 mg (0.85 mmol) of sodium methoxide. This solution was stirred for 7 min, at which time 1 mL of a saturated ammonium chloride solution was added. The resulting solution was washed with water, extracted with dichloromethane, dried (Na_2SO_4/K_2CO_3), and concentrated under reduced pressure (water aspirator). The compound was not placed under high vacuum. Chromatographic purification of the resulting oil eluting with 30% hexanes in ether yielded 0.12 g (97%) of ester **8**: IR ($CHCl_3$) 3350–3650 (br, OH), 1720 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 0.88 (d, 3 H, *J* = 6.76 Hz, *23*), 1.01 (d, 3 H, *J* = 6.55 Hz, *3*), 1.18 (d, 3 H, *J* = 7.23 Hz, *24*), 1.68 (dqq, 1 H, *J* = 8.0, 6.8, 6.6 Hz, *4*), 2.46 (d, 1 H, *J* = 4.09 Hz, O*H*), 3.57 (dd, 1 H, *J* = 3.60,

(26) Mitra, A.; Kahn, M.; Still, W. C. *J. Org. Chem.* **1978**, *43*, 2923–2925.

7.18 Hz, *6*), 3.71 (s, 3 H, O*Me*); ^{13}C NMR ($CDCl_3$) δ 10.3, 18.2, 19.0, 30.7, 42.0, 51.5, 76.8, 176.6; mass spectrum (70 eV), *m/e* (relative intensity) 145 (3, M − Me), 142 (2), 129 (6), 117 (41), 88 (100), 73 (13). Anal. Calcd for $C_8H_{16}O_3$: C, 59.97; H, 10.07. Found: C, 60.06; H, 10.04.

Methyl (2*S*,3*R*)-3-(*tert*-Butyldimethylsiloxy)-2,4-dimethylpentanoate (9). To a stirred solution of 0.32 mL (2.7 mmol) of lutidine in 2 mL of cold (0 °C) dichloromethane was added 0.46 mL (2.0 mmol) of *tert*-butyldimethylsilyl triflate.[8] To this mixture was added a solution of 0.29 g (1.8 mmol) of alcohol **8** in 3 mL of dichloromethane by cannulation. The solution was allowed to warm to room temperature and was stirred for 1 h. The solution was then poured into a 10% ammonium chloride solution and extracted with dichloromethane, dried (Na_2SO_4/K_2CO_3), and concentrated under reduced pressure. Chromatography with 5% ethyl acetate in hexanes yielded 0.48 g (95%) of silyl ether **9**: IR ($CHCl_3$) 1725 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ −0.02 (s, 3 H, *MeSi*), 0.03 (s, 3 H, *MeSi*), 0.86 (d, 3 H, *J* = 7 Hz, *23*), 0.87 [s, 9 H, (CH_3)$_3$C], 0.87 (d, 3 H, *J* = 7.1 Hz, *3*), 1.12 (d, 3 H, *J* = 7.1 Hz, *24*), 1.67 (sept d, 1 H, *J* = 7.1, 5.4 Hz, *4*), 2.58 (qd, 1 H, *J* = 7.1, 5.2 Hz, *6*), 3.64 (s, 3 H, O*Me*), 3.77 (t, 1 H, *J* = 5.2 Hz, *5*); ^{13}C NMR ($CDCl_3$) δ 12.4, 18.0, 18.4, 19.3, 26.1, 33.1, 43.1, 51.4, 77.9, 176.0; mass spectrum (70 eV), *m/e* (relative intensity) 274 (0.2, M$^+$), 217 (100), 88 (89). Anal. Calcd for $C_{14}H_{30}O_3Si$: C, 61.26; H, 11.02; Si, 10.23. Found: C, 61.41; H, 11.23; Si, 10.08.

(3*R*,4*S*)-3-(*tert*-Butyldimethylsiloxy)-2,4-dimethylhexan-5-one (10). To a stirred solution of 0.125 g (0.45 mmol) of ester **9** in 5 mL of cold THF cooled to −70 °C was added, over a 5-min period, 1.14 mL (0.93 mmol) of a 0.82 M solution of (lithiomethyl)trimethylsilane.[9] The reaction mixture was stirred for 30 min at −70 °C and then slowly allowed to warm to 0 °C. The flask was then transferred to an ice bath, and 1 mL of methanol was added. The resulting solution was stirred for 1 h, then poured into a 10% ammonium chloride solution, extracted with ether, washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to yield a clear oil. Chromatography eluting with 5% ethyl acetate in hexanes yielded 0.106 g (90%) of the methyl ketone **10**: IR ($CHCl_3$) 1700 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 3 H, *MeSi*), 0.05 (s, 3 H, *MeSi*), 0.84 (d, 3 H, *J* = 6.8 Hz, *23*), 0.88 [s, 9 H, (CH_3)$_3$C], 0.88 (d, 3 H, *J* = 6.7 Hz, *3*), 1.07 (d, 3 H, *J* = 7.1 Hz, *24*), 1.66 (qd, 1 H, *J* = 6.8, 4.5 Hz, *4*), 2.16 (s, 3 H, *8*), 2.66 (qd, 1 H, *J* = 7.1, 5.5 Hz, *6*), 3.76 (dd, 1 H, *J* = 4.5, 5.5 Hz, *5*); ^{13}C NMR ($CDCl_3$) δ −4.1, −3.9, 12.8, 17.8, 18.4, 19.6, 26.1, 29.4, 33.1, 50.9, 77.3, 211.3; mass spectrum (70 eV), *m/e* (relative intensity) 258 (0.5, M$^+$), 215 (57), 201 (100). Anal. Calcd for $C_{14}H_{30}O_2Si$: C, 65.06; H, 11.70; Si, 10.87. Found: C, 65.24; H, 11.50; Si, 11.06.

2-[[(Benzyloxy)methyl]oxy]-2-methyl-4-pentene (7). A stirred solution of 2 g (20 mmol) of alcohol **6**[12] and 5.6 mL (32 mmol) of *N,N*-diisopropylethylamine was cooled to 0 °C, and 3.05 mL (22 mmol) of benzyl chloromethyl ether[17] was added. This solution was stirred for 8 h, at which time 10 mL of dichloromethane was added, and the reaction mixture was stirred for an additional 2 h. The solution was then poured into 35 mL of ice-cold 1 M HCl, extracted with dichloromethane, dried (Na_2SO_4/K_2CO_3), and concentrated under reduced pressure. The resulting yellow oil was purified by chromatography eluting with 7% ethyl acetate in hexanes, yielding 4.2 g (97%) of ether **7**: IR ($CHCl_3$) 1634, 1452 cm^{-1} (Ph); ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 6 H, *13* and *14*), 2.32 (d, 2 H, *J* = 7.2 Hz, *11*), 4.63 (s, 2 H, *25*), 4.88 (s, 2 H, *26*), 5.00 (m, 1 H, *9*), 5.17 (q, 1 H, *J* = 1.2 Hz, *10*), 5.91 (m, 1 H, *9*), 7.33 (s, 5 H, *Ph*); ^{13}C NMR ($CDCl_3$) δ 26.18, 46.50, 69.20, 76.02, 89.14, 117.41, 127.76, 128.25, 134.48, 138.22; mass spectrum (70 eV), *m/e* (relative intensity) 91 (100), 179 (35). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.09; H, 9.10.

2-[[(Benzyloxy)methyl]oxy]-2-methyl-5-pentanol. A stirred solution of 1.85 g (8.4 mmol) of alkene **7** in 35 mL of THF was cooled to 0 °C. To this solution was added 0.42 mL (12.8 mequiv) of borane–methyl sulfide. The reaction mixture was allowed to warm to ambient temperature and then stirred for 2 h. The solution was then cooled to 0 °C, and 15 mL of water, 5 mL of a 15% sodium hydroxide solution, and 10 mL of 30% H_2O_2 were added. The solution was stirred for an additional 90 min, at which time it was poured into 10 mL of water and extracted with ether. The ether extract was dried first with brine solution and then with sodium sulfate and potassium carbonate and was then concentrated in vacuo to yield a clear oil. Chromatography eluting with 50% ethyl acetate in hexanes yielded 2.08 g (77%) of 2-[[(benzyloxy)methyl]oxy]-2-methyl-5-pentanol: IR ($CHCl_3$) 3600, 3600–3200 cm^{-1} (OH); ^{1}H NMR ($CDCl_3$) δ 1.21 (s, 6 H, *13* and *14*), 1.55 (m, 4 H, *10* and *11*), 2.35 (s, 1 H, O*H*), 3.52 (m, 2 H, *9*), 4.57 (s, 2 H, *25*), 4.83 (s, 2 H, *26*), 7.28 (s, 5 H, *Ph*); ^{13}C NMR ($CDCl_3$) δ 26.2, 27.2, 38.2, 62.9, 69.3, 76.2, 89.0, 127.4, 127.7, 128.2, 138.0; mass spectrum (70 eV), *m/e* (relative intensity) 91 (100), 101 (26). Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.36; H, 8.90.

4-[[(Benzyloxy)methyl]oxy]-4-methylpentanal (11). A stirred solution of 43 μL (0.50 mmol) of oxalyl chloride in 2 mL of dichloromethane was cooled to −78 °C, and 42 μL (0.58 mmol) of dimethyl sulfoxide was added. This solution was stirred until gas evolution had ceased, at which time a solution of 100 mg (0.42 mmol) of 2-[[(benzyloxy)methyl]oxy]-2-methyl-5-pentanol in 2 mL of dichloromethane was added by cannulation over a 5-min period. This solution was then stirred for 15 min before 0.35 mL (2.5 mmol) of triethylamine was added. After an additional 5 min of stirring, the cold bath was removed and the reaction mixture was allowed to warm to room temperature. The mixture was then poured into 5 mL of water, extracted with dichloromethane, dried (Na_2SO_4/K_2CO_3), and concentrated under reduced pressure. Chromatography eluting with 30% ethyl acetate in hexanes gave 93.8 mg (92%) of aldehyde **11** as a clear oil. This unstable aldehyde was used in the next step within 1 day: IR ($CHCl_3$) 1720 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 6 H, *13* and *14*), 1.85 (t, 2 H, *J* = 7.1 Hz, *11*), 2.53 (td, 2 H, *J* = 7.5, 2.7 Hz, *10*), 4.61 (s, 2 H, *25*), 4.85 (s, 2 H, *26*), 7.33 (s, 5 H, *Ph*), 9.76 (t, 1 H, *J* = 1.5 Hz, *9*); ^{13}C NMR ($CDCl_3$) δ 26.2, 34.4, 39.0, 69.5, 75.4, 89.2, 127.5, 127.8, 128.3, 138.2, 198.9; mass spectrum (70 eV), *m/e* (relative intensity) 91 (100), 99 (40); mass spectrum (CI$^-$) calcd for $C_{14}H_{20}O_3$ 235.1334, found 235.1341.

(3*R*,4*S*)-10-[[(Benzyloxy)methyl]oxy]-3-(*tert*-butyldimethylsiloxy)-2,4,10-trimethylundecane-5,7-dione (12). To a stirred solution of 0.49 mL (3.5 mmol) of diisopropylamine in 3 mL of THF at −20 °C was added 1.98 mL (3.1 mmol) of a 1.59 M *n*-butyllithium solution. The resulting solution was stirred at −20 °C for 10 min and then cooled to −70 °C. A solution of 0.45 g (1.8 mmol) of ketone **10** in 2 mL of THF was slowly added over a period of 10 min. The solution was then stirred for an additional 50 min, at which time it was allowed to warm to −45 °C. A solution of 0.50 g (2.1 mmol) of aldehyde **11** in 2 mL of THF was then added. The solution was stirred for 30 min while the bath temperature was kept between −40 and −50 °C. One milliliter of saturated ammonium chloride was then added, and the solution was poured into brine, extracted with ether, dried ($MgSO_4$), and concentrated under reduced pressure. After solvent removal, the crude aldol product was immediately taken up in 3 mL of dry dichloromethane for the next step.

To a stirred solution of 0.30 mL (3.5 mmol) of oxalyl chloride in 10 mL of dichloromethane at −70 °C was added 0.27 mL (3.8 mmol) of dimethyl sulfoxide. When gas evolution had ceased, the solution of aldol product was very slowly added by cannulation over a period of 15 min. The solution was stirred for an additional 15 min, and then 1.83 mL (10.5 mmol) of *N,N*-diisopropylethylamine was added. After an additional 5 min of stirring, the bath was removed and the solution was allowed to warm to room temperature. The solution was then poured into water, extracted with dichloromethane, dried (Na_2SO_4/K_2CO_3), and concentrated under reduced pressure. Chromatography of the residue eluting with 7% ethyl acetate in hexanes (R_f 0.31 with 10% ethyl acetate in hexanes) afforded 0.37 g (42% isolated yield, 66% yield based on 0.16 g of recovered ketone **10**) of diketone **12**: IR ($CHCl_3$) 3550, 3550–3250 (OH), 1610 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ −0.03 (s, 3 H, *MeSi*), 0.03 (s, 3 H, *MeSi*), 0.85 (d, 3 H, *J* = 6.9 Hz, *23*), 0.88 (d, 3 H, *J* = 6.6 Hz, *3*), 0.88 [s, 9 H, (CH_3)$_3$C], 1.09 (d, 3 H, *J* = 7.0 Hz, *24*), 1.26 (s, 6 H, *13* and *14*), 1.70 (sept d, 1 H, *J* = 6.8, 2.4 Hz, *4*), 1.81 (t, 2 H, *J* = 8.2 Hz, *11*), 2.39 (qd, 1 H, *J* = 6.1, 2.4 Hz, *6*), 2.39 (t, 2 H, *J* = 8.0 Hz, *10*), 3.72 (dd, 1 H, *J* = 4.4, 5.9 Hz, *5*), 4.61 (s, 2 H, *25*), 4.82 (s, 2 H, *26*), 5.49 (s, 1 H, *8*), 7.31 (s, 5 H, *Ph*); ^{13}C NMR ($CDCl_3$) δ −4.0, −3.8, 13.6, 17.6, 18.4, 19.8, 26.1, 26.3, 32.9, 33.6, 37.3, 46.7, 69.4, 78.0, 89.2, 99.0, 127.5, 127.8, 128.4, 138.2, 195.6, 195.8; mass spectrum (70 eV), *m/e* (relative intensity) 91 (100), 187 (55), 73 (38). Anal. Calcd for $C_{28}H_{48}O_5Si$:

C, 68.25; H, 9.82; Si, 5.70. Found: C, 68.09; H, 9.77; Si, 5.62.

(2*R*,3*S*,6*R*)-2-Isopropyl-3,8,8-trimethyl-1,7-dioxaspiro[4.5]decan-4-one (14). To a 60-mL plastic bottle equipped with a stir bar were added 100 mg (0.20 mmol) of diketone diether **12**, 20 mL of acetonitrile, and 0.83 mL (20 mmol) of concentrated aqueous hydrofluoric acid. After 10 h with stirring, the reaction mixture was quenched by addition of 2 mL (28 mmol) of concentrated ammonium hydroxide, and the resulting solution was concentrated in vacuo. The contents of the flask were washed into a separatory funnel with water and dichloromethane, the phases were separated, and the dichloromethane extract was dried (Na_2SO_4/K_2CO_3) and concentrated under reduced pressure. The resulting oil was purified by chromatography eluting with 10% ethyl acetate in hexanes. Once a day for the next 3 days, the column was reeluted, resulting in a 48.2-mg yield (99%) of spiroketal **14**: IR ($CHCl_3$) 1715 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.83 (d, 3 H, J = 5.1, *24*), 1.04 (d, 3 H, J = 6.5 Hz, *3*), 1.09 (d, 3 H, J = 7.1 Hz, *23*), 1.17 (s, 3 H, *14*), 1.32 (s, 3 H, *13*), 1.84 (m, 1 H, *4*), 1.7–2.2 (m, 4 H, *10* and *11*), 2.27 (dd, 1 H, J = 1.0, 14.2 Hz, *8* equat), 2.48 (qdd, 1 H, J = 1.0, 2.6, 7.1 Hz, *6*), 2.84 (d, 1 H, J = 14.2 Hz, *8* axial), 3.67 (dd, 1 H, J = 2.6, 10.0 Hz, *5*); ^{13}C NMR ($CDCl_3$) δ 10.4, 17.9, 20.5, 28.6, 28.9, 29.4, 37.0, 38.7, 46.4, 47.5, 75.6, 84.0, 107.2, 210.9; mass spectrum (70 eV), m/e (relative intensity) 240 (2, M^+), 225 (7), 197 (10), 168 (45), 126 (22), 112 (100). Anal. Calcd for $C_{14}H_{20}O_3$: C, 69.96; H, 10.07. Found: C, 69.80; H, 10.19.

(2*R*,3*R*,4*S*,6*R*)-2-Isopropyl-3,8,8-trimethyl-1,7-dioxaspiro[4.5]decan-4-ol (4, R = *i*-Pr, R′ = Methyl). To a stirred solution of 9.0 mg (38 μmol) of ketone **14** in 1 of mL THF at −78 °C was added 39 μL (39 μmol) of K-Selectride.[19] The solution was stirred for 3 h and then slowly warmed to −15 °C. The solution was then poured into phosphate buffer (pH 7), extracted with ether, washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the resultant oil eluting with 20% ethyl acetate in hexanes gave 7.6 mg (85%) of alcohol **4** (R = *i*-Pr, R′ = methyl): IR ($CHCl_3$) 3600–3200 cm^{-1} (br, OH, H bonding); ^1H NMR ($CDCl_3$) δ 0.81 (d, 3 H, J = 7.2 Hz, *24*), 0.81 (d, 3 H, J = 6.7 Hz, *3*), 0.97 (d, 3 H, J = 6.4 Hz, *23*), 1.17 (s, 3 H, *14*), 1.33 (s, 3 H, *13*), 1.54–2.06 (m, 8 H), 3.65 (dd, 1 H, J = 10.1, 2.4 Hz, *5*), 3.75 (dq, J = 9.7, 3.0 Hz, *7*), 4.18 (d, 1 H, J = 9.8 Hz, O*H*); ^{13}C NMR ($CDCl_3$) δ 107.0, 84.0, 72.4, 71.6, 38.9, 36.2, 35.7, 35.5, 29.6, 29.5, 28.9, 20.5, 18.2, 10.4; mass spectrum (CI^+), m/e (relative intensity) 243 (25, M + 1), 225 (90, M − 17). Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81. Found: C, 69.41; H, 10.87.

(4*R*,5*S*)-3-(3-Methylbut-2-enoyl)-4-methyl-5-phenyloxazolidin-2-one (19). To a stirred solution of 10.98 g (62 mmol) of norephedrine oxazolidone in 100 mL of THF at −60 °C was added, over a period of 5 min, slightly less than 39.0 mL (62 mmol) of 1.59 M *n*-butyllithium. Addition was terminated when a yellow color just appeared. This solution was stirred for 30 min, at which time 7.6 mL (68 mmol) of β-methylcrotonoyl chloride was added over a period of 5 min. The solution was stirred for an additional 15 min, at which time the cooling bath was removed and the solution was allowed to warm to room temperature. After a further hour of stirring, the solution was poured into a 10% ammonium chloride solution, extracted with ether, washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The resulting solid could be recrystallized from absolute ethanol to give 16 g (99%) of imide **19** as a white crystalline solid: mp 125.5–125.9 °C; IR ($CHCl_3$) 1768, 1672 (C=O), 1624 cm^{-1} (C=CH); ^1H NMR ($CDCl_3$) δ 0.90 (d, 3 H, J = 6.2 Hz, *18*), 1.97 (d, 3 H, J = 1.1 Hz, *27*), 2.18 (d, 3 H, J = 1.1 Hz, *8*), 4.79 (quint, 1 H, J = 6.8, *15*), 5.66 (d, 1 H, J = 17.3 Hz, *16*), 6.96 (t, 1 H, J = 1.1 Hz, *6*), 7.35 (s, 5 H, *Ph*); ^{13}C NMR ($CDCl_3$) δ 14.3, 21.0, 27.7, 54.4, 78.4, 115.6, 125.4, 128.3, 133.4, 152.7, 158.6, 164.4; mass spectrum (70 eV), m/e (relative intensity) 259 (24, M^+), 244 (10), 83 (100), 55 (20). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.77; H, 6.47; N, 5.40.

(4*R*,5*S*)-3-[(2*R*)-2,3-Dimethylbut-3-enoyl]-4-methyl-5-phenyloxazolidin-2-one (20). To a stirred solution of 27.7 mL (198 mmol) of diisopropylamine in 220 mL of THF at −20 °C was added 107 mL (169 mmol) of a 1.59 M solution of *n*-butyllithium. The resulting solution was stirred for 15 min, at which time it was cooled to −70 °C. The solution of LDA was then cannulated into a cooled, stirred solution of 36.6 g (141 mmol) of imide **19** in 230 mL of THF. The resulting solution was stirred for 1 h, at which time 22 mL (350 mmol) of freshly distilled methyl iodide was added. The cooling bath was removed, and the solution was stirred overnight at room temperature. At that time, the reaction mixture was poured into a 10% ammonium chloride solution, extracted with ether, washed with brine, and dried ($MgSO_4$). The ether extract was then filtered through a $^1/_2$-inch silica gel bed, and the filtrate was concentrated at reduced pressure. The resulting light yellow oil was generally carried on "as is". Compound **20** could, however, be purified by repeated chromatography on silica gel eluting with 15% ethyl acetate in hexanes, visualizing the fractions on TLC with an iodine chamber. In this manner a 50% yield of imide **20** could be realized. Recrystallization from pentane then gave very pure material with the following properties: mp 60.5–62.5 °C; IR ($CHCl_3$) 1776, 1692 (C=O), 1600 cm^{-1} (C=CH); ^1H NMR ($CDCl_3$) δ 0.89 (d, 3 H, J = 6.5 Hz, *18*), 1.28 (d, 3 H, J = 7.0 Hz, *24*), 1.82 (s, 3 H, *8*), 4.40 (q, 1 H, J = 6.8 Hz, *6*), 4.72 (dq, 1 H, J = 7.0, 6.5 Hz, *15*), 4.83 (m, 2 H, *27*), 5.61 (d, 1 H, J = 7.25 Hz, *16*), 7.33 (m, 5 H, *Ph*); ^{13}C NMR ($CDCl_3$) δ 14.0, 15.4, 20.9, 44.4, 54.6, 78.2, 111.4, 125.3, 128.1, 133.0, 144.7, 152.1, 173.4; mass spectrum (70 eV), m/e (relative intensity) 273 (10, M^+), 229 (10), 96 (100). Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.23; H, 6.74; N, 4.95.

(*R*)-2,3-Dimethyl-3-butenoic Acid (21). To a stirred solution of 15 g (55 mmol) of crude imide **20** in 110 mL of methanol at 0 °C was added 110 mL (220 mmol) of a 2 M potassium hydroxide solution. The resulting reaction mixture was stirred for 3.5 h, at which time it was poured into a separatory funnel containing 50 mL of a 10% sodium bicarbonate solution. The solution was brought to a pH of 7.5 by addition of phosphoric acid and then extracted with four portions (50 mL each) of ether. The combined ether extracts were washed with four portions (50 mL each) of 10% sodium bicarbonate, and the organic layer was dried and condensed in the normal fashion for recovery of the chiral auxiliary. The combined aqueous portions were brought to pH 4 by addition of phosphoric acid and then to pH 2.5 by addition of hydrochloric acid. This solution was then extracted with five portions (50 mL each) of ether, the combined ether extracts were washed with brine and dried over sodium sulfate, and the solvent was removed in vacuo. The residue was distilled (120 °C (42 mm)) to give 2.98 g (47% based on imide **19**) of acid **21**: $[\alpha]^{25}_D$ −27° (*c* 0.73, $CHCl_3$); IR ($CHCl_3$) 3600–2400 (CO_2H), 1702 (C=O), 1640 cm^{-1} (C=CH); ^1H NMR ($CDCl_3$) δ 1.26 (d, 3 H, J = 7.0 Hz, *24*), 1.76 (s, 3 H, *8*), 3.15 (q, 1 H, J = 7.1 Hz, *6*), 4.88 (s, 2 H, *27*), 11.87 (s, 1 H, CO_2H); ^{13}C NMR ($CDCl_3$) δ 15.6 20.3, 46.7, 113.0, 143.3, 181.0; mass spectrum (70 eV), m/e (relative intensity) 114 (3, M^+), 99 (31), 41 (100). Exact mass calcd for $C_6H_{10}O_2$ 114.0681, found 114.0678.

(*R*)-2,3-Dimethyl-3-buten-1-ol (22). To a flask fitted with a condenser and charged with 120 mL of ether was added 60 mL (240 mequiv) of a 3.9 N lithium aluminum hydride solution. This stirred solution was then cooled to 0 °C, and by slow cannulation, a solution of 2.98 g (26 mmol) of acid **21** in 10 mL of ether was added. The addition rate was limited by gas evolution. This solution was then stirred for an additional 15 min, at which time 2.3 mL of water, 3.4 mL of 15% sodium hydroxide, and an additional 6.9 mL of water were added. The white suspension was stirred for an hour, and magnesium sulfate was added as a drying agent. After a further 15 min of stirring, the suspension was filtered through a pad of Celite. The Celite pad was washed with methyl acetate until no further alcohol was detected in the filtrate by TLC. This required approximately 500 mL of methyl acetate. The filtrate was stripped by rotary evaporation at 60-mm pressure with ice/water cooling of the evaporation flask. Distillation of the resulting liquid (87 °C (78 mm)) gave a 2.18-g (83%) yield of alcohol **22**: IR ($CHCl_3$) 3600–3200 (OH), 1638 cm^{-1} (C=CH); ^1H NMR ($CDCl_3$) δ 0.99 (d, 3 H, J = 7.0, *24*), 1.88 (s, 1 H, O*H*), 2.36 (sextet, 1 H, J = 6.8 Hz, *6*), 3.48 (d, 2 H, J = 6.5 Hz, *5*), 4.80 (m, 2 H, *27*); ^{13}C NMR ($CDCl_3$) δ 15.5, 19.4, 43.3, 65.2, 111.2, 146.8; mass spectrum (70 eV), m/e (relative intensity) 100 (2, M^+), 82 (15), 41 (100). Exact mass calcd for $C_6H_{12}O$ 100.0888, found 100.0945.

(4*R*,5*S*)-3-[(2*R*,3*S*,4*R*)-3-Hydroxy-2,4,5-trimethylhex-5-enoyl]-4-methyl-5-phenyloxazolidin-2-one (24). To a stirred solution of 1.95 mL (28 mmol) of dimethyl sulfoxide in 60 mL of dichloromethane at −70 °C was added 2.0 mL (24 mmol) of

oxalyl chloride. This solution was stirred for 5 min, at which time a solution of 1.97 g (20.7 mmol) of alcohol **22** in 5 mL of dichloromethane was added by cannulation over a period of 10 min. This solution was stirred for an additional 15 min, at which time 20.5 mL (120 mmol) of diisopropylethylamine was added. After a further 5 min of stirring, the cooling bath was removed and the solution was allowed to warm to 0 °C. The reaction mixture was then poured into a mixture of 100 mL of 1.2 M HCl and 30 g of ice and extracted with dichloromethane. The organic extracts were washed with two further portions of cold HCl and a portion of pH 7 phosphate buffer. The organic layer was then dried with sodium sulfate, and the solvent was removed in vacuo at 70 Torr (ice-bath cooling of the evaporator flask), affording the highly unstable aldehyde **23**: ^{1}H NMR ($CDCl_3$) δ 1.18 (d, 3 H, J = 6.8 Hz, *24*), 1.72 (t, 3 H, J = 0.9 Hz, *8*), 300 (q, 1 H, J = 6.8 Hz, *6*), 4.90 (m, 2 H, *27*), 9.50 (d, 1 H, J = 2 Hz, *5*). This material was carried directly on to the next step.

Thus, to a stirred solution of 5.3 g (22 mmol) of norephedrine oxazolidone propyl imide in 30 mL of dichloromethane at 0 °C were added 5.1 mL (30 mmol) of diisopropylethylamine and 6.6 mL (26 mmol) of dibutylboron triflate. The solution was stirred for 1 h, at which time it was cooled to −70 °C. A solution of 1.89 g (20.7 mmol) of crude aldehyde **23** in 10 mL of dichloromethane was then slowly added by cannulation. The resulting reaction mixture was stirred for 30 min, then the cooling bath was removed, and the solution was stirred for an additional 90 min at room temperature. The solution was then poured into 50 mL of pH 7 phosphate buffer and extracted with dichloromethane. The extract was concentrated on a rotary evaporator, and to the residue was added 70 mL of methanol. The solution was cooled to 0 °C, and 26 mL of 30% aqueous hydrogen peroxide was slowly added. This solution was then stirred for 2 h, at which time 30 mL of water was added and most of the methanol was removed in vacuo. The solution was then extracted with dichloromethane and the extract dried (Na_2SO_4/K_2CO_3) and concentrated under reduced pressure. The resulting crude product could be purified by chromatography eluting with 30% ethyl acetate in hexanes, giving 5.04 g (77%) of aldol product **24**: IR ($CHCl_3$) 3600–3200 (OH), 1778, 1678 (C=O), 1640 cm^{-1} (C=CH); ^{1}H NMR ($CDCl_3$) δ 0.86 (d, 3 H, J = 6.6 Hz, *18*), 1.13 (d, 3 H, J = 6.6 Hz, *24*), 1.23 (d, 3 H, J = 6.9 Hz, *23*), 1.69 (t, 3 H, J = 1.1 Hz, *8*), 2.35 (qd, 1 H, J = 6.9, 6.0 Hz, *6*), 2.95 (d, 1 H, J = 2.2 Hz, O*H*), 3.7–3.95 (m, 2 H, *4* and *5*), 4.77 (quint, 1 H, J = 7.3 Hz, *15*), 4.81 (d, 2 H, J = 1.1 Hz, *27*), 5.66 (d, 1 H, J = 7.3 Hz, *16*), 7.36 (m, 5 H, *Ph*); ^{13}C NMR ($CDCl_3$) δ 10.5, 14.1, 15.8, 19.1, 40.0, 44.1, 54.5, 72.7, 78.6, 112.2, 125.4, 128.5, 133.0, 146.7, 152.1, 177.5; mass spectrum (70 eV), m/e (relative intensity) 331 (0.1, M^+), 313 (0.2), 262 (13), 91 (100). Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.76; H, 7.57; N, 4.37.

Methyl (2*R*,3*S*,4*R*)-3-Hydroxy-2,4,5-trimethylhex-5-enoate (25). To a stirred solution of 0.76 g (2.3 mmol) of imide **24** in 10 mL of methanol at 0 °C was added 0.14 g (2.7 mmol) of sodium methoxide. This solution was stirred for 45 min, at which time 2 mL of saturated ammonium chloride solution was added. The solution was poured into water, extracted with ether, washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The resulting oily residue was then triturated with 10 mL of 10% ethyl acetate in hexanes and then allowed to stand, with occasional swirling, for about 1 h. The liquid phase was then decanted, and the crystallized oxazolidone was washed with four further 2-mL portions of solvent. The combined liquid phases were concentrated in vacuo, and the resulting oil was distilled (Kugelrohr) to give 0.40 g (94%) of methyl ester **25**: IR ($CHCl_3$) 3600–3200 (OH), 1724, 1710 (C=O), 1640 cm^{-1} (C=CH); ^{1}H NMR ($CDCl_3$) δ 1.10 (d, 3 H, J = 7.0 Hz, *24*), 1.16 (d, 3 H, J = 7.2 Hz, *23*), 1.66 (t, 3 H, J = 1.1 Hz, *8*), 2.27 (dq, 1 H, J = 8.7, 7.0 Hz, *6*), 2.41 (d, 1 H, J = 3.4 Hz, O*H*), 2.58 (qd, 1 H, J = 7.2, 3.5 Hz, *4*), 3.67 (s, 3 H, O*Me*), 3.84 (dt, 1 H, J = 8.80, 3.4 Hz, *5*), 4.76 (d, 2 H, J = 1.3 Hz, *27*); ^{13}C NMR ($CDCl_3$) δ 9.9, 15.5, 19.1, 41.7, 44.1, 51.6, 72.9, 112.0, 147.0, 176.8; mass spectrum (70 eV), m/e (relative intensity) 169 (2, M − OH), 117 (35), 70 (100), 41 (74). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.34; H, 9.58.

Methyl (2*R*,3*S*,4*R*)-3-(*tert*-Butyldimethylsiloxy)-2,4,5-trimethylhex-5-enoate (26). To a stirred solution of 0.24 mL (2 mmol) of lutidine in 10 mL of dichloromethane was added 0.19 mL (0.81 mmol) of *tert*-butyldimethylsilyl triflate. This solution was stirred for 5 min, at which time a solution of 0.13 g (0.68 mmol) of alcohol **25** in 5 mL of dichloromethane was added by cannulation. The resulting reaction mixture was stirred for 3 h, at which time it was poured into 15 mL of 10% ammonium chloride solution and extracted with dichloromethane. The extract was dried (Na_2SO_4/K_2CO_3) and concentrated under reduced pressure to give an oil. This crude product was purified by chromatography eluting with 5% ethyl acetate in hexanes to give 0.17 g (72%) of silyl ether **26**: IR ($CHCl_3$) 1736 (C=O), 1622 cm^{-1} (C=CH); ^{1}H NMR ($CDCl_3$) δ −0.09 (s, 3 H, *MeSi*), 0.03 (s, 3 H, *MeSi*), 0.87 [s, 9 H, (CH_3)$_3$C], 1.04 (d, 3 H, J = 7.0 Hz, *24*), 1.08 (d, 3 H, J = 7.0 Hz, *23*), 1.67 (s, 3 H, *8*), 2.27 (dq, 1 H, J = 8.6, 7.0 Hz, *6*), 2.58 (qd, 1 H, J = 7.0, 2.3 Hz, *4*), 3.64 (s, 3 H, O*Me*), 4.12 (dd, 1 H, J = 8.5, 2.2 Hz, *5*), 4.71 (m, 2 H, *27*); mass spectrum (70 eV), m/e (relative intensity) 285 (1, M − Me), 73 (100), 59 (21). Anal. Calcd for $C_{16}H_{32}O_3Si$: C, 63.95; H, 10.73; Si, 9.35. Found: C, 63.73; H, 10.59; Si, 9.22.

(2*S*,3*S*,4*R*)-3-(*tert*-Butyldimethylsiloxy)-2,4,5-trimethylhex-5-en-1-ol (27). To a flask containing 15 mL of ether at −70 °C was added 5.8 mL (8.7 mmol) of a 1.5 M solution of diisobutylaluminum hydride. To this solution was added a solution of 0.65 g (2.2 mmol) of ester **26** in 5 mL of ether, and the resulting reaction mixture was allowed to warm to 0 °C. The solution was then stirred for an additional 2 h, at which time it was poured onto a mixture of 10 g of ice and 10 mL of 1.2 M hydrochloric acid. A further 40 mL of hydrochloric acid was then added, the resulting mixture was extracted with ether, and the extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the resultant oil eluting with 10% ethyl acetate in hexanes gave 0.47 g (79%) of alcohol **27**. Approximately 38 mg of starting ester **26** was also recovered, affording an 85% yield based on recovered starting material. Alcohol **27** had the following properties: IR ($CHCl_3$) 3650–3100 (OH), 1638 cm^{-1} (C=CH); ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 3 H, *MeSi*), 0.06 (s, 3 H, *MeSi*), 0.80 (d, 3 H, J = 6.8 Hz, *23*), 0.89 [s, 9 H, (CH_3)$_3$C], 1.04 (d, 3 H, J = 7.0 Hz, *24*), 1.64 (t, 3 H, J = 1.1 Hz, *8*), 1.78 (s, 1 H, *OH*), 1.78 (qt, 1 H, J = 1.9, 6.8 Hz, *4*), 2.38 (quint, 1 H, J = 1.5, 6.9 Hz, *6*), 3.49 (m, 1 H, *3*), 3.74 (dd, 1 H, J = 1.9, 8.5 Hz, *5*), 4.68 (m, 2 H, *27*); ^{13}C NMR ($CDCl_3$) δ −3.9, −3.7, 10.5, 17.7, 18.4, 19.5, 26.1, 39.5, 44.8 65.7, 74.5, 111.3, 148.5; mass spectrum (70 eV), m/e (relative intensity) 255 (0.2, M − OH), 203 (44), 73 (100). Anal. Calcd for $C_{15}H_{32}O_2Si$: C, 66.11; H, 11.84; Si, 10.31. Found: C, 66.42; H, 11.92; Si, 10.27.

(2*R*,3*S*,4*R*)-3-(*tert*-Butyldimethylsiloxy)-2,4,5-trimethyl-5-hexenal (28). To a stirred solution of 93 μL (1.3 mmol) of dimethyl sulfoxide in 5 mL of dichloromethane cooled to −70 °C was added 96 μL (1.1 mmol) of oxalyl chloride. The resulting solution was stirred for 5 min, at which time a solution of 0.255 g (94 mmol) of alcohol **27** in 3 mL of dichloromethane was slowly added by cannulation. The reaction mixture was stirred for an additional 20 min before 1.0 mL (5.6 mmol) of diisopropylethylamine was added. After an additional 10 min of stirring, the cold bath was replaced with an ice bath and the solution was stirred for a further 30 min. The solution was then poured into water and extracted with dichloromethane and the extract dried (Na_2SO_4/K_2CO_3) and concentrated under reduced pressure. The resulting crude product could be purified by chromatography with 5% ethyl acetate in hexanes to give 0.244 g (96%) of aldehyde **28** as a colorless solid (mp ≅20 °C). Recrystallization of this solid from hexanes at −30 °C gave analytically pure aldehyde **28**: IR ($CHCl_3$) 2710 (OCH), 1720 (C=O), 1640 cm^{-1} (C=CH); ^{1}H NMR ($CDCl_3$) δ −0.08 (s, 3 H, *MeSi*), 0.04 (s, 3 H, *MeSi*), 0.83 [s, 9 H, (CH_3)$_3$C], 1.04 (d, 3 H, J = 7.0 Hz, *24*), 1.07 (d, 3 H, J = 7.0 Hz, *23*), 1.65 (t, 3 H, J = 1.2 Hz, *8*), 2.32 (dq, 1 H, J = 8.8, 6.9 Hz, *4*), 2.40 (dq, 1 H, J = 2.2, 6.9 Hz, *6*), 4.12 (dd, 1 H, J = 2.0, 8.8 Hz, *5*), 4.72 (m, 2 H, *27*), 9.66 (s, 1 H, *3*); ^{13}C NMR ($CDCl_3$) δ −4.1, −3.9, 6.7, 17.0, 18.3, 19.3, 26.0, 45.6, 50.6, 73.2, 112.4, 147.5, 205.3; mass spectrum (70 eV), m/e (relative intensity) 255 (0.2, M − Me), 213 (13), 73 (100). Anal. Calcd for $C_{15}H_{30}O_2Si$: C, 66.61; H, 11.18; Si, 10.38. Found: C, 66.72; H, 11.04; Si, 10.23.

(4*S*)-3-[(2*S*,3*R*,4*S*,5*S*,6*R*)-5-(*tert*-Butyldimethylsiloxy)-3-hydroxy-2,4,6,7-tetramethyloct-7-enoyl]-4-isopropyloxazolidin-2-one (29). To a stirred solution of 0.98 g (5.3 mmol) of valinol oxazolidone propyl imide in 3 mL of dichloromethane at 0 °C were added 1.2 mL (7.0 mmol) of diisopropylethylamine and 1.5 mL (5.9 mmol) of dibutylboron triflate. The solution was

stirred for 1 h, at which time it was cooled to −78 °C and a solution of 1.19 g (4.4 mmol) of aldehyde **28** in 2 mL of dichloromethane was added. The solution was stirred at this temperature for 30 min, at which time the cooling bath was removed and the solution was allowed to warm to room temperature. After an additional 2 h of stirring, the reaction mixture was quenched, oxidized, and worked up by using a procedure identical with that used for aldol product **24**, but using 6 mL of 30% aqueous H_2O_2 in 20 mL of methanol. Recrystallization of the resulting solid from hexanes gave 1.10 g of aldol product **29**. Chromatography of the condensed mother liquor eluting with 15% ethyl acetate in hexanes gave an additional 0.26 g of pure material, for a total yield of 1.36 g (68%) of aldol **29**: IR ($CHCl_3$) 3600–3200 (OH), 1777, 1677 (C=O), 1620 cm^{-1} (C=CH); ^1H NMR ($CDCl_3$) δ 0.06 (s, 6 H, Me_2Si), 0.75 (d, 3 H, J = 6.9 Hz, *23*), 0.85 (d, 3 H, J = 7.7 Hz, *20*), 0.87 [s, 9 H, $(CH_3)_3C$], 0.88 (d, 3 H, J = 8.2 Hz, *19*), 1.04 (d, 3 H, J = 6.9 Hz, *24*), 1.14 (d, 3 H, J = 7.0 Hz, *21*), 1.64 (s, 3 H, *8*), 1.65 (m, 1 H, J = 4.4, 7.3 Hz, *4*), 2.33 (sept d, 1 H, J = 7.1, 4.0 Hz, *18*), 2.38 (dq, 1 H, J = 9.3, 6.7 Hz, *6*), 3.37 (d, 1 H, J = 1.8 Hz, O*H*), 3.79 (m, 2 H, J = 7.4, 1.4 Hz, *2* and *3*), 4.04 (dd, 1 H, J = 9.3, 0.9 Hz, *5*), 4.22 (m, 2 H, *16*), 4.46 (m, 1 H, *15*), 4.66 (m, 1 H, *27*), 4.71 (m, 1 H, *27*); ^{13}C NMR ($CDCl_3$) δ −3.8, 9.3, 14.8, 17.9, 18.1, 18.6, 19.0, 26.3, 28.6, 38.3, 39.6, 45.8, 58.4, 63.4, 71.1, 73.6, 111.3, 148.9, 153.4, 178.5; mass spectrum (70 eV), m/e (relative intensity) 398 (2, M − *t*-Bu), 386 (2), 73 (100). Anal. Calcd for $C_{24}H_{45}NO_5Si$: C, 63.26; H, 9.95; N, 3.07; Si, 6.16. Found: C, 63.41; H, 10.05; N, 3.06; Si, 6.02.

(4*S*)-3-[(2*S*,3*R*,4*S*,5*S*,6*R*)-5-(*tert*-Butyldimethylsiloxy)-3-methoxy-2,4,6,7-tetramethyloct-7-enoyl]-4-isopropyloxazolidin-2-one (30). To a stirred solution of 1.54 mL (14 mmol) of methyl triflate in 6.14 mL (27 mmol) of di-*tert*-butylpyridine was added 207 mg (0.46 mmol) of alcohol **29** in 6 mL of chloroform. A condenser was then affixed to the flask, and the solution was brought to reflux. After 15 h of stirring, the solution was allowed to cool and 2 mL (28 mmol) of concentrated ammonium hydroxide was added. After a further 2 h of stirring, the mixture was poured into water and extracted with dichloromethane. The combined organic layers were then extracted with three 100-mL portions of 10% hydrochloric acid. The organic layer was dried (Na_2SO_4/K_2CO_3) and concentrated under reduced pressure. The resulting oil could be purified by chromatography eluting with 15% ethyl acetate in hexanes to give 175 mg (82%) of the methyl ether **30** as a clear oil. The di-*tert*-butylpyridine could be recovered by neutralization of the aqueous layer and extraction into dichloromethane. Methyl ether **30** had the following properties: IR ($CHCl_3$) 1772, 1692 (C=O), 1637 cm^{-1} (C=CH); ^1H NMR ($CDCl_3$) δ 0.07 (s, 3 H, *MeSi*), 0.09 (s, 3 H, *MeSi*), 0.77 (d, 3 H, J = 7.0, *23*), 0.86 (d, 3 H, J = 7.0 Hz, *19*), 0.90 (d, 3 H, J = 6.9 Hz, *20*), 0.90 [s, 9 H, $(CH_3)_3C$], 1.03 (d, 3 H, J = 6.9 Hz, *24*), 1.13 (d, 3 H, J = 6.9 Hz, *21*), 1.63 (m, 3 H, J = 0.7 Hz, *8*), 1.71 (dqd, 1 H, J = 9.6, 7.5, 0.8 Hz, *4*), 2.27 (dq, J = 8.3, 6.9 Hz, *6*), 2.43 (quint d, 1 H, J = 7.0, 3.7 Hz, *18*), 3.35 (s, 3 H, O*Me*), 3.47 (dd, 1 H, J = 9.7, 3.5 Hz, *3*), 3.81 (dd, 1 H, J = 8.4, 0.8 Hz, *5*), 3.92 (qd, 1 H, J = 7.0, 3.5 Hz, *2*), 4.20 (m, 2 H, *16*), 4.34 (ddd, 1 H, J = 3.7, 4.8, 5.8 Hz, *15*); ^{13}C NMR ($CDCl_3$) δ −3.8, −2.8, 9.7, 10.3, 14.5, 17.5, 18.1, 18.7, 19.2, 26.3, 28.4, 39.9, 40.3, 46.9, 59.2, 59.6, 63.2, 73.8, 82.7, 111.4, 148.7, 153.5, 176.3; mass spectrum (70 eV), m/e (relative intensity) 368 (36), 99 (100), 73 (40). Anal. Calcd for $C_{25}H_{47}NO_5Si$: C, 63.92; H, 10.09; N, 2.98 Si, 5.98. Found: C, 63.87; H, 10.01; N, 3.03; Si, 5.87.

(4*S*)-3-[(2*S*,3*R*,4*S*,5*R*,6*S*)-5-(*tert*-Butyldimethylsiloxy)-3-methoxy-7-oxo-2,4,6-trimethyloctanoyl]-4-isopropyloxazolidin-2-one (31). To a stirred solution of 45 mg (96 μmol) of alkene **30** in 18 mL of a 1:1 mixture of dichloromethane and methanol was added about 10 mg of solid sodium bicarbonate. A portion remained undissolved. Through the solution, which was left open to the air, was bubbled a slow stream of oxygen for about 30 min. During this time, the solution was cooled to −78 °C. A stream of ozone (flow rate 0.5 standard liters/min (SLPM), 70 V) was then bubbled through the solution for approximately 2 min. When a faint blue color was noticed in the solution, ozone ebullition was terminated and argon ebullition started. When the blue color had disappeared, about 1 mL of dimethyl sulfide was added to the solution and argon ebullition was terminated. The flask was then transferred to a 0 °C bath and stirred for 10 h, during which time the bath temperature was allowed to climb to room temperature. The solution was tested for the presence of ozonide (R_f 0.15 with 30% ethyl acetate in hexanes), and when the results were negative, the solvent was removed in vacuo. The mixture was then dissolved in dichloromethane and water and extracted with dichloromethane and the extract dried (Na_2SO_4/K_2CO_3) and concentrated under reduced pressure. The resulting crude product was purified by chromatography eluting with 30% ethyl acetate in hexanes, to give 42 mg (92%) of methyl ketone **31**: IR ($CHCl_3$) 1778, 1700 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.04 (s, 3 H, *MeSi*), 0.09 (s, 3 H, *MeSi*), 0.84 (d, 3 H, J = 7.1 Hz, *23*), 0.86 (d, 3 H, J = 7.0 Hz, *19*), 0.89 [s, 9 H, $(CH_3)_3C$], 0.90 (d, 3 H, J = 7.0, *20*), 1.04 (d, 3 H, J = 7.5 Hz, *24*), 1.18 (d, 3 H, J = 7.0 Hz, *21*), 1.62 (quint d, 1 H, J = 7.1, 2.6 Hz, *4*), 2.15 (s, 3 H, *8*), 2.36 (sept d, 1 H, J = 7.2, 3.4 Hz, *18*), 2.65 (dq, 1 H, J = 6.0, 7.0 Hz, *6*), 3.36 (s, 3 H, O*Me*), 3.43 (dd, 1 H, J = 5.7, 7.1 Hz, *3*), 4.00 (quint d, 1 H, J = 5.7, 6.7 Hz, *2*), 4.04 (dd, 1 H, J = 2.7, 5.9 Hz, *5*), 4.27 (m, 3 H, *15* and *16*); ^{13}C NMR ($CDCl_3$) δ −3.9, −3.8, 11.4, 12.3, 13.0, 14.7, 18.5, 26.1, 28.5, 34.5, 40.1, 40.3, 52.8, 58.9, 59.9, 63.4, 72.4, 83.5, 153.6, 176.0, 211.6; mass spectrum (CI^-), 470 (M − 1). Anal. Calcd for $C_{24}H_{45}NO_6Si$: C, 61.11; H, 9.62; N, 2.97; Si, 5.95. Found: C, 60.95; H, 9.59; N, 3.09; Si, 5.81.

(4*S*)-3-[(2*S*,3*R*,4*S*,5*R*,6*S*)-12-[[(Benzyloxy)methyl]oxy]-5-(*tert*-butyldimethylsiloxy)-7,9-dioxo-3-methoxy-2,4,6,12-tetramethyltridecanoyl]-4-isopropyloxazolidin-2-one (33). To a stirred solution of 0.16 mL (1.13 mmol) of diisopropylamine in 2 mL of THF at −20 °C was added 0.65 mL (1.0 mmol) of a 1.59 M *n*-butyllithium solution. The resulting solution was stirred for 15 min, at which time it was cooled to −70 °C. To this solution was then added, by cannulation over a period of 15 min, a solution of 0.27 g (0.57 mmol) of ketone **31** in 2 mL of THF. The resulting solution was stirred for 45 min, at which time a solution of 0.17 g (0.70 mmol) of aldehyde **7** in 2 mL of THF was added. The solution was stirred for 20 min, then warmed to −40 °C, and stirred for a further 40 min. At this time, 1 mL of saturated ammonium chloride solution was added. The suspension was warmed to ambient temperature, poured into brine, and extracted with ether and the extract dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with 30% ethyl acetate in hexanes resulted in 0.28 g (69%) of β-hydroxy ketone **32** as a mixture of diastereomers. Also recovered was 19.1 mg of the starting ketone, so the yield was 75% based on recovered starting material. This material was oxidized as follows.

To a stirred solution of 45 μL (0.63 mmol) of dimethyl sulfoxide in 5 mL of dichloromethane at −70 °C was added 44 μL (0.51 mmol) of oxalyl chloride. The solution was stirred until gas evolution had ceased (about 10 min), and a solution of 0.28 g (0.40 mmol) of alcohol **32** in 2 mL of dichloromethane was then added over a period of 15 min. The solution was stirred for a further 15 min, at which time 0.41 mL (2.4 mmol) of diisopropylethylamine was added. After an additional 5 min of stirring, the cooling bath was removed and the solution allowed to warm to room temperature. The solution was poured into water and extracted with dichloromethane and the extract dried (Na_2SO_4/K_2CO_3) and concentrated under reduced pressure. Chromatography of the residue eluting with 25% ethyl acetate in hexanes gave 0.22 g (78%) of β-diketone **33** (58% from ketone **31**). β-Diketone **33** had the following properties: IR ($CHCl_3$) 1772, 1692 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.01 (s, 3 H, *MeSi*), 0.08 (s, 3 H, *MeSi*), 0.84 (d, 3 H, J = 7.0 Hz, *23*), 0.85 (d, 3 H, J = 7.0 Hz, *20*), 0.88 [s, 9 H, $(CH_3)_3C$], 0.89 (d, 3 H, J = 7.1 Hz, *19*), 1.10 (d, 3 H, J = 7.0 Hz, *24*), 1.18 (d, 3 H, J = 6.9 Hz, *21*), 1.25 (s, 6 H, *13* and *14*), 1.77 (m, 3 H, *4* and *11*), 2.38 (m, 4 H, *6*, *10*, and *18*), 3.34 (s, 3 H, *Me*O), 3.47 (dd, 1 H, J = 7.7, 5.2 Hz, *3*), 3.99 (qd, 1 H, J = 7.0, 5.2 Hz, *2*), 4.04 (dd, 1 H, J = 6.0, 2.5 Hz, *5*), 4.21 (m, 2 H, *16*), 4.36 (m, 1 H, *15*), 4.60 (s, 2 H, *25*), 4.81 (s, 2 H, *26*), 5.50 (s, 1 H, *8*), 7.31 (m, 5 H, *Ph*); ^{13}C NMR ($CDCl_3$) δ 195.6, 194.9, 175.9, 153.5, 138.2, 128.3, 127.7, 99.5, 89.2, 83.3, 75.4, 73.1, 69.4, 63.3, 59.4, 58.9, 47.9, 40.4, 40.2, 37.4, 33.5, 28.5, 26.2, 26.1, 18.5, 17.9, 14.7, 13.3, 12.3, 11.2, −3.7, −4.1; mass spectrum (CI^-) calcd for $C_{38}H_{62}NO_9Si$ (M − 1) 704.4193, found 704.4243; isotope peak calcd 705.4227, found 705.4254.

(4*S*)-3-[(2*S*,3*R*,4*S*)-3-Methoxy-2-methyl-4-[(2*R*,3*S*,6*R*)-4-oxo-3,8,8-trimethyl-1,7-dioxaspiro[4.5]dec-2-yl]pentanoyl]-4-isopropyloxazolidin-2-one (34). To a solution of 23.4 mg (33 μmol) of diketone diether **33** in 15 mL of acetonitrile, stirred

in a polyethylene bottle open to the air, was added 0.65 mL (15 mmol) of concentrated hydrofluoric acid. The solution was stirred for 10 h, at which time 1.35 mL (19 mmol) of concentrated ammonium hydroxide was added. The solution was poured into a flask and the acetonitrile removed in vacuo. The resulting suspension was washed with water and extracted with dichloromethane and the extract dried (Na_2SO_4/K_2CO_3) and concentrated under reduced pressure. Chromatography of the residue eluting with 30% ethyl acetate in hexanes, followed by daily elutions of the column for the next 3 days, afforded 12.7 mg (85%) of spiroketal **34**: IR ($CHCl_3$) 1780, 1715 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.84 (d, 3 H, J = 7.0 Hz, *23*), 0.91 (d, 3 H, J = 7.0 Hz, *19*), 0.96 (d, 3 H, J = 6.9 Hz, *20*), 1.09 (d, 3 H, J = 7.1 Hz, *24*), 1.14 (s, 3 H, *14*), 1.21 (d, 3 H, J = 7.0 Hz, *21*), 1.30 (s, 3 H, *13*), 1.8–2.15 (m, 4 H, *10* and *11*), 2.16 (qt, 1 H, J = 8.7, 2.4 Hz, *4*), 2.24 (dd, 1 H, J = 14.5, 1.0 Hz, *8* equat), 2.34 (quint d, 1 H, J = 7.0, 3.9 Hz, *18*), 2.57 (qdd, 1 H, J = 7.2, 3.1, 1.0 Hz, *6*), 2.79 (d, 1 H, J = 14.5 Hz, *8* axial), 3.36 (s, 3 H, O*Me*), 3.45 (dd, 1 H, J = 6.6, 4.9 Hz, *3*), 3.76 (dd, 1 H, J = 9.1, 3.1 Hz, *5*), 4.05 (dq, 1 H, J = 8.3, 6.8 Hz, *2*), 4.16 (dd, 1 H, J = 8.9, 2.6 Hz, *16*), 4.23 (t, 1 H, J = 8.3 Hz, *16*), 4.36 (ddd, 1 H, J = 7.7, 3.9, 2.6 Hz, *15*); ^{13}C NMR ($CDCl_3$) δ 10.5, 11.5, 13.9, 14.9, 17.9, 28.6, 28.7, 29.3, 37.0, 37.1, 38.7, 38.8, 46.6, 48.0, 58.9, 63.5, 65.3, 71.7, 81.4, 84.1, 107.3, 126.9, 127.5, 128.5, 141.1, 153.4, 176.0, 210.3; mass spectrum (CI^-) M - 1 peak calcd for $C_{24}H_{38}NO_7$ 452.2649, found 452.2654.

(4*S*)-3-[(2*S*,3*R*,4*S*)-3-Methoxy-2-methyl-4-[(2*R*,3*R*,4*S*,6*R*)-4-hydroxy-3,8,8-trimethyl-1,7-dioxaspiro[4.5]dec-2-yl]pentanoyl]-4-isopropyloxazolidin-2-one (35). To a stirred solution of 35.3 mg (78 μmol) of ketone **34** in 1 mL of THF cooled to -78 °C with a Flexi-cool cooling bath was added 93 μL (93 μmol) of a 1 M K-Selectride solution. The resulting reaction mixture was stirred for 22 h, at which time 1.5 mL of a pH 7 phosphate buffer was added. The reaction mixture was extracted with dichloromethane and the extract dried (Na_2SO_4/K_2CO_3) and concentrated under reduced pressure. Chromatography of the residue eluting with 25% ethyl acetate in hexanes gave 21.6 mg of spiroketal **35** (61%) and 8.6 mg of recovered ketone **34**, affording an 81% yield of compound **35** based on recovered starting material. Crystallization of this material from hexane gave sharp-melting (mp 124–125 °C) crystals suitable for X-ray analysis. Spiroketal **35** had the following properties: IR ($CHCl_3$) 3550–3300 (br, OH), 1778, 1695 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.84 (d, 3 H, J = 7.1 Hz, *24*), 0.85 (d, 3 H, J = 6.9 Hz, *20*), 0.89 (d, 3 H, J = 7.0 Hz, *19*), 0.96 (d, 3 H, J = 6.7 Hz, *23*), 1.16 (s, 3 H, *14*), 1.22 (d, 3 H, J = 7.0 Hz, *21*), 1.34 (s, 3 H, *13*), 1.55 (ddd, 1 H, J = 19.8, 5.9, 0.5 Hz, *8* equat), 1.6–2.1 (m, 7 H), 2.33 (quint d, 1 H, J = 7.0, 4.0 Hz, *18*), 3.37 (s, 3 H, *Me*O), 3.54 (dd, 1 H, J = 6.71, 3.84 Hz, *3*), 3.67 (m, 1 H, *7*), 3.72 (dd, 1 H, J = 10.5, 2.2 Hz, *5*) 3.97 (d, 1 H, J = 9.1 Hz, O*H*), 4.20 (m, 3 H, *2* and *16*), 4.52 (m, 1 H, *15*); ^{13}C NMR ($CDCl_3$) δ 10.8, 11.1, 14.9, 15.0, 17.9, 28.6, 28.8, 30.0, 35.5, 35.6, 36.2, 37.5, 38.0, 39.0, 58.4, 58.7, 63.5, 67.6, 71.5, 80.4, 84.4, 107.0, 153.5, 176.6; mass spectrum, m/e (relative intensity) (FAB^+) 454 (46, M - 1), 438 (75), 228 (100). Anal. Calcd for $C_{24}H_{40}NO_7$: 454.2805. Found: 454.2777.

Crystal Structure Determination for Compound 35. Compound **35** was recrystallized from hexane. A crystal of dimensions 0.2 × 0.4 × 0.5 mm was selected and mounted on a glass fiber by using epoxy resin. Unit cell dimensions, a = 10.7836 (23) Å, b = 14.2153 (28) Å, c = 16.9969 (33) Å, vol = 2605.4 (9) Å^3, were determined on a Nicolet P3/F diffractometer using graphite-monochromated Cu Kα radiation (λ = 1.5418 Å). The material crystallized in space group $P2_12_12_1$ with four molecules of formula $C_{24}H_{41}NO_7$ (M_r 455.60) present in the unit cell (ρ_{calcd} = 1.16 g/cm^3). In all, 5632 reflections were measured by using θ–2θ scans to $2\theta_{max}$ = 100°. These were empirically corrected for absorption and averaged to 2673 unique reflections of which 2555 were observed ($F_o > 6.0\sigma(F_o)$). The structure was solved by direct methods and refined by using cascading block least squares techniques.[19] At convergence, with all non-hydrogen atoms refined anisotropically and hydrogen atoms included in idealized positions, the final residuals were R = 0.033, wR = 0.047 for observed data and R = 0.035, wR = 0.054 for all data. There are no significant features in the final difference Fourier map.

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Supplementary Material Available: Tables of final atomic and positional parameters, atomic thermal parameters, and bond distances and angles for $C_{24}H_{41}NO_7$ (8 pages). Ordering information is given on any current masthead page.

Oxidation of β-Anilinoacrylate Alkaloids Vincadifformine and Tabersonine by Fremy's Salt. A Mechanistic Insight into the Rearrangement of *Aspidosperma* to *Hunteria* Alkaloids

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β-Anilinoacrylate *Aspidosperma* alkaloids vincadifformine (**2a**) and tabersonine (**2b**) react with Fremy's salt in aqueous acidic conditions via radical coupling at C-16. The resulting zwitterionic compounds **7a** and **10** rearrange to isoxazolidines **8** and then ultimately to azepino[2,3-*b*]indoles **9**. The mechanism of these reactions is discussed, and the structures of **7a**, **8b**, and **9a** were established by single-crystal X-ray analysis. Diazotization of amine **20b** (X = NH_2) affords fragmentation–cyclization products corresponding to eburnanes **18** and **21**. This reaction mimics the skeletal rearrangement of *Aspidosperma* → *Hunteria* alkaloids, and these findings support Wenkert's biogenetic proposal.

The monoterpenoid indole alkaloids represent an area of the wealth of natural products that continues to be a source of fascinating and informative investigations. In recent years, the chemistry of these compounds has elicited considerable synthetic interest and mechanistic scrutiny and such studies have been particularly important in development of a comprehensive rationalization of the relationship between different alkaloid skeleta. Moreover,

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