Total Synthesis and Structure Assignment of the Antitumor Antibiotic Aranorosin

Peter Wipf,* Yuntae Kim, and Paul C. Fritch

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

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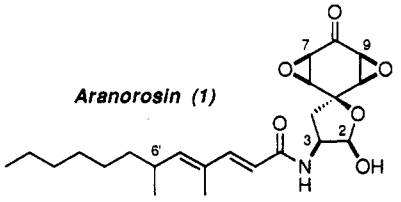
The structurally unique antifungal and antitumor antibiotic aranorosin was prepared in a convergent, stereoselective sequence. Oxidative cyclization of *N*-protected L-tyrosine, followed by face-selective 1,2-addition of [(benzyloxy)methyl]lithium, Henbest oxidation in the presence of Kishi's radical inhibitor, and simultaneous *N,O*-deprotection led to an amino diol which was *N*-acylated with the fatty acid side-chain segment. After a low-temperature reduction of the lactone moiety to the lactol, the carbonyl function was regenerated under neutral conditions by diol cleavage with sodium periodate. Preparation of the acid side chain involved a diastereoselective imide α-alkylation directed by Evans' oxazolidinone auxiliary, followed by a series of Wittig–Horner chain extensions. Since the relative configuration at the C(6′) position of the natural product had not been determined, we prepared both the (6′*S*) and the (6′*R*) isomers of aranorosin. Comparison of synthetic material with the reported spectral data for natural (−)-aranorosin, especially ^{1}H and ^{13}C NMR and $[\alpha]_D$, did not allow a definitive assignment. After purification of a sample of the isolated material from *Pseudoarachniotus roseus*, the corrected $[\alpha]_D$ strongly indicated the (6′*R*)-stereochemistry for the natural compound. This assignment was confirmed by circular dichroism spectra for (6′*S*)- and (6′*R*)-aranorosin and the natural material.

Aranorosin (1) is a structurally unique antibiotic isolated by Fehlhaber, Mukhopadhyay, and co-workers from a fungal strain, *Pseudoarachniotus roseus* Kuehn, collected in Maharashtra, India.[1] Its constitution and the relative stereochemistry of the core was assigned based upon high resolution and fragmentation pattern mass spectral analyses and extensive NOE and COSY NMR experiments as well as some chemical degradation work. These techniques, however, did not provide the information necessary for the assignment of the absolute stereochemistry of the molecule or the relative configuration at C(6′) of the side chain.



Our interest in aranorosin was prompted by the combination of the promising biological profile and the highly unusual structural features. *In vitro* biological testing of the lipophilic natural product showed activities against a variety of bacteria and fungi on a micromolar scale. Aranorosin also has cytostatic properties and is potentially useful for the treatment of malign tumors and leukemia.[2] The novel diepoxy 1-oxaspiro[4.5]decane ring system is a highly reactive electrophile capable of multiple alkylation reactions at various electrophilic sites.

Retrosynthetic Plan. The densely substituted spirocyclic core of aranorosin combines $\alpha,\beta,\gamma,\delta$-unsaturated amide, lactol, and diepoxy ketone moieties. We were mostly concerned with the lability of the presumably both acid- and base-sensitive activated oxiranes during protective group manipulations. Therefore, we decided to introduce the C(8) keto function in the last step of the synthesis by mild sodium periodate cleavage after *N*-acylation of 1,2-diol **3** (Scheme I). The carbon skeleton of this key building block could be generated via oxidative spirocyclization of L-tyrosine **9**,[3] followed by functional group manipulations on lactone **6**.

Since the relative configuration at C(6′) of the fatty acid side chain of aranorosin had not been elucidated by the Hoechst team,[1] we planned a synthesis of both the (6′*S*)- and the (6′*R*)-isomers of **1**. Diastereoselective alkylation of Evans' benzyl oxazolidinone **8** with methyl iodide (for R′ = C_6H_{13}) or hexyl iodide (for R′ = CH_3), respectively, would provide both enantiomers of aldehyde **4**, which could be converted to acid **2** by a series of Wittig reactions (Scheme I). In the following discussion, we report the application of this strategy toward the total synthesis of the structurally unique antibiotic aranorosin.[4,5]

Results and Discussion

Synthesis of the C(1′) to C(12′) Side Chain. Acylation of the (*S*)-phenylalanine-derived oxazolidinone **10**[6] with

• Abstract published in *Advance ACS Abstracts*, November 1, 1993.

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(2) Roy, K.; Mukhopadhyay, T.; Reddy, G. C. S.; Vijayakumar, E. K. S.; Ganguli, B. N.; Rupp, R. H.; Fehlhaber, H. W.; Kogler, H. Eur. Pat. Appl. EP 341649 A1; *Chem. Abstr.* **1990**, 112, 233994y.

(3) We have previously applied oxidative cyclizations of tyrosines toward the synthesis of *Stemona* alkaloids: Wipf, P.; Kim, Y. *Tetrahedron Lett.* **1992**, *33*, 5477.

(4) For a preliminary communication on the core structure of aranorosin from this laboratory, see: Wipf, P.; Kim, Y. *J. Org. Chem.* **1993**, *58*, 1649.

(5) For other efforts toward the synthesis of aranorosin, see: (a) Rama Rao, A. V.; Gurjar, M. K.; Sharma, P. A. *Tetrahedron Lett.* **1991**, *32*, 6613. (b) McKillop, A.; McLaren, L.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *Synlett* **1992**, 201. (c) McKillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *J. Chem. Soc., Chem. Commun.* **1992**, 1589. (d) McKillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *Synlett* **1992**, 1005.

(6) Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 77.

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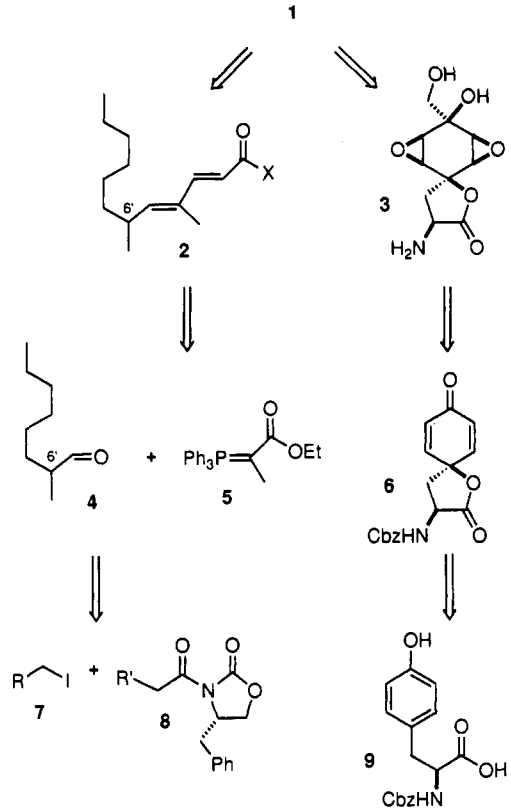
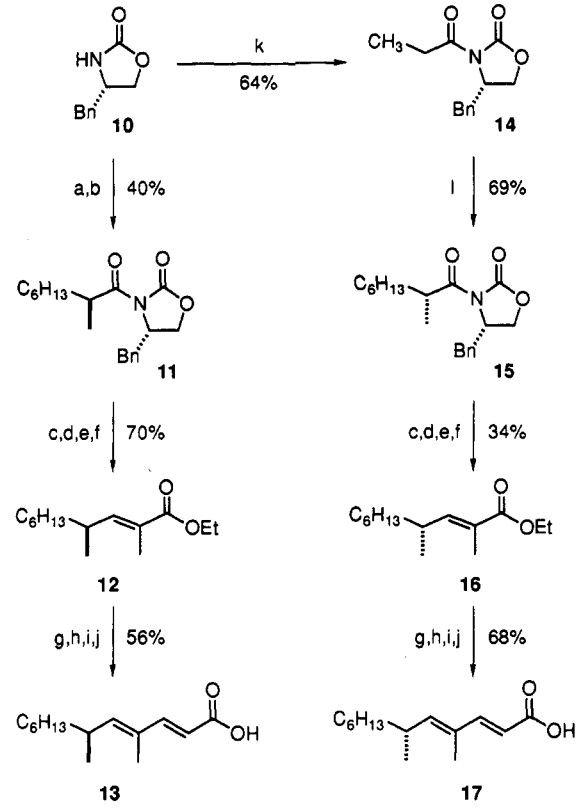
Scheme I



Scheme II[a]



[a] (a) *n*-BuLi, $C_7H_{15}COCl$, THF, −78 °C to +20 °C; (b) NaHMDSA, MeI, THF, −78 °C; (c) LiOH, H_2O_2, THF/H_2O, 0 °C to +20 °C; (d) LAH, Et_2O, 0 °C to +20 °C; (e) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, −60 °C; (f) $Ph_3P{=}C(CH_3)CO_2Et$, CH_2Cl_2; (g) DIBAl-H, CH_2Cl_2, −78 °C; (h) $BaMnO_4$, Celite, CH_2Cl_2; (i) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2; (j) LiOH, MeOH/THF/H_2O; (k) *n*-BuLi, C_2H_5COCl, THF, −78 °C to +21 °C; (l) NaHMDSA, $C_6H_{13}OTf$, THF, −78 °C.

octanoyl chloride, followed by enolization with NaHMDSA (1.1 equiv., THF, −78 °C) and reaction with an excess of methyl iodide gave the imide **11** in 57% yield after chromatographic purification and in >96% diastereomeric excess according to NMR and GC analyses (Scheme II). The stereochemical assignment of **11** was made in accordance with the highly *si*-face-selective enolate alkylations reported by Evans and co-workers.[7] After hydrolysis with LiOOH (LiOH, H_2O_2, 3:1 THF/H_2O, 0 °C, 5 h),[8] the chiral auxiliary **10** was recovered in 73% yield in addition to 90% of (*S*)-2-methyloctanoic acid. Reduction of the acid with LAH in ether (rt, 1 h) gave the primary alcohol cleanly in 88% yield. Swern oxidation,[9] immediately followed by Wittig olefination with (carbethoxyethylidene)triphenylphosphorane (CH_2Cl_2, 84 h) converted the alcohol to the α,β-unsaturated ester **12** in 88% yield. Attempted direct reduction of ester **12** to the corresponding aldehyde with 1 equiv of DIBAl-H at −85 °C led to the formation of significant amounts of the allylic alcohol. Therefore, ester **12** was quantitatively converted to the allylic alcohol by treatment with 2.3 equiv of DIBAl-H in CH_2Cl_2 at −78 °C. Subsequently, half-oxidation with 10 equiv of $BaMnO_4$ (CH_2Cl_2, rt, 21 h) and Wittig chain extension with 5 equiv of (carbethoxymethylidene)triphenylphosphorane (CH_2Cl_2, rt, 7 d) afforded 58% of the bisunsaturated ethyl ester. Saponification with 10 equiv of LiOH in MeOH/THF/H_2O (2:1:2) at rt for 36 h gave (2*E*,4*E*,6*S*)-4,6-dimethyl-2,4-dodecadienoic acid (**13**, $[\alpha]_D$ +63.3° (*c* 1.0, CH_2Cl_2)) in 10 steps and 16% overall yield from oxazolidinone **10**.

For the preparation of the enantiomeric acid segment **17**, the chiral auxiliary **10** was acylated with propanoyl chloride (THF, −78 °C to +21 °C, 1 h) to give imide **14**. Whereas α-alkylation of the potassium, sodium, as well as the lithium enolate of **14** with hexyl iodide failed, use of the more reactive hexyl triflate[10] afforded a 69% yield of the desired (2*R*)-isomer **15** in >96% de. Subsequent hydrolysis, reduction, and Wittig chain extensions provided (2*E*,4*E*,6*R*)-4,6-dimethyl-2,4-dodecadienoic acid (**17**, $[\alpha]_D$ −63.9° (*c* 2.1, CH_2Cl_2)) in 10 steps and 10% overall yield from oxazolidinone **10**.

Synthesis of the Spirocyclic Core. Oxidation of tyrosine derivatives provides an elegant entry to heterocyclic ring systems.[11,3] Treatment of *N*-protected tyrosine **9** with the readily available hypervalent iodine reagent $PhI(OAc)_2$[12] (MeOH, 0 °C, 30 min) afforded the spirolactone **6** in 35–40% yield (Scheme III). At this stage, further protection of the secondary amide function of **6** proved to be necessary, since the addition of organolithium reagents to **6** led to significant lactone opening, probably

(7) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
(8) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.
(9) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
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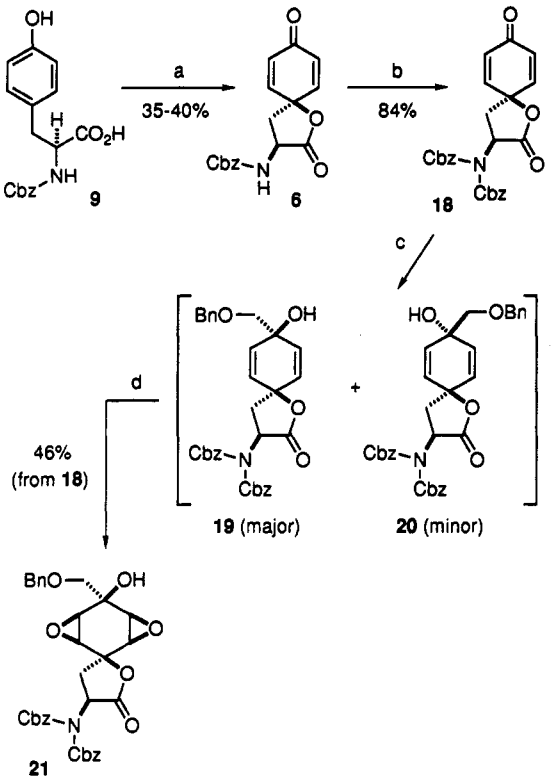
(11) (a) Schmir, G. L.; Cohen, L. A.; Witkop, B. *J. Am. Chem. Soc.* **1959**, *81*, 2228. (b) Meyers, M. B.; McCapra, F.; Dodson, P. A.; Scott, A. I. *J. Am. Chem. Soc.* **1963**, *85*, 3702. (c) Inoue, T.; Naitoh, K.; Kosemura, S.; Umezawa, I.; Sonobe, T.; Serizawa, N.; Mori, N.; Itokawa, H. *Heterocycles* **1983**, *20*, 397. (d) Schwartz, M. A.; Hudec, T. T. *Synth. Commun.* **1986**, *16*, 1599. (e) Pelter, A.; Elgendy, S. *Tetrahedron Lett.* **1988**, *29*, 677. (f) Kita, Y.; Tohma, H.; Inagaki, M.; Hatanaka, K.; Kikuchi, K.; Yakura, T. *Tetrahedron Lett.* **1991**, *32*, 2035. (g) Pelter, A.; Ward, R. S.; Abd-El-Ghani, A. *J. Chem. Soc. Perkin Trans. 1* **1992**, 2249.
(12) (a) Moriarty, R. M.; Prakash, O. *Acc. Chem. Res.* **1986**, *19*, 244. (b) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927. (c) Pelter, A.; Elgendy, S. *Tetrahedron Lett.* **1988**, *29*, 677.

Scheme III[a]



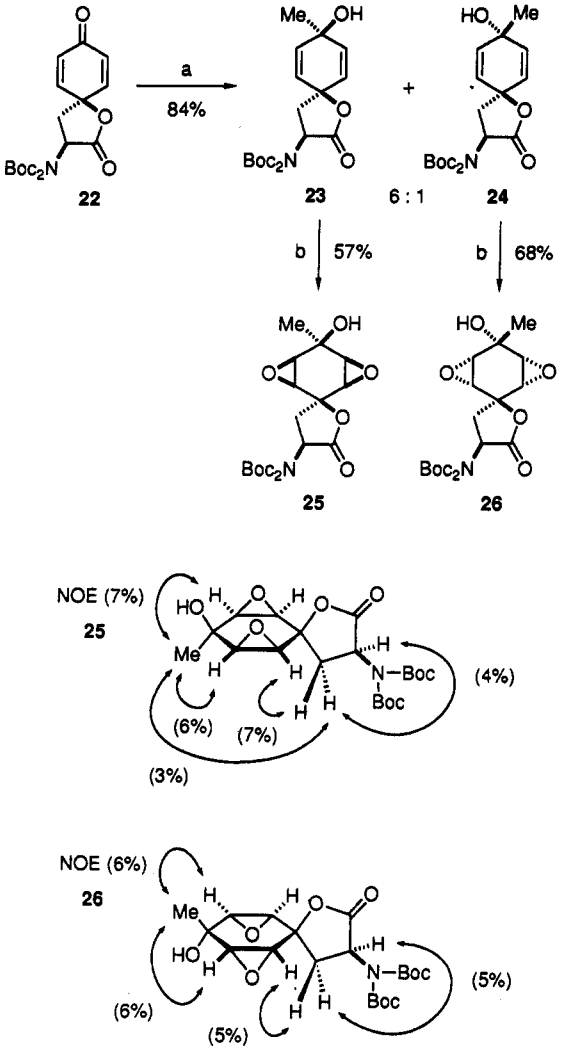
[a] (a) $PhI(OAc)_2$, MeOH, 0 °C; (b) $(BnOCO)_2O$, DMAP, MeCN; (c) $BnOCH_2Li$, THF, −100 °C; (d) *m*-CPBA, 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide, CCl_4, 70 °C.

directed by an initial deprotonation of the amide hydrogen. However, after introduction of a second Cbz group with 5 equiv of dibenzyl pyrocarbonate[13] (DMAP, MeCN, rt, 30 min), addition of 1.5 equiv of [(benzyloxy)methyl]-lithium[14] (THF, −100 °C, 5 min) occurred chemoselectively in a 1,2-fashion at the dienone moiety and resulted in the formation of an approximately 5:1 mixture of alcohols **19** and **20**. These bisallylic tertiary alcohols proved to be quite sensitive even toward mildly basic or acidic workup conditions. An increase in the reaction temperature to −78 °C, for example, led to a significant decomposition of both isomers. After extraction with 5% $NaHCO_3$ and ethyl acetate, the crude mixture of bisallylic alcohols was therefore immediately subjected to bisepoxidation with 5 equiv of *m*-CPBA in CCl_4 in the presence of Kishi's[15] radical inhibitor. After 2 h reaction time at 70 °C, diepoxy alcohol **21** was isolated in 46% overall yield from dienone **18**. Interestingly, the stability of the bisallylic alcohols **19** and **20** was found to be a function of the *N*-protective groups. The di-Boc analogs of **19** and **20** proved extremely unstable, whereas the stability of the corresponding *N*-Boc,*N*-Cbz-alcohols was improved but still inferior to the di-Cbz alcohols **19** and **20**.

The introduction of the (benzyloxy)methyl group fulfills several purposes. First, the additional C,C-bond at C(8) of the spirocycle inhibits the fragmentation and rearomatization of this ring system, which otherwise occurs readily in the presence of electrophilic or reducing reagents.

(13) Sennyey, G.; Barcelo, G.; Senet, J.-P. *Tetrahedron Lett.* **1986**, *27*, 5375.
(14) (a) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481. (b) Johnson, C. R.; Medich, J. R. *J. Org. Chem.* **1988**, *53*, 4131.
(15) Kishi, Y.; Aratani, M.; Tanino, H.; Fukuyama, T.; Goto, T.; Inoue, S.; Sugiura, S.; Kakoi, H. *J. Chem. Soc., Chem. Commun.* **1972**, 64.

Scheme IV[a]



[a] (a) MeMgBr, THF, −78 °C; (b) *m*-CPBA, 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide, CCl_4, 70 °C.

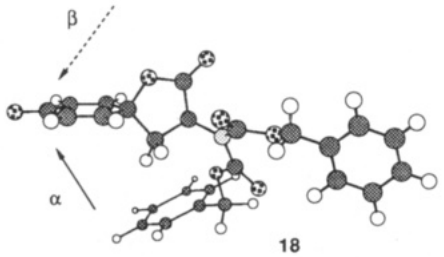
Second, the tertiary alcohol function in **19** directs the face-selectivity of the peracid through hydrogen bonding,[16] resulting in a clean syn-diepoxidation of the diene. Most importantly, however, the (benzyloxy)methyl group serves as a protective group for the C(8) ketone that can be removed under very selective, neutral conditions after the reduction of the lactone to the C(2) lactol moiety present in the natural product.

The selectivity observed in the conversion of dienone **18** to alcohol **21** deserves some further comments. In a model study, addition of methylmagnesium bromide to dienone **22** at −78 °C resulted in a 6:1 mixture of allylic alcohols **23** and **24** (Scheme IV). In contrast to the (benzyloxy)methyl addition products **19** and **20**, the methyl diallyl alcohols **23** and **24** were resistant to mild acid/base treatment. After chromatographic separation, these alcohols were individually subjected to epoxidation with *m*-CPBA at 70 °C for 5 and 6 h, respectively. The stereochemistry of the oxidation products was determined by NOE measurements, some of the most informative of which are illustrated in Scheme IV.[17] Interestingly, the experimental NOE's for both α- and β-diepoxy cyclohex-

(16) Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc.* **1957**, 1958.
(17) A complete listing of NOE effects is included in the supplementary material.

anes are almost identical, a consequence of the pseudoaxial fusion of the oxiranes on the flattened six-membered ring. An unambiguous assignment of the stereochemistry of **25** and **26** was only possible due to the observation of a 3% NOE between the C(8)-methyl substitutuent and the C(4)-methylene group in **25**, derived from the major isomer of the Grignard addition to dienone **22**.[18]

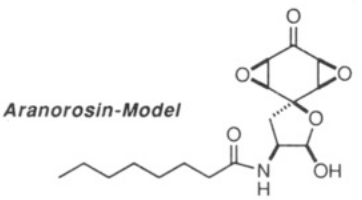
Molecular mechanics minimization[19] of the geometry of dienones **18** and **22** revealed little steric bias for a face-selective addition of organometallics. In fact, the observed attack mainly from the α-face of the planar[20] dienone seems to be sterically slightly more cumbersome due to the vicinity of the C(4) methylene and the C(3) amino groups vs the O(1) lactone oxygen.[21]



18

Due to the relative distance of the *para*-substituents of the dienone from the reaction center (approximately 4 Å) and the absence of charged, strongly haptophilic groups, steric and torsional effects,[22,23] as well as ligand-assisted nucleophilic addition[24] appear to be of minor significance. Therefore, 4,4-disubstituted dienones are ideally suited for the critical analysis of various models for stereoelectronic control in carbonyl additions, e.g. the antiperiplanar effect,[25] homoconjugation,[26] the principle of orbital distortion,[27] and Cieplak's hypothesis.[28] Several simplified model systems that we have investigated showed moderate to high selectivity for attack of organometallic nucleophiles *anti* to the C(4) oxygen substituent.[29] The observed face-selectivities correlate well with the dipole moment of the dienones. Therefore, we consider electrostatic effects[30] to be the dominant source for the directing effect of C(4) substituents on cyclohexadienones.

Coupling and Final Functional Group Manipulations. The strategy that we had successfully exercised for the preparation of the aranorosin model,[4] e.g. selective removal of the *N*-Cbz groups of diepoxide **21**, followed by *N*-acylation and hydrogenolytic deprotection of the benzyl ether, was impractical for the natural product due to the high degree of unsaturation in the side chain.



After some unsuccessful attempts to modify the protective group at the C(8) methylene center, we decided to remove *both N*- and *O*-protective groups of diepoxide **21** in a single operation. Perhydrogenation of **21**, however, proved to be experimentally challenging due to the extremely high lability of amino diol **30** (Scheme V). Several hydrogenation protocols (Pd/C, catalytic hydrogen transfer, etc.) led only to partial deprotection or complete decomposition of the starting material. Treatment of **21** with 20% $Pd(OH)_2$ on carbon in absolute MeOH under an atmosphere of H_2 (rt, 2 h) led to a very polar product that was immediately treated with a THF solution of diphenylphosphinic chloride,[31] NMM, and (6*S*)- or (6*R*)-acid side chains **13** and **17**, respectively. Amides **31** and **32** were thus prepared in a very satisfactory 40 and 42% overall yield from **21**. Reduction of the lactone moiety to the desired lactol was controlled by treatment of amides **31** and **32** with $NaBH_4$ in the presence of $CeCl_3$[32] (5:3 $EtOH/H_2O$, −30° C, 30 min). Due to their high polarity and dense functionalization, the resulting intermediates were difficult to purify and were directly cleaved with sodium periodate (3:1 $MeOH/H_2O$, rt, 30 min) to give the (6′*S*)- and the (6′*R*)-isomers of aranorosin as 4:1 mixtures of lactol anomers in 57 and 55% yield, respectively, after SiO_2 chromatographic purification.

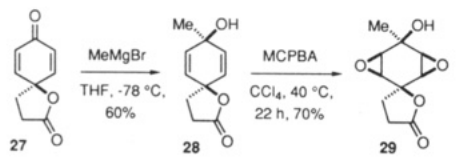
Somewhat surprisingly, *both* the (6′*S*)- and the (6′*R*)-isomer of aranorosin were spectroscopically (MS, ^1H and ^{13}C NMR) identical to the natural product, except for its optical rotation. The Hoechst group reported the optical rotation of natural aranorosin as $[\alpha]_D$ −2.42° (*c* 2.58, $CHCl_3$).[1] After purification of a sample of the natural compound,[33] we determined its $[\alpha]_D$ −7.8° (*c* 0.17, $CHCl_3$, 21 °C).[34] The optical rotation of our synthetic material

(18) Analogously, we observed a 3% NOE between the C(4)-methylene group and the C(8)-(benzyloxy)methylene substituent in diepoxy alcohol **21**.

(19) MM calculations were performed with the MM2* force field of MacroModel V3.5X: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Lipton, M.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

(20) Several structurally related dienones show complete planarity in the solid state: Pilotti, A.-M. *Acta Crystallogr.* **1972**, *B28*, 2123. (b) Hara, H.; Hoshino, O.; Umezawa, B.; Itaka, Y. *Acta Crystallogr.* **1978**, *B34*, 3825.

(21) The presence of the relatively bulky C(3)-$N(Cbz)_2$ substituent does indeed appear to reduce the regioselectivity of the addition process. Treatment of spirolactone **27** with methylmagnesium bromide at −78 °C in THF, for example, led to the isolation of alcohol **28** and 60% yield. Only traces (<3%) of the *anti* isomer of **28** were observed in ^{13}C NMR.



27 **28** **29**

(22) For a recent scholarly analysis of steric effects in the diastereoselective addition to chiral aldehydes, see: Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353.

(23) For a discussion of the torsional strain model in the nucleophilic 1,2-addition to cyclohexenones, see: Wu, Y.-D.; Houk, K. N.; Florez, J.; Trost, B. M. *J. Org. Chem.* **1991**, *56*, 3656.

(24) For the use of alkoxide groups for controlling regio- and stereoselectivity in additions to γ-hydroxy enones, see: (a) Fischer, A.; Henderson, G. N. *Tetrahedron Lett.* **1980**, *21*, 701. (b) Solomon, M.; Jamison, W. C. L.; McCormick, M.; Liotta, D.; Cherry, D. A.; Mills, J. E.; Shah, R. D.; Rodgers, J. D.; Maryanoff, C. A. *J. Am. Chem. Soc.* **1988**, *110*, 3702. (c) Swiss, K. A.; Liotta, D. C.; Maryanoff, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 9393. (d) Swiss, K. A.; Hinkley, W.; Maryanoff, C. A.; Liotta, D. C. *Synthesis* **1992**, 127.

(25) Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61.

(26) (a) Simmons, H. E.; Fukunaga, T. *J. Am. Chem. Soc.* **1967**, *89*, 5208. (b) Ishiyama, J.; Senda, Y.; Imaizumi, S. *J. Chem. Soc., Perkin Trans. 2* **1982**, 71.

(27) (a) Eisenstein, O.; Klein, J.; Lefour, J. M. *Tetrahedron* **1979**, *35*, 225. (b) Burgess, E. M.; Liotta, C. L. *J. Org. Chem.* **1981**, *46*, 1703.

(28) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.

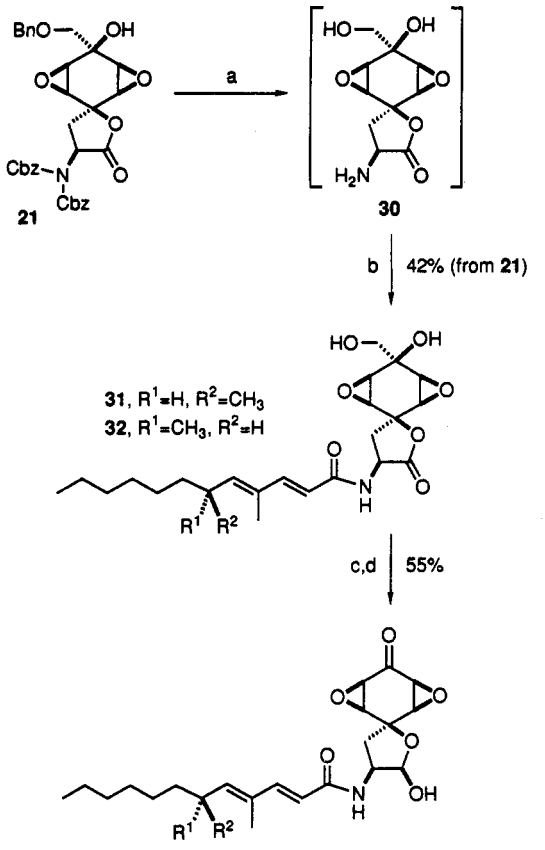
(29) Wipf, P.; Kim, Y., manuscript in preparation.

(30) For a theoretical analysis of the influence of electrostatic effects in π-facial stereoselection, see: (a) Wong, S. S.; Paddon-Row, M. N. *Aust. J. Chem.* **1991**, *44*, 765. (b) Wu, Y.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018.

(31) Bernasconi, S.; Comini, A.; Corbella, A.; Gariboldi, P.; Sisti, M. *Synthesis* **1980**, 385.

(32) Luche, J.-L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848.

Scheme V[a]



[a] (a) H_2, $Pd(OH)_2/C$, MeOH; (b) 13 or 17, Ph_2POCl, NMM, THF; (c) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, $EtOH/H_2O$, −25 °C; (d) $NaIO_4$, $MeOH/H_2O$.

is $[\alpha]_D$ +34.6 ° (*c* 0.15, $CHCl_3$) for the (6′*S*)-isomer and $[\alpha]_D$ −7.7° (*c* 0.21, $CHCl_3$) for the (6′*R*)-isomer. On the basis of the similarity of the latter $[\alpha]_D$ value with the sample of purified natural aranorosin, the stereochemistry at C(6′) of the natural product was tentatively assigned to be *R*. NOE measurements for the synthetic material were identical to the data reported for natural aranorosin.[1,17]

Circular Dichroism Studies. CD spectra served as a second, independent proof for the stereochemical equivalency of our synthetic material with natural aranorosin. Whereas the spectrum for the (6′*R*)-isomer ("synthetic aranorosin") in $CHCl_3$ was, within the limits of accuracy at relatively low wavelengths and molar ellipticities, identical to the purified natural product,[35] the circular dichroism of the corresponding (6′*S*)-isomer

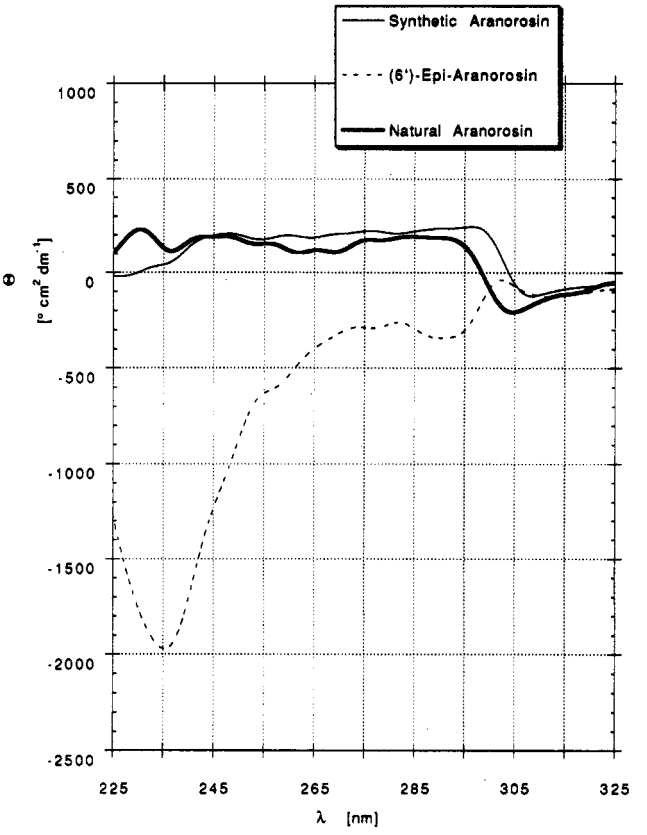


Figure 1. CD spectra of purified natural and synthetic aranorosin and (6′)-epi-aranorosin in $CHCl_3$.

("(6′)-epi-aranorosin") proved to be very different (Figure 1). Both relative and absolute configuration of aranorosin have therefore unambiguously been confirmed as assigned in Scheme V.

Conclusion

The total syntheses of the antibiotic aranorosin and its (6′)-epimer have been accomplished and the relative as well as the absolute configuration of the natural product have been established. The convergent synthesis plan includes several key features that are of general interest, such as the diastereoselective addition of an α-alkoxy lithium reagent to 4,4-disubstituted dienone **18**, the use of a diol as a protective group for the diepoxy ketone moiety, and the various chemoselective functional group manipulations that lead to the natural product.

Experimental Section

General Methods. IR spectra were recorded on a IBM IR/32 spectrophotometer. NMR spectra were recorded on Bruker AM-500 or AM-300 spectrometers in $CDCl_3$ unless otherwise noted. Mass spectra were obtained on a VG-70-70 HF. CD spectra were obtained on a Jasco-710 spectrometer. Anhydrous solvents were freshly distilled from either sodium benzophenone ketyl, P_2O_5, or CaH_2. All reactions were performed in oven-dried glassware under an argon or nitrogen atmosphere. Analytical TLC used Merck silica gel 60 F-254 plates, and flash chromatography was used to separate and purify the crude reaction mixtures.

[3(2′*S*),4*S*]-3-(2-Methyl-1-oxooctyl)-4-(phenylmethyl)-2-oxazolidinone (11). To a solution of 3.00 g (16.93 mmol) of 4-(phenylmethyl)-2-oxazolidinone (**10**) in 50 mL of THF at −78 °C were added 11.6 mL (17.0 mmol) of *n*-butyllithium (1.6 M in hexane) and 3.09 g (19.0 mmol) of octanoyl chloride. The reaction mixture was stirred for 30 min at −78 °C, warmed to ambient temperature over 30 min, and quenched with 10.2 mL of saturated

(33) We would like to thank the microbiology laboratory of Hoechst India, especially Drs. B. N. Ganguli and Mukhopadhyay, for providing us with a sample of natural aranorosin.

(34) Crude natural aranorosin (2.4 mg) exhibited an $[\alpha]_D$ −3.8° (*c* 0.24, $CHCl_3$, 21 °C). After purification on SiO_2, the $[\alpha]_D$ increased to −1.5° (*c* 0.2, $CHCl_3$, 21 °C). The ^1H NMR of both samples did not suggest the presence of any impurities. However, addition of MeOH to the natural aranorosin led to the precipitation of an impurity (0.6 mg) with an $[\alpha]_D$ +4.2° (*c* 0.1, $CHCl_3$, 21 °C). A copy of the ^1H NMR of this contamination, which is not identical but overlaps with aranorosin, is enclosed in the supplementary material. The remaining sample (1.6 mg) was clean aranorosin according to ^1H NMR.

(35) Quite confusingly for us at the time, the CD spectrum of natural aranorosin before precipitation with methanol was almost the mirror image of the synthetic (*R*)-isomer. The impurity did indeed exhibit itself a strongly negative Cotton effect.

aqueous NH_4Cl. The volatiles were removed in vacuo, and the resulting slurry was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were washed with 1 M NaOH (15 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated. Chromatography on SiO_2 (15% EtOAc/hexanes) afforded 3.65 g (71%) of (4*S*)-3-(1-oxooctyl)-4-(phenylmethyl)-2-oxazolidinone (**33**) as a colorless oil: $[\alpha]_D$ +64.2° (*c* 1.1, CH_2Cl_2, 22 °C); IR (neat) 3000, 2965, 2897, 1800, 1708, 1399, 1365, 1222, 1110, 775, 715 cm^{-1}; ^1H NMR δ 7.38–7.22 (m, 5 H), 4.73–4.65 (m, 1 H), 4.24–4.16 (m, 2 H), 3.31 (dd, 1 H, *J* = 13.3, 3.2 Hz), 3.03–2.90 (m, 2 H), 2.79 (dd, 1 H, *J* = 13.3, 9.6 Hz), 1.75–1.65 (m, 2 H), 1.42–1.26 (m, 8 H), 0.92 (t, 3 H, *J* = 6.8 Hz); ^{13}C NMR δ 173.3, 153.4, 135.2, 129.3, 128.8, 127.2, 66.0, 55.0, 37.8, 35.4, 31.6, 29.0, 24.1, 22.5, 14.0; MS (EI) *m/e* (rel inten) 303 (M^+, 2), 232 (1), 212 (12), 178 (2), 143 (1), 127 (100), 117 (10), 91 (15), 84 (35), 57 (68); HRMS *m/e* calcd for $C_{18}H_{25}NO_3$ 303.1834, found 303.1834.

A cold (−78 °C) solution of 5.520 g (18.9 mmol) of oxazolidinone **33** in 13.2 mL of dry THF was added to a solution of 20.0 mL (20.0 mmol) of NaHMDSA (1.0 M in THF) at −78 °C, stirred for 30 min, and treated with 5.65 mL (91 mmol, 5.0 equiv) of MeI. After 4–5 h at −78 °C, the reaction mixture was quenched with 30 mL of saturated aqueous NH_4Cl, and the solvents were evaporated. The residue was extracted with CH_2Cl_2 (5 × 75 mL), and the combined organic extracts were washed with 1 M $NaHSO_4$ (250 mL) and 1.5 M NaS_2O_5 (200 mL), dried (Na_2SO_4), and concentrated. Chromatography on SiO_2 (5% EtOAc/hexanes) afforded 3.302 g (57%) of imide **11** as a solid: $[\alpha]_D$ +82.2° (*c* 1.0, CH_2Cl_2, 22 °C); IR ($CHCl_3$) 2955, 2890, 1790, 1700, 1462, 1390, 1358, 1245, 1218, 1105, 977, 768, 702 cm^{-1}; ^1H NMR δ 7.45–7.18 (m, 6 H), 4.69–4.62 (m, 1 H), 4.19–4.14 (m, 2 H), 3.72–3.65 (m, 1 H), 3.26 (dd, 1 H, *J* = 13.3, 3.2 Hz), 2.75 (dd, 1 H, *J* = 13.3, 3.7 Hz), 1.75–1.67 (m, 1 H), 1.44–1.30 (m, 1 H), 1.30–1.15 (m, 8 H), 1.21 (d, 3 H, *J* = 6.8 Hz), 0.86 (t, 3 H, *J* = 6.6 Hz); ^{13}C NMR δ 177.2, 152.9, 135.2, 129.3, 128.8, 127.2, 65.8, 55.2, 37.7, 37.6, 33.3, 31.6, 29.2, 27.1, 22.5, 17.2, 14.0; MS (EI) *m/e* (rel inten) 317 (m^+, 8), 226 (18), 178 (11), 158 (2), 141 (100), 133 (8), 113 (20), 91 (18), 86 (20, 71 (70); HRMS *m/e* calcd for $C_{19}H_{27}NO_3$ 317.1991, found 317.1991.

Ethyl (2*E*,4*S*)2,4-Dimethyl-2-decenoate (12). A solution of 5.255 g (16.55 mmol) of imide **11** in 175 mL of 3:1 THF/H_2O at 0 °C was treated with 8.55 mL (82.8 mmol) of H_2O_2 (30% in H_2O) and 1.388 g (33.10 mmol) of LiOH·H_2O. The reaction mixture was allowed to warm to ambient temperature over a period of 5 h, quenched with 1.5 M $Na_2S_2O_3$ (62 mL), and basified with saturated aqueous $NaHCO_3$. The solvent was evaporated, and the residue was extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated, and the residual solid was recrystalized from EtOAc/hexanes to yield 2.146 g (73%) of oxazolidinone **10** as a white solid. The aqueous layer was acidified with 3 M HCl, extracted with Et_2O, dried (Na_2SO_4), and concentrated to yield 2.363 g (90%) of (2*S*)-2-methyloctanoic acid (**34**) as an oil.

A solution of 2.2636 g (14.40 mmol) of the crude acid **34** in 10 mL of dry Et_2O was added dropwise to a suspension of 696 mg (18.35 mmol, 1.2 equiv) of LAH in 50 mL of dry Et_2O at 0 °C. The reaction mixture was warmed to ambient temperature, stirred for 1 h, and quenched by addition of 700 μL of H_2O, 2.1 mL of 15% aqueous NaOH, and 700 μL of H_2O. The colorless suspension was filtered, dried ($MgSO_4$), and concentrated to yield 1.803 g (88%) of (2*S*)-2-methyl-1-octanol (**35**) as an oil: $[\alpha]_D$ −10.8° (*c* 0.7, CH_2Cl_2, 22 °C); IR (neat) 3337, 2957, 2926, 2856, 1466, 1379, 1034 cm^{-1}; ^1H NMR δ 3.49 (dd, 1 H, *J* = 10.5, 5.7 Hz), 3.40 (dd, 1 H, *J* = 10.5, 6.5 Hz), 2.0–1.7 (m, 1 H), 1.65–1.55 (m, 1 H), 1.40–1.15 (m, 8 H), 1.15–1.0 (m, 1 H), 0.91 (d, 3 H, *J* = 6.7 Hz), 0.88 (t, 3 H, *J* = 6.8 Hz); ^{13}C NMR δ 68.1, 35.6, 33.1, 31.8, 29.5, 26.9, 22.6, 16.5, 14.0.

To solution of 40 mL of dry CH_2Cl_2 was added 0.41 mL (4.66 mmol) of oxalyl chloride, followed by 0.66 mL (9.31 mmol) of DMSO at −60 °C. The reaction mixture was stirred for 10 min and treated dropwise with a solution of 602.1 mg (3.878 mmol of alcohol **35** in 2.0 mL of CH_2Cl_2. After 15 min stirring at −60 °C, 1.62 mL (11.64 mmol) of triethylamine was added, stirring was continued for 5 min, and the dry ice bath was removed. After 40 min, a solution of 7.021 g (19.39 mmol, 5.0 equiv) of (1-carbethoxyethylidene)triphenylphosphorane in 20.0 mL of dry CH_2Cl_2 was added. The reaction mixture was stirred for 2 d, treated with a solution of 1.370 g (3.878 mmol, 1.0 equiv) of (1-carbethoxyethylidene)triphenylphosphorane in 5.0 mL of CH_2Cl_2, stirred for an additional 36 h, diluted with 150 mL of CH_2Cl_2, and quenched with saturated aqueous NH_4Cl (150 mL). The aqueous layer was extracted with Et_2O (2 × 75 mL), and the combined organic layers were washed with brine (150 mL), dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (8% EtOAc/hexanes) afforded 0.7725 g (88%) of ethyl (2*E*,4*S*)-2,4-dimethyl-2-decenoate (**12**) as an oil: $[\alpha]_D$ + 30.8° (*c* 0.8, CH_2Cl_2, 22 °C); IR (neat) 2977, 2932, 1717, 1273, 1248, 1125, 750 cm^{-1}; ^1H NMR δ 6.55 (dd, 1 H, *J* = 10.0, 1.4 Hz), 4.19 (q, 2 H, *J* = 7.1 Hz), 2.55–2.45 (m, 1 H), 1.83 (d, 3 H, *J* = 1.4 Hz), 1.31 (t, 3 H, *J* = 7.1 Hz), 1.35–1.15 (m, 10 H), 0.99 (d, 3 H, *J* = 6.6 Hz), 0.88 (t, 3 H, *J* = 7.0 Hz); ^{13}C NMR δ 168.5, 148.1, 126.1, 60.3, 36.8, 33.2, 31.7, 29.4, 27.4, 22.6, 20.0, 14.2, 14.0, 12.5; MS (EI) *m/e* (rel inten) 226 (M^+, 30), 181 (32), 156 (22), 141 (6), 125 (35), 113 (60), 102 (100), 95 (20), 87 (28), 83 (71), 74 (14), 69 (78), 55 (41); HRMS *m/e* calcd for $C_{14}H_{26}O_2$: 226.1933, found 226.1915.

(2*E*,4*E*,6*S*)-4,6-Dimethyl-2,4-dodecadienoic Acid (13). To a solution of 375.4 mg (1.66 mmol) of ester **12** in 15.0 mL of CH_2Cl_2 at −78 °C added dropwise 3.8 mL (3.8 mmol) of DIBAI-H (1.0 M in hexanes). The reaction mixture was stirred for 1 h, quenched with 500 μL of MeOH, and poured into 15 mL of saturated aqueous sodium potassium tartrate. After addition of CH_2Cl_2 and H_2O, the aqueous layer was extracted with EtOAc (2 × 30 mL), and the combined organic layers were washed with brine (60 mL), dried (Na_2SO_4), filtered through a plug of Na_2SO_4/SiO_2, and concentrated to yield 305.6 mg (100%) of (2*E*,4*S*)-2,4-dimethyl-2-decen-1-ol (**36**) as an oil: $[\alpha]_D$ +12.8° (*c* 0.4, CH_2Cl_2, 22 °C); IR (neat) 3318, 2957, 2924, 2856, 1458, 1377, 1070, 1010, 858 cm^{-1}; ^1H NMR δ 5.17 (d, 1 H, *J* = 9.4 Hz), 4.00 (s, 2 H), 2.40–2.35 (m, 1 H), 1.67 (s, 3 H), 1.45–1.15 (m, 10 H), 0.93 (d, 3 H, *J* = 6.6 Hz), 0.88 (t, 3 H, *J* = 6.9 Hz); ^{13}C NMR δ 133.0, 132.9, 68.9, 37.5, 32.0, 31.9, 29.5, 27.4, 22.6, 20.9, 14.1, 13.8; MS (EI *m/e* (rel inten) 184 (M^+, 2), 166 (2), 153 (20), 129 (91), 109 (15), 97 (20), 83 (20), 69 (55), 55 (35); HRMS *m/e* calcd for $C_{11}H_{21}$ (M − H_2O) 153.1643, found 153.1641.

To a stirred suspension of 10.12 g (39.48 mmol, 10.0 equiv) of $BaMnO_4$ and 10.0 g of Celite in 150 mL of CH_2Cl_2 was added a solution of 727.7 mg (3.948 mmol) of alcohol **36** in 10.0 mL of CH_2Cl_2. After 21 h, the reaction mixture was filtered through a plug of Celite and concentrated to yield 647.3 mg (90%) of (2*E*,4*S*)-2,4-dimethyl-2-decenal as an oil. A solution of the crude aldehyde in 30 mL of CH_2Cl_2 was treated with a solution of 4.956 g (14.20 mmol, 4.0 equiv) of (carbethoxymethylene) triphenylphosphorane in 20 mL of CH_2Cl_2. The reaction mixture was stirred for 5 d, treated with a solution of 1.236 g (3.55 mmol, 1.0 equiv) of (carbethoxymethylene)triphenylphosphorane in 5.0 mL of CH_2Cl_2, stirred for an additional 2 d, diluted with 150 mL of CH_2Cl_2, and quenched with saturated aqueous NH_4Cl (150 mL). The aqueous layer was extracted with Et_2O (2 × 75 mL), and the combined organic extracts were washed with brine (150 mL) and concentrated. Purification by chromatography on SiO_2 (CH_2Cl_2) yielded 576.3 mg (64%) of ethyl (2*E*,4*E*,6*S*)-4,6-dimethyl-2,4-dodecadienoate (**37**) as an oil: $[\alpha]_D$ +49.2° (*c* 1.3, CH_2Cl_2, 22 °C); IR (neat) 2959, 2926, 2856, 1717, 1626, 1302, 1265, 1170, 983 cm^{-1}; ^1H NMR δ 7.32 (d, 1 H, *J* = 15.9 Hz), 5.78 (d, 1 H, *J* = 15.9 Hz), 5.67 (d, 1 H, *J* = 9.5 Hz), 4.21 (q, 2 H, *J* = 7.1 Hz), 2.56–2.46 (m, 1 H), 1.78 (s, 3 H), 1.32 (t, 3 H, *J* = 7.1 Hz), 1.30–1.21 (m, 10 H), 0.98 (d, 3 H, *J* = 6.6 Hz), 0.88 (t, 3 H, *J* = 6.8 Hz); ^{13}C NMR δ 167.6, 149.9, 148.7, 131.2, 115.4, 60.1, 37.2, 33.2, 31.8, 29.4, 27.4, 22.6, 20.5, 14.3, 14.1, 12.3; MS (EI) *m/e* (rel inten) 252 (M^+, 4), 237 (2), 223 (1), 207 (20), 179 (30), 167 (100), 151 (7), 139 (50), 121 (18), 111 (17), 93 (35), 81 (9); HRMS *m/e* calcd for $C_{16}H_{28}O_2$ 252.2089, found 252.2050.

A solution of 48 mg (0.19 mmol) of ester **37** in 5 mL of 2:1:2 MeOH/THF/H_2O was treated with 46 mg (1.90 mmol) of LiOH, stirred for 36 h at ambient temperature, and diluted with 20 mL of 1 M HCl and 20 mL of EtOAc. The organic layer was washed with brine, separated, and dried ($MgSO_4$). Filtration and concentration gave a pale yellow oil which was chromatographed on SiO_2 (98% hexane/EtOAc) to give 42 mg (97%) of (2*E*,4*E*,6*S*)-4,6-dimethyl-2,4-dodecadienoic acid (**13**) as a colorless oil: TLC R_f = 0.17 (80% EtOAc/hexanes); $[\alpha]_D$ +63.3° (*c* 1.0, CH_2Cl_2, 21 °C); IR (neat) 2959, 2926, 2857, 2685, 2590, 1688, 1651, 1617, 1456, 1418, 1283, 1208, 1026, 984, 851 cm^{-1}; ^1H NMR δ 7.30 (d,

1 H, J = 15.6 Hz), 5.77 (d, 1 H, J = 15.6 Hz), 5.71 (d, 1 H, J = 9.9 Hz), 2.55–2.45 (m, 1 H), 1.78 (s, 3 H), 1.35–1.15 (m, 10 H), 0.97 (d, 3 H, J = 6.6 Hz), 0.86 (t, 3 H, J = 6.1 Hz); ^{13}C NMR ($CDCl_3$) δ 173.4, 152.4, 150.1, 131.4, 114.8, 37.2, 33.4, 31.9, 29.4, 27.5, 22.7, 20.4, 14.1, 12.3; MS (EI) m/z (rel inten) 224 (M^+, 2), 209 (3), 195 (2), 179 (13), 167 (3), 139 (100), 125 (10), 111 (80), 93 (50), 81 (25), 69 (35), 55 (45); HRMS (EI) m/e calcd for $C_{13}H_{23}$ (M – CO_2H) 179.1804, found 179.1800.

(4*S*)-3-(1-Oxopropyl)-4-(phenylmethyl)-2-oxazolidinone (14). According to the procedure described for **33**, 3.00 g (16.93 mmol) of **10** and 1.63 mL (19.0 mmol) of propanoyl chloride afforded 2.51 g (64%) of **14** as a solid: $[\alpha]_D$ +77.5° (c 1.0, CH_2Cl_2, 22 °C); IR (neat) 3020, 2980, 1800, 1722, 1403, 1368, 1280, 1223, 1092, 777, 758, 720 cm^{-1}; ^{1}H NMR δ 7.34–7.17 (m, 5 H), 4.70–4.60 (m, 1 H), 4.18–4.05 (m, 2 H), 3.30 (dd, 1 H, J = 11.2, 3.2 Hz), 3.0–2.8 (m, 2 H), 2.77 (dd, 1 H, J = 13.3, 9..6 Hz), 1.20 (t, 3 H, J = 7.4 Hz); ^{13}C NMR δ 174.0, 135.3, 129.4, 128.9, 127.3, 66.2, 55.1, 37.9, 29.2, 8.2.

[3(2′*R*),4*S*]-3-(2-Methyl-1-oxooctyl)-4-(phenylmethyl)-2-oxazolidinone (15). According to the procedure described for **11**, 826 mg (3.54 mmol) of imide **14** and 4.149 g (17.7 mmol) of hexyl triflate afforded 306 mg (37%) of recovered **14** as a solid and 486 mg (43%) of **15** as a colorless oil: $[\alpha]_D$ +40.7° (c 0.6, CH_2Cl_2, 22 °C); IR (neat) 2928, 2856, 1782, 1697, 1456, 1387, 1350, 1211, 1099, 972, 702 cm^{-1}; ^{1}H NMR δ 7.37–7.22 (m, 5 H), 4.74–4.65 (m, 1 H), 4.23–4.13 (m, 2 H), 3.80–3.70 (m, 1 H), 3.31 (dd, 1 H, J = 13.2, 3.2 Hz), 2.74 (dd, 1 H, J = 13.3, 9.7 Hz), 1.82–1.73 (m, 1 H), 1.50–1.24 (m, 9 H), 1.18 (d, 3 H, J = 6.7 Hz), 0.89 (t, 3 H, J = 6.5 Hz); ^{13}C NMR δ 177.4, 153.1, 135.3, 129.4, 128.9, 127.3, 65.9, 55.3, 38.0, 37.4, 33.8, 31.7, 29.3, 27.0, 22.6, 16.7, 14.0; MS (EI) m/e (rel inten) 317 (M^+, 3), 246 (4), 233 (9), 226 (15), 204 (1), 190 (2), 178 (10), 160 (3), 141 (100), 133 (10), 113 (25), 98 (7), 91 (20), 86 (18), 71 (42), 57 (30); HRMS (EI) m/e calcd for $C_{19}H_{27}NO_3$ 317.1991, found 317.2056.

Ethyl (2*E*,4*R*)-2,4-Dimethyl-2-decenoate (16). According to the procedure described for **34**, 450 mg (1.42 mmol) of **15** afforded 229 mg (91%) of **10** as a white solid and 176 mg (78%) of (2*R*)-2-methyloctanoic acid (**38**) as an oil.

According to the procedure described for **35**, 176 mg (1.12 mmol) of acid **38** afforded 136 mg (85%) of (2*R*)-2-methyl-1-octanol (**39**) as an oil: $[\alpha]_D$ +10.3° (c 1.0, CH_2Cl_2, 22 °C); IR (neat) 3341, 2957, 2926, 2856, 1491, 1398, 1076, 736 cm^{-1}; ^{1}H NMR δ 3.48 (dd, 1 H, J = 10.4, 5.6 Hz), 3.37 (dd, 1 H, J = 10.4, 6.6 Hz), 2.06 (br s, 1 H), 1.65–1.55 (m, 1 H), 1.45–1.22 (m, 9 H), 1.15–1.03 (m, 1 H), 0.90 (d, 3 H, J = 6.6 Hz), 0.87 (t, 3 H, J = 7.0 Hz); ^{13}C NMR δ 68.2, 35.7, 33.1, 31.8, 29.6, 26.9, 22.6, 16.5, 14.0.

According to the procedure described for **12**, 115 mg (0.80 mmol) of alcohol **39** afforded 92.0 mg (51%) of ester **16** as an oil: ^{1}H NMR δ 6.50 (d, 1 H, J = 10.3 Hz), 4.15 (q, 2 H, 7.1 Hz), 2.44 (m, 1 H), 1.80 (s, 3 H), 1.27 (t, 3 H, J = 7.1 Hz), 1.22 (m, 10 H), 0.97 (d, 3 H, J = 6.7 Hz), 0.85 (t, 3 H, J = 6.9 Hz). This compound was directly used for the next step.

(2*E*,4*E*,6*R*)-4,6-Dimethyl-2,4-dodecadienoic acid (17). According to the procedure described for **36**, 62.6 mg (0.277 mmol) of ester **16** afforded 51.5 mg (100%) of (2*E*,4*R*)-2,4-dimethyl-2-decen-1-ol (**40**) as an oil: $[\alpha]_D$ –10.4° (c 1.7, CH_2Cl_2, 22 °C); IR (neat) 3316, 2957, 2924, 2855, 1456, 1377, 1070, 1010, 858, 725 cm^{-1}; ^{1}H NMR δ 5.15 (d, 1 H, J = 8.4 Hz), 3.97 (s, 2 H), 2.42–2.28 (m, 1 H), 1.89 (s, 1 H); 1.65 (s, 3 H), 1.32–1.20 (m, 10 H), 0.91 (d, 3 H, J = 6.6 Hz), 0.88 (t, 3 H, J = 6.3 Hz); ^{13}C NMR δ 133.0, 132.9, 68.9, 37.5, 31.9, 31.8, 29.5, 27.4, 22.6, 20.9, 14.1, 13.8; MS (EI) m/e (rel inten) 184 (M^+, 3), 167 (3), 153 (15), 129 (100), 109 (20), 99 (25), 95 (25), 83 (50), 79 (18), 69 (100), 55 (85); HRMS m/e calcd for $C_{11}H_{21}$ (M – H_2O) 153.1643, found 153.1637.

According to the procedure described for **37**, 51.0 mg (0.275 mmol) of alcohol **40** afforded 48.9 mg (70%) of ethyl (2*E*,4*E*,6*R*)-4,6-dimethyl-2,4-dodecadienoate (**41**) as an oil: $[\alpha]_D$ –46.0° (c 1.1, CH_2Cl_2, 22 °C); IR (neat) 1717, 1624, 1300, 1265, 1169, 982 cm^{-1}; ^{1}H NMR δ 7.32 (d, 1 H, J = 16.0 Hz), 5.78 (d, 1 H, J = 15.6 Hz), 5.67 (d, 1 H, J = 9.8 Hz), 4.21 (q, 2 H, J = 7.1 Hz), 2.55–2.45 (m, 1 H), 1.77 (s, 3 H), 1.30 (t, 3 H, J = 7.1 Hz), 1.30–1.18 (m, 10 H), 0.97 (d, 3 H, J = 6.6 Hz), 0.87 (t, 3 H, J = 6.9 Hz); ^{13}C NMR δ 167.5, 149.9, 148.7, 131.2, 115.4, 60.0, 37.2, 33.2, 31.8, 29.4, 27.4, 22.6, 20.5, 14.3, 14.0, 12.3; MS (EI) m/e (rel inten) 252 (M^+, 3), 207 (20), 179 (42), 167 (100), 139 (62), 121 (28), 107 (30), 93 (80), 81 (20), 69 (21), 55 (29); HRMS (EI) m/e calcd for $C_{16}H_{28}O_2$ 252.2089, found 252.2146.

According to the procedure described for **13**, 48 mg (0.19 mmol) of ester **41** afforded 42 mg (98%) of acid **17** as a colorless oil: TLC R_f = 0.17 (80% EtOAc/hexanes); $[\alpha]_D$ –63.9° (c 2.1, CH_2Cl_2, 21 °C); IR (neat) 2959, 2926, 2857, 2687, 1688, 1617, 1418, 1285, 1208, 984 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.40 (d, 1 H, J = 15.5 Hz), 5.78 (d, 1 H, J = 15.5 Hz), 5.73 (d, 1 H, J = 10.1 Hz), 2.55–2.45 (m, 1 H), 1.79 (s, 3 H), 1.35–1.15 (m, 10 H), 0.98 (d, 3 H, J = 6.6 Hz), 0.87 (t, 3 H, J = 6.1 Hz); ^{13}C NMR ($CDCl_3$) δ 173.4, 152.5, 150.3, 131.4, 114.7, 37.3, 33.4, 31.9, 29.5, 27.6, 22.7, 20.5, 14.2, 12.4; MS (EI) m/z (rel inten) 224 (M^+, 2), 209 (5), 195 ([M – C_2H_5]$^+$, 5), 179 (14), 167 (4), 153 (15), 139 (100), 125 (20), 111 (90), 98 (80), 93 (60), 83 (40), 77 (30), 69 (60), 55 (70); HRMS (EI) calcd for $C_{12}H_{19}O_2$ (M – C_2H_5) 195.1385, found 195.1416.

(3*S*)-3-[(Benzyloxycarbonyl)amino]-1-oxaspiro[4.5]deca-7,10-diene-2,8-dione (6). To a stirred solution of 1.0 g (3.17 mmol) of *N*-Cbz-tyrosine (**9**) in 29 mL of absolute CH_3OH at 0 °C was added 1.15 g (3.49 mmol) of iodobenzenediacetate. The reaction mixture was stirred for 30 min at the same temperature, diluted with EtOAc, and extracted with saturated aqueous $NaHCO_3$ (2 × 40 mL) and brine. The combined organic layers were dried ($MgSO_4$) and concentrated to give a dark brown residue which was chromatographed on SiO_2 (50% EtOAc/hexanes) to give 348 mg (35%) of spirolactone **6** as a white solid: TLC R_f = 0.43 (50% EtOAc/hexanes); mp 44–46 °C; $[\alpha]_D$ –14.3° (c 2.62, CH_2Cl_2, 21 °C); IR (Nujol) 3300, 2920, 2860, 1760, 1720, 1680, 1630, 1540, 1260, 1210 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.35 (s, 5 H), 6.86 (d, 2 H, J = 9.7 Hz), 6.29 (d, 1 H, J = 9.3 Hz), 6.28 (d, 1 H, J = 9.7 Hz), 5.61 (d, 1 H, J = 6.2 Hz), 5.12 (s, 2 H), 4.62 (ddd, 1 H, J = 11.6, 9.3, 6.2 Hz), 2.73 (dd, 1 H, J = 13.1, 9.3 Hz), 2.48 (dd, 1 H, J = 13.1, 11.6 Hz); ^{13}C NMR ($CDCl_3$) δ 184.1, 173.8, 155.8, 146.3, 144.6, 135.5, 129.1, 128.4, 128.3, 128.0, 127.7, 75.7, 67.0 50.0, 36.9; MS (EI) m/z (rel inten) 269 ([M – CO_2]$^+$, 7), 225 (5), 207 (4), 179 (1), 164 (3), 149 (1), 134 (10), 107 (90), 91 (100), 79 (20), 75 (10), 65 (15), 51 (10), 44 (20).

(3*S*)-3-[Bis(benzyloxycarbonyl)amino]-1-oxaspiro[4.5]-deca-7,10-diene-2,8-dione (18). A solution of 1.46 g (4.66 mmol) of spirolactone **6** in 5 mL of CH_3CN was treated with 0.11 g (0.90 mmol) of DMAP and 6.66 g (23.3 mmol) of dibenzyl pyrocarbonate in 10 portions at 1-min intervals at 22 °C. The reaction mixture was stirred for 30 min, CH_3CN was removed in vacuo, the residue was diluted in 10 mL of dry CH_2Cl_2, and 3.51 g (23.3 mmol) of TBDMSCl and 3.17 g (41.4 mmol) of imidazole were added successively. After 30 min of being stirred at ambient temperature, the reaction mixture was diluted with 50 mL of EtOAc and washed with H_2O and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated to give a yellow residue which was chromatographed on SiO_2 (25% EtOAc/hexanes) to afford 1.75 g (84%) of **18** as a viscous colorless oil: TLC R_f = 0.65 (50% EtOAc/hexanes); $[\alpha]_D$ –59.9° (c 0.84, CH_2Cl_2, 21 °C); IR (neat) 3036, 1790, 1701, 1740, 1765, 1676, 1227 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.32 (s, 10 H), 6.82 (dd, 1 H, J = 7.7, 3.0 Hz), 6.43 (dd, 1 H, J = 9.9, 3.0 Hz), 6.15 (dd, 1 H, J = 7.7, 1.5 Hz), 6.08 (d, 1 H, J = 9.9 Hz), 5.54 (t, 1 H, J = 10.3 Hz), 5.26, 5.22 (AB, 4 H, J = 12.0 Hz), 2.55 (d, 2 H, J = 10.3 Hz); ^{13}C NMR ($CDCl_3$) δ 183.9, 171.5, 152.3, 146.0, 144.9, 134.1, 128.9, 128.7, 128.6, 128.4, 75.5, 69.9, 54.3, 35.1; MS (EI) m/z (rel inten) 403 ([M – CO_2]$^+$, 9), 359 (2), 341 (5), 315 (3), 268 (10), 254 (100), 224 (20), 206 (40), 197 (80), 178 (40), 163 (20), 134 (25), 120 (15), 107 (100), 92 (100), 79 (70), 65 (100); HRMS (EI) calcd for $C_{24}H_{21}NO_5$ (M – CO_2) 403.1420, found 403.1437.

(3*S*,5*S*,6*S*,7*R*,8*S*,9*S*,10*R*)-3-[Bis(benzyloxycarbonyl)amino]-8-[(benzyloxy)methyl]-6,7:9,10-diepoxy-8-hydroxy-1-oxaspiro[4.5]decan-2-one (21). To a stirred solution of 617 mg (1.50 mmol) of [(benzyloxy)methyl]tri-*n*-butylstannane in 5 mL of dry THF at –78 °C was added dropwise 0.75 mL (1.50 mmol) of *n*-BuLi (2.01 M in hexanes). After 10 min, the deep yellow solution was cooled to –100 °C and cannulated to a cooled (–100 °C) solution of 447 mg (1.0 mmol) of spirolactone **18** in 4 mL of dry THF. Immediately after the addition of **18** was complete, 10 mL of aqueous 5% $NaHCO_3$ was added to the reaction mixture under vigorous stirring. The resulting cloudy solution was extracted with EtOAc (3 × 15 mL), the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give an oily residue. After the addition of 3 mL of

hexanes, two immiscible layers formed. The top layer was decanted and diluted with 5 mL of CCl_4, and 880 mg (4.57 mmol) of MCPBA and 330 mg (0.91 mmol) of 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide were added. The resulting slurry was heated at 70 °C for 3 h, the solvent was evaporated under reduced pressure, and 5 mL of CH_2Cl_2 was added to dissolve the solid residue. Chromatography on SiO_2 (50% EtOAc/hexanes) gave a viscous oil that was precipitated from CH_3OH as a colorless solid to give 275 mg of **21** (46% from **18**): TLC R_f = 0.16 (50% EtOAc/hexanes): mp 268–269 °C; $[\alpha]_D$ −13.8° (*c* 4.2, CH_2Cl_2, 21 °C); IR (CH_2Cl_2) 3470, 3034, 2959, 2865, 1790, 1738, 1701, 1455, 1406, 1345, 1233, 941, 737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–7.11 (m, 15 H), 5.31 (dd, 1 H, *J* = 7.2, 8.8 Hz), 5.26, 5.21 (AB, 4 H, *J* = 12.1 Hz), 4.48, 4.42 (AB, 2 H, *J* = 11.0 Hz), 3.61, 3.55 (AB, 2 H, *J* = 9.1 Hz), 3.29–3.25 (m, 2 H), 3.17 (m, 1 H), 3.08 (m, 1 H), 2.28 (dd, 1 H, *J* = 13.9, 8.8 Hz), 1.89 (dd, 1 H, *J* = 13.9, 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 171.9, 152.4, 137.0, 134.3, 128.7, 128.6, 128.5, 128.4, 128.1, 79.5, 74.0, 72.9, 69.8, 68.6, 59.2, 59.1, 58.5, 58.4, 54.1, 32.3; MS (FAB) *m/z* (rel inten) 624 ([M + Na]$^+$).

(3*S*,5,8*syn*)-3-[Bis(*tert*-butoxycarbonyl)amino]-8-hydroxy-8-methyl-1-oxaspiro[4.5]deca-7,10-dien-2-one (23) and (3*S*,5,8-*anti*)-3-[Bis(*tert*-butoxycarbonyl)amino]-8-hydroxy-8-methyl-1-oxaspiro[4.5]deca-7,10-dien-2-one (24). To a stirred solution of 620 mg (1.64 mmol) of spiroenone **22** in 30 mL of dry THF was added dropwise at −78 °C 1.3 mL (1.97 mmol) of a 1.5 M solution of CH_3MgBr in Et_2O. After 10 min, the deep yellow solution was quenched by addition of 30 mL of 5% $NaHCO_3$ solution. The mixture was extracted with EtOAc (2 × 100 mL), and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to give an oily residue. Chromatography on SiO_2 (34% EtOAc/hexanes) gave 468 mg (72%) of **23** and 77 mg (12%) of **24** as colorless solids.

23: TLC R_f = 0.60 (50% EtOAc/hexanes); mp 140 °C; $[\alpha]_D$ −25.7° (*c* 1.2, CH_2Cl_2, 21 °C); IR (CH_2Cl_2) 468, 2979, 1784, 1732, 1696, 1456, 1385, 1368, 1296, 1235, 1169, 1142, 943, 779 cm^{-1}; ^1H NMR (CD_3OD) δ 6.04, 5.89 (AB, 2 H, *J* = 9.3 Hz), 5.99 (s, 2 H), 5.42 (dd, 1 H, *J* = 10.9, 9.6 Hz), 4.86 (s, 1 H), 2.48 (dd, 1 H, *J* = 12.5, 10.9 Hz), 2.38 (dd, 1 H, *J* = 12.5, 9.6 Hz), 1.52 (s, 18 H), 1.27 (s, 3 H); ^{13}C NMR (CD_3OD) δ 175.1, 152.9, 137.8, 136.7, 127.9, 127.2, 85.3, 77.9, 65.6, 56.0, 39.5, 29.3, 28.2; MS (EI) *m/z* (rel inten) 333 ([M − CO_2 − H_2O]$^+$, 1), 265 (1), 239 (1), 221 (2), 177 ([M − 2CO_2 − C_4H_8 − H_2O]$^+$, 25), 160 (15), 133 (15), 121 (10), 105 (15), 57 (100); HRMS (EI) calcd for $C_{10}H_{11}NO_2$ (M − 2CO_2 − C_4H_8 − H_2O) 177.0790, found 177.0793.

24: TLC R_f = 0.51 (50% EtOAc/hexanes); mp 52 °C; $[\alpha]_D$ −30.6° (*c* 1.0, CH_2Cl_2, 21 °C); IR (CH_2Cl_2) 3476, 2980, 1784, 1734, 1700, 1653, 1456, 1387, 1368, 1298, 1237, 1198, 1169, 1144, 1003, 941, 779, 669 cm^{-1}; ^1H NMR (CD_3OD) δ 6.11–5.86 (m, 4 H), 5.42 (t, 1 H, *J* = 10.2 Hz), 4.83 (s, 1 H), 2.49 (d, 2 H, *J* = 10.2 Hz), 1.52 (s, 18 H), 1.31 (s, 3 H); ^{13}C NMR (CD_3OD) δ 175.2, 153.0, 139.4, 137.8, 128.5, 127.3, 85.3, 78.3, 65.4, 56.2, 39.0, 28.5, 28.3; MS (EI) *m/z* (rel inten) 233 (2), 221 (1), 177 ([M − 2CO_2 − 2C_4H_8 − H_2O]$^+$, 20), 160 (10), 133 (10), 121 (10), 105 (20), 91 (8), 77 (7), 57 (100); HRMS (EI) calcd for $C_{10}H_{11}NO_2$ (M − 2CO_2 − 2C_4H_8 − H_2O) 177.0790, found 177.0800.

(3*S*,5*S*,6*S*,7*R*,8*S*,9*S*,10*R*)-3-[Bis(*tert*-butoxycarbonyl)amino]-6,7:9,10-diepoxy-8-hydroxy-8-methyl-1-oxaspiro[4.5]-decan-2-one (25). A solution of 153 mg (0.39 mmol) of alcohol **23** in 25 mL of CCl_4 was treated with 240 mg (1.39 mmol) of mCPBA and 22 mg (0.06 mmol) of 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide and heated for 5 h at 70 °C. The solvent was evaporated under reduced pressure and 10 mL of CH_2Cl_2 was added to dissolve the solid residues. Chromatography on SiO_2 (50% EtOAc/hexanes) gave 95 mg (57%) of **25** as a colorless solid: TLC R_f = 0.21 (50% EtOAc/hexanes); mp 180 °C dec; $[\alpha]_D$ −14.4° (*c* 0.8, CH_2Cl_2, 21 °C); IR (CH_2Cl_2) 3486, 2977, 1790, 1723, 1688, 1651, 1393, 1366, 1269, 1246, 1211, 1165, 1136, 1063, 1038, 936, 860, 731 cm^{-1}; ^1H NMR (CD_3OD) δ 5.49 (dd, 1 H, *J* = 10.5, 9.6 Hz), 3.51–3.49 (m, 2 H), 3.23–3.21 (m, 2 H), 2.64 (dd, 1 H, *J* = 13.1, 10.5 Hz), 2.46 (dd, 1 H, *J* = 13.1, 9.6 Hz), 1.52 (s, 18 H), 1.32 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 172.8, 151.4, 83.8, 79.5, 65.6, 59.5, 57.0, 56.5, 53.8, 32.4, 27.6, 23.7.

(3*S*,5*S*,6*R*,7*S*,8*R*,9*R*,10*S*)-3-[Bis(*tert*-butoxycarbonyl)amino]-6,7:9,10-diepoxy-8-hydroxy-8-methyl-1-oxaspiro[4.5]-decan-2-one (26). According to the procedure described for **25**, 130 mg (0.44 mmol) of alcohol **24** gave 97 mg (68%) of **26** as a colorless solid: TLC R_f = 0.51 (50% EtOAc/hexanes); mp 158 °C; $[\alpha]_D$ −17.7° (*c* 1.1, CH_2Cl_2, 21 °C); IR (CH_2Cl_2) 3739, 3729, 3644, 3420, 2980, 1800, 1761, 1730, 1698, 1455, 1393, 1368, 1300, 1285, 1239, 1167, 1140, 1125, 1026, 932 cm^{-1}; ^1H NMR (CD_3OD) δ 5.51 (dd, 1 H, *J* = 10.5, 9.9 Hz), 3.49–3.45 (m, 2 H), 3.22–3.20 (m, 2 H), 2.92 (dd, 1 H, *J* = 13.2, 10.5 Hz), 2.63 (dd, 1 H, *J* = 13.2, 9.9 Hz), 1.53 (s, 18 H), 1.38 (s, 3 H); ^{13}C NMR (CD_3OD) δ 174.4, 153.2, 85.5, 76.5, 67.2, 60.9, 60.5, 59.2, 58.0, 54.9, 34.7, 28.3, 23.7.

[3*S*,3(2′*E*,4′*E*,6′*S*),5*S*,6*S*,7*R*,8*S*,9*S*,10*R*]-3-[(4′,6′-Dimethyl-2′,4′-dodecadienoyl)amino]-6,7:9,10-diepoxy-8-hydroxy-8-(hydroxymethyl)-1-oxaspiro[4.5]decan-2-one (31). A solution of 25 mg (0.041 mmol) of diepoxide **21** in 2 mL of dry MeOH was treated with 10 mg of $Pd(OH)_2$/C (20%) under H_2 atmosphere. After 2 h at 22 °C, the reaction mixture was filtered through Celite. To the resulting solution was added at 5 °C a preformed solution of 19 mg (0.083 mmol) of acid **13**, 20 mg (0.082 mmol) of diphenylphosphinic chloride, and 34 mg (0.340 mmol) of *N*-methylmorpholine in 1 mL of dry THF. Stirring was continued for 3 h at 5 °C. The reaction mixture was concentrated and the residue was chromatographed on SiO_2 (20% EtOAc/MeOH) to give 12.5 mg (40%) of diol **31**: TLC R_f = 0.32 (67% $CHCl_3$/hexanes); ^1H NMR ($CDCl_3$/DMSO-d_6) δ 7.96 (d, 1 H, *J* = 7.4 Hz), 6.93 (d, 1 H, *J* = 15.4 Hz), 5.62 (d, 1 H, *J* = 15.4 Hz), 5.34 (d, 1 H, *J* = 9.8 Hz), 4.46 (ddd, 1 H, *J* = 10.3, 10.0, 7.4 Hz), 3.35 (s, 2 H), 3.25 (dd, 1 H, *J* = 3.4, 3.0 Hz), 3.08 (dd, 1 H, *J* = 3.3, 3.0 Hz), 3.00–2.95 (m, 2 H), 2.51 (dd, 1 H, *J* = 13.7, 10.3 Hz), 2.28–2.15 (m, 1 H), 2.09 (dd, 1 H, *J* = 13.7, 10.0 Hz), 1.50 (s, 3 H), 1.05–0.95 (m, 10 H), 0.70 (d, 3 H, *J* = 6.6 Hz), 0.60 (t, 3 H, *J* = 6.2 Hz); ^{13}C NMR (DMSO-d_6) δ 174.4, 165.5, 146.6, 145.2, 130.9, 118.2, 79.9, 68.8, 65.7, 58.7, 57.7, 56.7, 48.3, 36.7, 34.0, 32.5, 31.3, 28.8, 26.9, 22.1, 20.6, 14.0, 12.4; MS (EI) *m/z* (rel inten) 449 (M$^+$, 7), 431 (1), 418 (2), 392 (2), 385 (1), 365 (5), 350 (20), 336 (30), 323 (15), 299 (10), 250 (10), 217 (25), 206 (35), 199 (20), 179 (50), 162 (10), 149 (20), 139 (20), 121 (60), 109 (25), 95 (100), 77 (30), 66 (30), 55 (40).

[3*S*,3(2′*E*,4′*E*,6′*R*),5*S*,6*S*,7*R*,8*S*,9*S*,10*R*]-3-[(4′,6′-Dimethyl-2′,4′-dodecadienoyl)amino]-6,7:9,10-diepoxy-8-hydroxy-8-(hydroxymethyl)-1-oxaspiro[4.5]decan-2-one (32). According to the procedure described for **31**, 41 mg (0.068 mmol) of diepoxide **21** and 31 mg (0.136 mmol) of acid **17** afforded 13 mg (42%) of diol **32**: TLC R_f = 0.32 (67% $CHCl_3$/hexanes); ^1H NMR (DMSO-d_6) δ 8.68 (d, 1 H, *J* = 7.4 Hz), 7.06 (d, 1 H, *J* = 15.5 Hz), 5.90 (d, 1 H, *J* = 15.5 Hz), 5.65 (d, 1 H, *J* = 9.7 Hz), 5.58 (s, 1 H), 5.08 (broad s, 1 H), 4.74 (ddd, 1 H, *J* = 10.7, 9.5, 7.4 Hz), 3.52 (dd, 1 H, *J* = 3.6, 2.8 Hz), 3.42–3.38 (m, 3 H), 2.57 (dd, 1 H, *J* = 13.5, 10.7 Hz), 2.60–2.45 (m, 1 H), 2.17 (dd, 1 H, *J* = 13.5, 9.5 Hz), 1.73 (s, 3 H), 1.35–1.15 (m, 10 H), 0.93 (d, 3 H, *J* = 6.5 Hz), 0.83 (t, 3 H, *J* = 6.2 Hz); ^{13}C NMR (DMSO-d_6) δ 174.6, 165.7, 146.9, 145.5, 131.1, 118.2, 80.1, 68.9, 65.6, 58.7, 57.8, 56.8, 48.4, 36.9, 34.0, 32.7, 31.4, 28.9, 27.1, 22.2, 20.7, 14.1, 12.5; MS (EI) *m/z* (rel inten) 449 (M$^+$, 30), 437 (10), 418 (10), 364 (25), 350 (15), 336 (40), 323 (10), 306 (10), 263 (10), 252 (20), 222 (30), 206 (50), 191 (10), 179 (60), 166 (20), 149 (30), 139 (25), 132 (20), 121 (50), 107 (30), 95 (100), 78 (30), 69 (30), 63 (40), 55 (40).

Aranorosin. A solution of 12 mg (0.027 mmol) of diol **32** and 50 mg (0.134 mmol) of $CeCl_3 \cdot 7H_2O$ in 0.8 mL of 5:3 EtOH/H_2O was treated at −25 °C with 2 mg (0.054 mmol) of $NaBH_4$. After 30 min, several drops of acetone were added to the reaction mixture. The solution was diluted with 10 mL of EtOAc, washed with brine, and the organic layer was dried (Na_2SO_4) and concentrated. The oily residue was diluted with 1 mL of MeOH and a solution of 17 mg (0.081 mmol) of $NaIO_4$ in 0.3 mL of H_2O was added. After 30 min, the reaction mixture was diluted with 15 mL of EtOAc and washed with 10 mL of brine. The organic layer was dried (Na_2SO_4), concentrated in vacuo, and chromatographed on SiO_2 (75% CH_2Cl_2/EtOAc) to give 6 mg (55%) of a 4:1 ratio of lactol epimers of aranorosin (**1**) as a white solid: TLF R_f = 0.50 (86% $CHCl_3$/MeOH); mp 148 °C dec; $[\alpha]_D$ −7.7°, $[\alpha]_{546}$ −9.4°, $[\alpha]_{365}$ −41.3° (*c* 0.21, $CHCl_3$, 21 °C); $[\alpha]_D$ −21.1°, $[\alpha]_{546}$ −24.1°, $[\alpha]_{365}$ −84.7° (*c* 0.21, MeOH, 21 °C); IR (CH_2Cl_2) 3295, 2957, 2926, 2855, 1725, 1702, 1649, 1613, 1530, 1453, 1343, 1244, 1115, 1026, 982, 928, 882, 845, 791, 737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26 (d, 1 H, *J* = 15.3 Hz), 6.10 (d, 1 H, *J* = 8.3 Hz), 5.76 (d, 1 H, *J* = 15.3 Hz), 5.70–5.60 (m, 2 H), 4.80 (ddd, 1 H, *J* = 10.7, 8.7, 8.3 Hz), 4.39 (broad s, 1 H), 3.69 (t, 1 H, *J* = 3.7 Hz), 3.57 (t, 1 H, *J* = 3.6 Hz), 3.48–3.43 (m, 2 H), 2.63 (dd, 1 H, *J* = 13.0,

8.7 Hz), 2.58–2.48 (m, 1 H), 2.03 (dd, 1 H, J = 13.0, 10.7 Hz), 1.77 (s, 3 H), 1.40–1.20 (m, 10 H), 0.97 (d, 3 H, J = 6.6 Hz), 0.86 (t, 1 H, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 198.4, 166.7, 148.6, 147.5, 130.9, 116.9, 96.7, 79.1, 64.3, 62.9, 55.9, 55.6, 52.1, 37.3, 36.0, 33.3, 31.9, 29.5, 27.5, 22.7, 20.6, 14.2, 12.6; MS (EI) m/z (rel inten) 419 (M^+, 5), 401 ($[M - H_2O]^+$, 80), 386 (10), 330 (10), 316 (25), 306 (20), 288 (100), 277 (10), 248 (10), 237 (10), 222 (10), 207 (40), 195 (10), 179 (30), 166 (10), 150 (20), 136 (20), 121 (60), 109 (50), 95 (100), 79 (30), 69 (40); HRMS (EI) calcd for $C_{23}H_{31}NO_5$ ($M - H_2O$) 401.2202, found 401.2165.

Natural aranorosin after purification: $[\alpha]_D$ −7.8°, $[\alpha]_{546}$ −8.4°, $[\alpha]_{365}$ −44.6° (c 0.17, $CHCl_3$, 21 °C); $[\alpha]_D$ −19.6°, $[\alpha]_{546}$ −23.0°, $[\alpha]_{365}$ −84.6° (c 0.17, MeOH, 21 °C).

6′-*epi*-Aranorosin. According to the procedure described for 1, 8.1 mg (0.018 mmol) of diol **31** afforded 4.3 mg (57%) of a 4:1 ratio of lactol epimers of 6′-*epi*-aranorosin as a white solid: TLF R_f = 0.50 (86% $CHCl_3$/MeOH); mp 145 °C dec; $[\alpha]_D$ +34.6° (c 0.15, $CHCl_3$, 21 °C); $[\alpha]_D$ +32.0°, $[\alpha]_{546}$ +39.7°, $[\alpha]_{365}$ +155.1° (c 0.36, MeOH, 21 °C); IR (CH_2Cl_2) 3295, 2957, 2926, 2855, 1711, 1651, 1612, 1535, 1455, 1344, 1266, 1244, 1117, 1026, 984, 928, 882, 790, 737, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.26 (d, 1 H, J = 15.3 Hz), 6.04 (d, 1 H, J = 8.2 Hz), 5.76 (d, 1 H, J = 15.3 Hz), 5.67 (d, 1 H, J = 9.9 Hz), 5.63–5.62 (m, 1 H), 4.78 (ddd, 1 H, J = 10.0, 8.6, 8.2 Hz), 3.87 (broad s, 1 H), 3.67 (t, 1 H, J = 3.5 Hz), 3.55 (t, 1 H, J = 3.5 Hz), 3.52–3.44 (m, 2 H), 2.61 (dd, 1 H, J = 13.0, 8.6 Hz), 2.58–2.48 (m, 1 H), 2.04 (dd, 1 H, J = 13.0, 10.0 Hz), 1.77 (s, 3 H), 1.40–1.20 (m, 10 H), 0.97 (d, 3 H, J = 6.6 Hz), 0.86 (t, 1 H, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 198.4, 166.8, 148.6, 147.5, 130.9, 117.0, 96.7, 79.1, 64.3, 63.0, 55.9, 55.6, 52.1, 37.3, 36.1, 33.3, 31.9, 29.5, 27.6, 22.7, 20.6, 14.2, 12.6; MS (EI) m/z (rel inten) 419 (M^+, 10), 401 ($[M - H_2O]^+$, 40), 391 (6), 285 (5), 330 (15), 316 (20), 306 (15), 288 (40), 277 (10), 250 (12), 224 (20), 207 (90), 179 (60), 149 (15), 136 (15), 121 (40), 109 (30), 95 (100), 79 (30), 69 (40), 55 (50); HRMS (EI) calcd for $C_{23}H_{31}NO_5$ ($M - H_2O$) 401.2202, found 401.2194.

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra for compounds **6**, **11–15**, **17**, **18**, **21–26**, **31**, **32**, 6-*epi*-aranorosin, synthetic aranorosin, and natural aranorosin and impurities; 1D NOE studies for **25**, **26**, and synthetic aranorosin (43 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.