and the extent of CF bond breaking. In general, the more exothermic the reaction the less advanced the transition structure, in accord with the Hammond postulate. Nevertheless, the reactions of oxygen nucleophiles have lower activation energies than those of carbon nucleophiles. The extent of distortion of the enolate system is slightly larger during C-alkylation than during O-alkylation, but in both transition structures, the enolate moiety is distorted about 50% from the geometry of the reactant to that of a product. Analysis of the Mulliken charges indicates that a similar extent of charge transfer (35%) from enolate to methyl fluoride occurs in the transition structures for both C- and O-alkylation, whereas qualitative arguments predict a constant 50% charge transfer.[20]

There are obvious similarities between the transition structures of the enolate alkylations and the geometries of the products. The angle of approach of the electrophilic methyl fluoride on the enolate carbon is 106°, only slightly smaller than the corresponding CCC angle in the product. Attack occurs in a plane perpendicular to the enolate plane as shown in A. This agrees with the empirical deductions by Corey about the stereoelectronic factors controlling the direction of attack of electrophiles on enolates.[6,7] None of the deviation from perpendicular attack proposed by Agami[8] is observed, but it is possible that the earlier transition states for MeI reactions could have such distortions.

Attack on oxygen occurs in the plane of the enolate, syn to the double bond, and with a CO—C angle of 119°. These geometrical features are identical with those of the product of O-alkylation, and the energetic preference for this geometry is similar to that found in the product.[21] The reactant complex (not shown) has a CO—C angle of 134°, which places the electrophilic methyl fluoride at the site of the largest negative electrostatic potential. The stereoelectronic preference for syn-O-alkylation is related to the suggestion by Gandour that syn-attack of electrophiles such as a proton will be favored for carboxylates.[22] In both cases, the electrophile approaches the oxygen in such a manner as to minimize internal electrostatic repulsions between oxygen lone pairs and the π electron density at the other terminus of the π system. Similarly, stereoelectronic effects generally favor product-like conformations in transition structures of a variety of organic reactions.[23,24] In general, reactions with activation barriers, even those with early transition states, have conformational preferences resembling those of products.

Acknowledgment. We are grateful to the National Science Foundation and the National Institutes of Health for financial support of this research.

Registry No. CH_2=CH—O^-, 35731-40-9; CH_3F, 593-53-3.

(20) Pross, A.; Shaik, S. S. *Acc. Chem. Res.* **1983**, *16*, 363.

(21) Rigid rotation of this transition structure into the planar *anti* geometry causes an energy increase of 1.2 kcal/mol, while rotation to a geometry with methyl fluoride attack in a plane perpendicular to the enolate plane increases the energy by 4.4 kcal/mol. Changing the CO—C angle from 119° to 180° causes an energy increase of 14.2 kcal/mol. These energy changes are only slightly smaller than those calculated at the 4-31G level for methyl vinyl ether: John, I. G.; Radom, L. *J. Mol. Struct.* **1977**, *36*, 133.

(22) Gandour, R. D. *Bioorg. Chem.* **1981**, *10*, 169.

(23) Deslongchamps, P. "Stereoelectronic Effects in Organic Chemistry"; Pergamon: Oxford, 1983.

(24) Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N., *J. Am. Chem. Soc.*, **1982**, *104*, 7162.

Milbemycin–Avermectin Studies. 5. Total Synthesis of Milbemycin β_3 and Its C(12) Epimer[1]

Steven R. Schow, Jonathan D. Bloom, Andrew S. Thompson, Kevin N. Winzenberg, and Amos B. Smith, III*[2]

Contribution from the Department of Chemistry, The Laboratory for Research on the Structure of Matter, and The Monell Chemical Senses Center, The University of Pennsylvania, Philadelphia, Pennsylvania 19104. *Received September 16, 1985*

Abstract: The total synthesis of milbemycin β_3 (**1**) and its epimer, 12-epimilbemycin β_3, is described. The central features of the synthetic strategy are (a) construction of the spiro ketal unit by nitrile oxide dipolar addition, (b) introduction of the requisite C(12) methyl center via a chelation-controlled cuprate addition in tandem with a stereocontrolled Ireland–Claisen rearrangement, and (c) construction of the southern hemisphere via a novel S_N2' reaction of lithium diphenylphosphide with a γ-vinyl-γ-lactone (i.e., **10**).

In 1974, Mishima et al.[3] announced the isolation and structure elucidation of the milbemycins, a new family of architecturally novel antibiotics, the simplest member of which is milbemycin β_3 (**1**). Now numbering 20 members, the milbemycins possess remarkably potent insecticidal activity.[4] Contemporary with this discovery, the Merck group, led by Albers-Schonberg, uncovered

(1) For the previous paper in this series, see: Smith, A. B., III; Kilenyi, S. N. *Tetrahedron Lett.* **1985**, *26*, 4419. See also: Smith, A. B., III; Thompson, A. S. *Tetrahedron Lett.* **1985**, *26*, 4279. Smith, A. B., III; Thompson, A. S. *Tetrahedron Lett.* **1985**, *26*, 4283.

(2) Camille and Henry Dreyfus Teacher Scholar, 1978–1983; National Institutes of Health (National Cancer Institute) Career Development Award, 1980–1985; J. S. Guggenheim, 1985–1986.

(3) Symposium Abstracts of the 18th Symposium on the Chemistry of Natural Products, Kyoto, Japan, 1974; pp 309.

(4) (a) Milbemycins β_1–β_3: Mishima, H.; Kurabayashi, M.; Tamura, C. *Tetrahedron Lett.* **1975**, 711. (b) Milbemycins α_1–α_{10} and β_1–β_3: Takiguchi, Y.; Mishima, H.; Okuda, M.; Terao, M.; Aoki, A.; Fukuda, R. *J. Antibiot.* **1980**, *33*, 1120. (c) Milbemycins D–K: Okazaki, T.; Ono, M.; Muramatsu, S.; Ide, J.; Mishima, H.; Terao, M. *J. Antibiot.* **1983**, *36*, 502. Ono, M.; Mishima, H.; Takiguchi, Y.; Terao, M. *J. Antibiot.* **1983**, *36*, 509. Mishima, H.; Ide, J.; Muramatsu, S.; Ono, M. *J. Antibiot.* **1983**, *36*, 980. (d) Biosynthetic studies: Ono, M.; Mishima, H.; Takiguchi, Y.; Terao, M.; Kobayashi, H.; Iwasaki, S.; Okuda, S. *J. Antibiot.* **1983**, *36*, 991.

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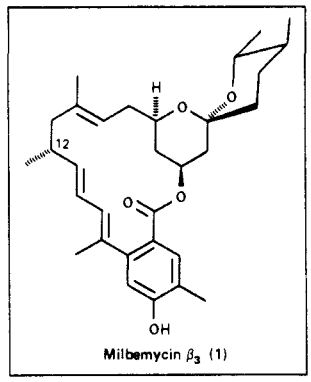
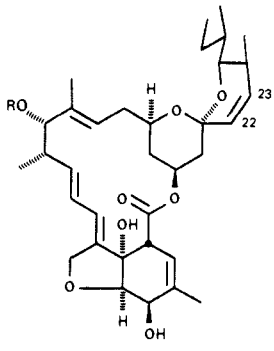
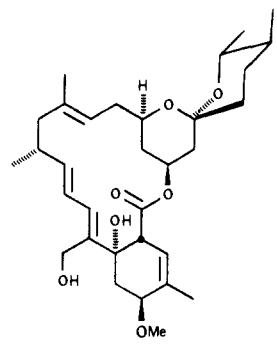
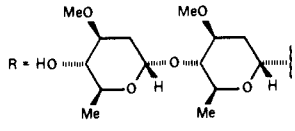






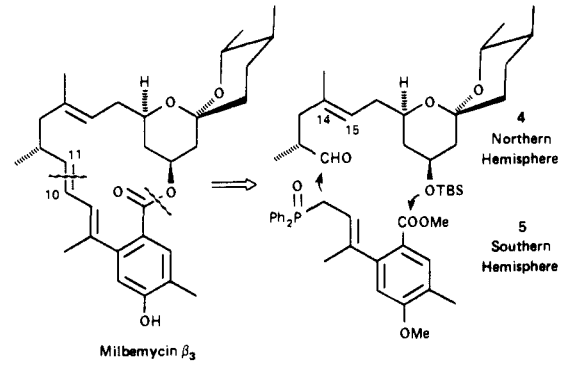


a closely related class of antibiotics which they termed the avermectins [e.g., β_{1a} (**2**)],[5] the most notable difference being the presence of a disaccharide unit attached at C(13). In addition to the insecticidal activity, the avermectins proved to be extremely potent anthelmintic agents.[6] This observation led Merck to develop and market a broad spectrum anthelmintic drug known as Ivermectin.

Structural assignments for the milbemycins, initially based on detailed ^1H and ^{13}C NMR analyses in conjunction with high-resolution mass spectral data, were secured through aegis of a single-crystal X-ray analysis of milbemycin β_1 (**3**).[4a] The central structural features of the milbemycin-avermectin class proved to be the spiro pyranoketal unit, the 16-membered macrolide ring, and in the case of the more complex members, the highly functionalized mono- or bicyclic "southern hemisphere".

In this, a full account, we record the first total synthesis of milbemycin β_3 and its C(12) epimer **1b**. We note in advance that our approach is short (longest linear sequence, 16 steps), convergent, and for the most part highly stereocontrolled. Furthermore, significant improvements have been made in the synthetic sequence since we first[7] announed completion of milbemycin β_3 in 1982.[8,9]

Synthetic Strategy for Milbemycin β_3. At the outset we set as our principal goal the development of a unified strategy that would not only afford milbemycin β_3 but also the more complex members of the avermectin–milbemycin class, as well as structural analogues of potential biological interest. Toward this end, strategic disconnections at the ester and C(10,11) olefinic linkages led to northern and southern hemispheres **4** and **5**, respectively. Given the structural similarity of many of the avermectins and milbemycins, development of an effective approach to the β_3 northern unit would fulfill our requirement for a unified approach.



For union, we envisioned a Horner–Wittig coupling[10] between aldehyde **4** and phosphine oxide **5**, followed by closure of the 16-membered ring by employing one of the now numerous lactonization protocols.[11] The requisite phosphine oxide **5**, a vinylogously stabilized Horner–Emmons reagent, was anticipated to afford the desired *E* configuration at the C(10,11) linkage, due to the extended conjugation inherent in the phosphine oxide structure.[12]

A detailed inspection of the northern hemisphere **4** suggested that the requisite trisubstituted (*E*)-olefin at C(14,15) and the secondary methyl at C(12) could be installed in a stereocontrolled fashion via an Ireland–Claisen rearrangement[13] of propionate **6**. This ester in turn was seen to derive from aldehyde **7** via addition of an isopropenyl unit followed by acylation. For complete stereocontrol, it would be essential that both the addition of the isopropenyl unit and the Ireland–Claisen rearrangement proceed with high stereoselectivity.

Further analysis of the northern hemisphere was facilitated by recognition that aldehyde **7** is thermodynamically the most stable of all possible isomers possessing this connectivity. In particular, the spiro ketal benefits markedly from the anomeric effect.[14]

(5) For leading references on the avermectins, see: Albers-Schonberg, G.; Arison, B. H.; Chabala, J. C.; Douglas, A. W.; Eskola, P.; Fisher, M. H.; Hirshfield, J. M.; Hoogsteen, K.; Lusi, A.; Mrozik, H.; Smith, J. L.; Springer, J. P.; Tolman, R. L. *Intersci. Conf. Antimicrob. Agents Chemother.* **1978**, Abstract No. 464. Albers-Schonberg, G.; Arison, B. H.; Chabala, J. C.; Douglas, A. W.; Eskola, P.; Fisher, M. H.; Lusi, A.; Mrozik, H.; Smith, J. L.; Tolman, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 4216. Springer, J. P.; Arison, B. H.; Hirshfield, J. M.; Hoogsteen, K. *J. Am. Chem. Soc.* **1981**, *103*, 4221.

(6) Egerton, J. R.; Ostlind, D. A.; Blair, L. S.; Eary, C. H.; Suhayda, D.; Cifelli, S.; Riek, R. F.; Campbell, W. F. *Antimicrob. Agents. Chemother.* **1979**, *15*, 372. Ostlind, D. A.; Cifelli, S.; Lang, R. *Vet. Rec.* **1979**, *105*, 168.

(7) Smith, A. B., III; Schow, S. R.; Bloom, J. D.; Thompson, A. S.; Winzenberg, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 4015. Shortly after our work appeared, Professor David Williams (Indiana University) reported completion of a total synthesis of (+)-milbemycin β_3; see ref 8.

(8) Williams, D. R.; Barner, B. A.; Nishitani, K.; Phillips, J. G. *J. Am. Chem. Soc.* **1982**, *104*, 4708.

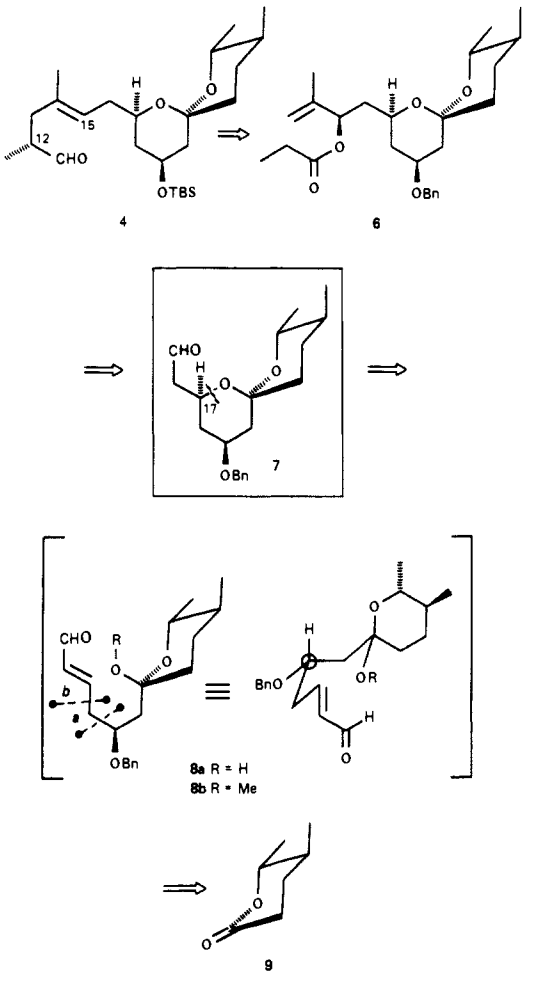
(9) For reports on synthetic approaches to the milbemycin–avermectin class, see: Attwood, S. V.; Barrett, A. G. M.; Florent, J. C. *J. Chem. Soc., Chem. Commun.* **1981**, 556. Baker, R.; Boyes, R. H. O.; Broom, D. M. P.; Devlin, A.; Swain, C. J.; *J. Chem. Soc., Chem. Commun.* **1983**, 829. Turnbull, M. D.; Matter, G.; Ledgerwood, D. E. *Tetrahedron Lett.* **1984**, 5449. Hughes, M. J.; Thomas, E. J.; Turnbull, M. D.; Jones, R. H.; Warner, R. E. *J. Chem. Soc., Chem. Commun.* **1985**, 755. Kay, I. T.; Turnbull, M. D. "Synthetic Approaches to the Avermectin Toxophore" In *Recent Advances in the Chemistry of Insect Control*; James, N. F., Ed.; The Royal Society of Chemistry Burlington House: London, 1985; p 229. Baker, R.; Swain, C. J.; Head, J. *Recent Advances in the Chemistry of Insect Control*; p 245. Attwood, S. V.; Barrett, A. G. M.; Carr, R. A.; Finch, M. A. W.; Richardson, G. *Ibid.* p 257.

(10) Horner, L.; Hoffmann, H.; Wippel, H. G. *Chem. Ber.* **1958**, *91*, 61. For the use of allylic phosphine oxide stabilized anions, see: Lythgoe, B.; Moran, T. A.; Nambudiry, M. E. N.; Ruston, S.; Tideswell, J.; Wright, P. W. *Tetrahedron Lett.* **1975**, 3863.

(11) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, *49*. Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614. Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, 16, 585.

(12) Cadogan, J. I. G. *Organophosphorus Reagents in Organic Synthesis*; Academic: London, 1979; Chapter 2.

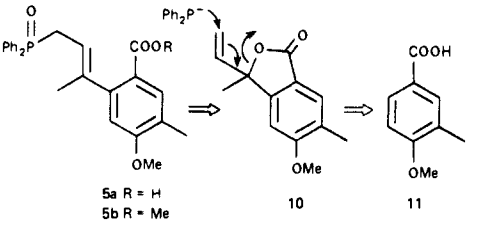
(13) (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1972**, *94*, 897. (b) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.



Furthermore, the alkyl and alkoxy substituents occupy equatorial positions. Thus we could be confident that generation of the spiro ketal system under equilibrating (i.e., thermodynamic) conditions would lead to spiro ketal **7** as the major, if not the sole, product.[15] Continuing with this analysis, disconnection at the C(17) carbon–oxygen bond of **7** led to enal **8a**. Here we anticipated that a "Michael-like" closure under equilibrating conditions would occur so as to minimize 1,3-diaxial interactions between the pyran ring and the substituent at C(17), thereby delivering the benzyloxy and acetaldehyde units with the desired equatorial orientation.[16]

To execute this strategy, we required an effective protocol to append a six-carbon chain containing an acrolein unit onto lactone **9**.[17] As will be discussed, we explored a number of strategies involving a [2 + 4] and [3 + 3] stepwise buildup of the requisite six-carbon chain (see disconnections a and b, respectively, in structure **8**). In each case, we took advantage of the propensity of δ-valerolactones (i.e., **9**) to undergo monoaddition with organometallic reagents at low temperature.[18] In retrospect, elaboration of aldehyde **8** and its conversion to spiro ketal **7** proved to be the central challenge of the β_3 synthetic venture.

For construction of the southern hemisphere **5**, we envisioned a novel S_N2' addition of lithium diphenylphosphide[19] to lactone **10**. A significant question here concerned the stereochemical outcome of the S_N2' process.[20] Lactone **10** in turn was seen to derive from 3-methyl-*p*-anisic acid (**11**) (vide infra).



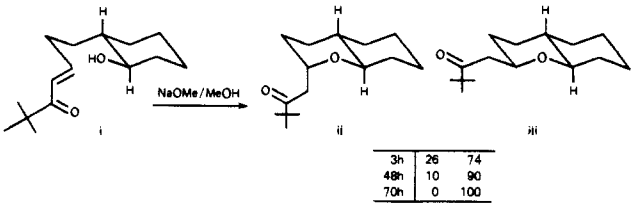
Results and Discussion

The [2 + 4] Strategy: An Initial Assault on the Milbemycin Spiro Ketal Unit. To explore the feasibility of a [2 + 4] construction of spiro ketal **7**, we initiated a model study employing commercially available δ-valerolactone (**12**). Treatment of **12** with allyl Grignard in THF at −78 °C afforded an unstable hemiketal **13a**, which was converted without purification to mixed methyl ketal **13b** via treatment with trimethyl orthoformate containing a catalytic amount of $CeCl_3$.[21] Ozonolysis followed by reduction with triphenylphosphine gave aldehyde **14**.[22] Subsequent addition of the dianion derived from ethyl acetoacetate led to a mixture

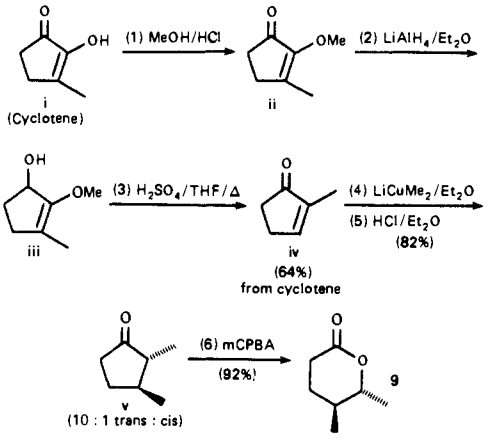
(14) For an excellent review of the anomeric effect, see: (a) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: New York, 1983. (b) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Toronto, 1983; Chapter 2.

(15) For earlier exploiting examples of the anomeric effect to control the stereochemistry of spiro ketals, see: Evans, D.; Sacks, C.; Kleschick, W.; Taber, T. *J. Am. Chem. Soc.* **1979**, *101*, 6789. Fukuyama, T.; Akasaka, K.; Karanewsky, D.; Wang, C.; Schmid, G.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 262. Kishi, Y. *Lect. Heterocycl. Chem.* **1980**, *5*, 595.

(16) After completion of an β_3 synthesis, Seebach reported an interesting example of the equilibration of an α,β-unsaturated ketone system (i.e., ii → iii). Other work from our laboratory suggest that similar equilibrations are feasible with aldehydes and ketones but not esters. Seebach, D.; Pohmakotr, M.; Schregenberger, C.; Weidman, B.; Mali, R. S.; Ophmakotr, S. *Helv. Chim. Acta* **1982**, *65*, 419.



(17) Lactone **9** has been prepared in our laboratory in both racemic and chiral forms, and latter from (−)-citronellol. The racemic approach beginning with cyclotene is illustrated below. For other approaches to lactone **9**, see: Dev, S.; Rai, C. *J. Ind. Chem. Soc.* **1975**, *34*, 266. Honkanen, E.; Moisio, T.; Karvonen, P.; Virtanen, A. I. *Acta Chem. Scand.* **1968**, *22*, 2041.



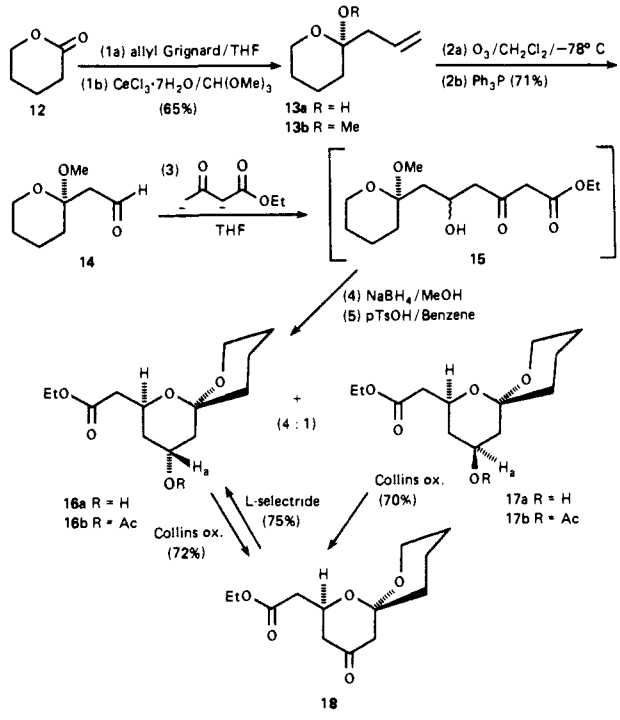
(18) (a) Duggan, A.; Adams, M.; Brynes, P.; Meinwald, J. *Tetrahedron Lett.* **1978**, 4323. Duggan, A.; Adams, M.; Meinwald, J. *Tetrahedron Lett.* **1978**, 432. (b) Raphael, R.; Colvin, E.; Roberts, J. *Chem. Commun.* **1971**, 858. Chabala, J.; Vincent, J. *Tetrahedron Lett.* **1978**, 937.

(19) Mann, F. G.; Tong, B. P.; Wystrach, V. P. *J. Chem. Soc.* **1963**, 1155. Mann, F. G.; Pragnell, M. J. *J. Chem. Soc.* **1965**, 4120. Ireland, R. E.; Welch, S. C. *J. Am. Chem. Soc.* **1970**, *92*, 7232.

(20) For a review on the S_N2' process, see: Magid, M. R. *Tetrahedron*, **1980**, *36*, 1901.

(21) For one example of $CeCl_3$ as a catalyst in ketalization, see: Luche, J.-L.; Gemal, A. L. *J. Chem. Soc., Chem. Commun.* **1978**, 976.

(22) Monoaddition of acetaldehyde equivalents (i.e., the dimethylhydrazone of acetaldehyde or the lithium anion of *tert*-butyl acetate) proved unworkable. That is, while these reagents could be added successfully to δ-valerolatcone, no further transformations could be effected. For example, all attempts to effect hydrolysis of the hydrazone or ketalization of the resultant adducts led to decomposition. Presumably, this is a result of the unstable nature of aldehyde **14**.

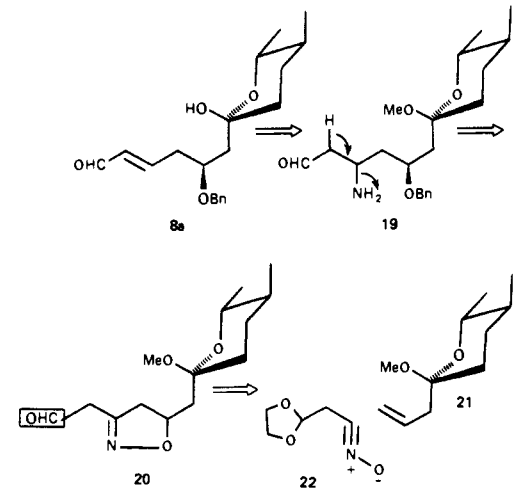


of unstable alcohols, **15**, which were directly reduced with excess sodium borohydride and then treated with a catalytic amount of *p*-toluenesulfonic acid in dry benzene to yield spiro ketals **16a** and **17a** in 31% and 8% yield, respectively.

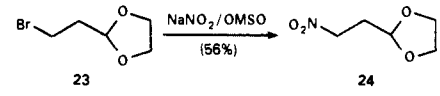
Structural assignments for **16a** and **17a** were based on a combination of spectroscopic and chemical observations. Particularly significant were the multiplicities observed for the C(19) protons (H_a) in the derived acetates **16b** and **17b**. For example, in **17b** this resonance displayed a broad septet centered at δ 5.18 with a peak width at half-height of 30.4 Hz. A similar pattern is present in milbemycin β_3.[4] Acetate **16b** on the other hand presented the C(19) proton as a multiplet centered at δ 5.05, with a peak width at half-height of 9.6 Hz.[23]

Chemical evidence for the structure and stereochemistry of **16a** and **17a** derived from Collins[24] oxidation of each alcohol to a common ketone **18**, which in turn underwent reduction with L-Selectride to yield a single alcohol, identical in all respects with the major alcohol (i.e., **16a**) obtained from aldehyde **14**. Given the propensity for L-Selectride to afford axial alcohols,[25] in conjunction with the above chemical correlation and spectral data, we concluded that the major product **16a** possessed the *undesired* stereochemistry at C(19) vis-à-vis milbemycin β_3. Unfortunately, all attempts to improve the stereochemical outcome of the [2 + 4] sequence, including the addition of metal salts ($MgCl_2$, $ZnCl_2$, or CuBr·DMS) and/or the use of different cosolvents, proved unsuccessful.

The [3 + 3] Strategy: Elaboration of Spiro Ketal 7. Having limited success with the [4 + 2] strategy, we turned to the development of a [3 + 3] strategy. We conjectured that the desired α,β-unsaturated aldehyde **8a**, precursor to spiro ketal **7**, might be prepared at least as a reactive intermediate from isoxazoline **20** which in turn could be constructed in a single operation via a 1,3-dipolar addition of nitrile oxide **22** to ketal **21** (i.e., a [3 + 3] strategy). Exhaustive reduction of the isoxazoline nitrogen–oxygen and carbon–nitrogen bonds followed by elimination of the β-amino group and acid hydrolysis of the methyl ketal would then lead to α,β-unsaturated aldehyde **8a** and in turn to aldehyde **7**.[26]



To explore this approach, we required a viable source of olefin **21** as well as an appropriate precursor of nitrile oxide **22**. Toward this end, ketal **21** was prepared in multigram quantities from known lactone **9**[17] by employing the procedure previously outlined for the desdimethyl system. A serviceable precursor of nitrile oxide **22** proved to be the ethylene ketal of 3-nitropropanal (**24**), which in turn was available from the ethylene ketal of 3-bromopropanal (**23**)[29] via treatment with $NaNO_2$ in Me_2SO.



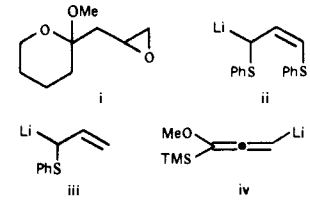
With both **21** and **24** in hand, nitrile oxide **22** was generated in the presence of **21** via treatment with methyl isocyanate[30] and a catalytic amount of triethylamine. The result was a 2:1 mixture (68%) of isoxazolines **25a** and **25b**.[31] Fortunately, this mixture proved to be of little long-term consequence. That is, reduction with $LiAlH_4$ led in near quantitative yield to amino alcohols **26a–d**, which in turn were treated with excess KH and 1.1 equiv of benzyl iodide followed by excess methyl iodide and finally aqueous acid. The result was a *single* crystalline aldehyde (**7**)! While the overall yield was only 24–30%, the economy of operations (i.e., five steps)

(23) Such multiplicities, and in particular peak widths at half-height, are characteristic of the axial and equatorial orientations; see: Jackman, M. L.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*; Pergamon: Oxford, 1969; pp 238–241 and references cited therein.

(24) Collins, J. C.; Hess, W. W.; Frank, F. J. *Tetrahedron Lett.* **1968**, 3363.

(25) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159.

(26) Initial efforts with the [3 + 3] strategy focused on epoxide i, available as a 1:1 mixture of diastereomers upon *m*-CPBA epoxidation of **13b** in the presence of sodium bicarbonate. With this epoxide in hand, nucleophilic addition of an appropriate three-carbon unit and cyclization would complete construction of the spiro ketal system. Unfortunately, all attempts to effect nucleophilic opening of epoxide i by employing a variety of α-acyl vinyl anion equivalents (e.g., ii and iii[27] or iv[28]) met with little or no success.



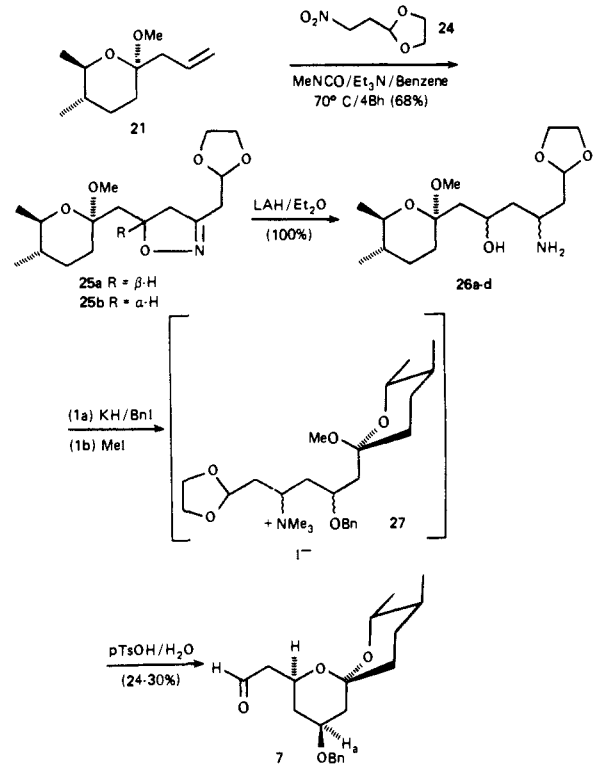
(27) Corey, E. J.; Erickson, B. W.; Noyori, R. *J. Am. Chem. Soc.* **1971**, *93*, 1974. Cohen, T.; Bennett, D. A.; Mura, A. J. *J. Org. Chem.* **1976**, *41*, 2506.

(28) Reich, H. J.; Kelly, M. J. *J. Am. Chem. Soc.* **1982**, *104*, 1119.

(29) Buchi, G.; Wuest, H. *J. Org. Chem.* **1969**, *34*, 1122. For a recent example of the nitrile oxide derived from **24**, see: Kozikowski, A. P.; Li, Chan-Sing *J. Org. Chem.* **1985**, *50*, 778.

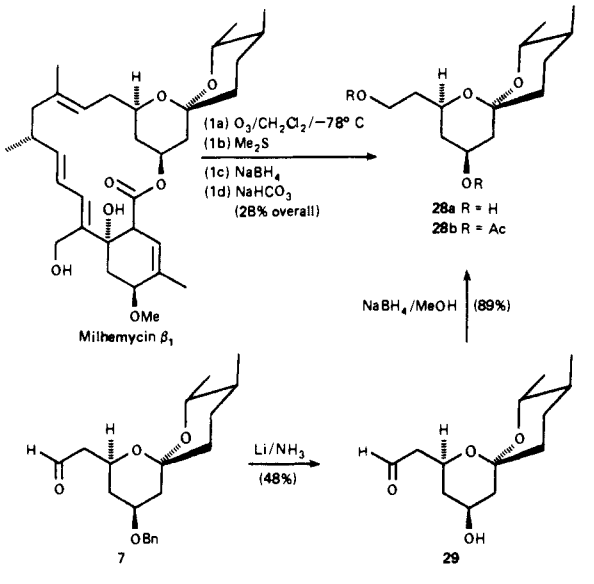
(30) The choice of methyl isocyanate in place of the more commonly employed phenyl isocyanate was based on the observation that the byproduct, dimethylurea, is water soluble, whereas diphenylurea is not. For use of phenyl isocyanate, see: Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339.

(31) While at the time we were unable to assign the stereostructures to diastereomers **25a** and **25b**, we did attempt to modify the observed ratio. However, given the inability of others to control the stereoselectivity of intermolecular nitrile oxide addition, it came as no surprise that we also were unable to improve the selectivity; see: Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826.



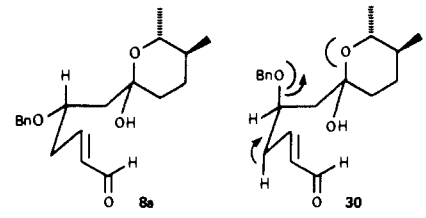
more than compensated for the modest yield. That the desired aldehyde was in hand was suggested by the characteristic septet (δ 3.92, H_a) in the ^1H NMR spectrum identical with the pattern observed previously for the C(19) axial hydrogen in model spiro ketal **17b**.

Degradation of Milbemycin β_1: A Structure Proof of 7. To secure rigorously the structure and stereochemistry of spiro ketal **7**, we undertook a chemical degradation of milbemycin β_1, a sample of which was kindly provided by Dr. Takiguchi.[32] Our focus here was to liberate the spiro ketal unit and thereby provide an intermediate for spectral comparison. Toward this end, ozonolysis of β_1 followed by reduction with $NaBH_4$ and saponification with aqueous $NaHCO_3$ afforded diol **28a**; the yield for the three-step sequence was 28%.



To correlate our synthetic material with diol **28a**, the benzyl protecting group in **7** was removed with lithium in liquid ammonia; direct formation of diol **28a** was anticipated. Somewhat surprisingly, however, aldehyde **29** was obtained. This result is understandable if the aldehyde carbonyl is protected in situ during the dissolving metal reduction via transient aminal formation. With **29** available, hydride reduction afforded a diol which proved identical with that derived from milbemycin β_1; comparisons here were made both on the diols (**28a**) and the corresponding diacetates (**28b**).

A Detailed Examination of the Spiro Ketal Reaction Sequence: Cornerstone of the Milbemycin β_3 Venture. The centrality of the isoxazoline–spiro ketal conversion to the success of the β_3 venture demanded that we examine this sequence in detail. Given our initial observations, we conjectured that isoxazoline **25a**, possessing the correct relative configuration at C(19), would undergo facile ring closure via enal **8a** to form spiro ketal **7**. On the other hand, isoxazoline **25b**, possessing the alternate configuration at C(19), would experience a serious 1,3-diaxial interaction in the transition state for ring closure (i.e., **30**) and thereby be less likely to undergo the cyclization process.



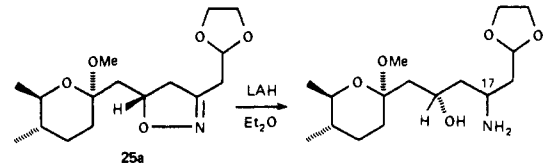
To explore this possibility, the mixture of isoxazolines was separated by HPLC and each diastereomer in turn subjected to reduction and spiro ketal formation.[33] As expected, *only the major diastereomer* ***25a*** *afforded aldehyde* **7**; the yield, however, was only 33%. The minor isoxazoline **25b** underwent complete decomposition.[34] Careful NMR examination of the reaction mixture derived from the minor isoxazoline **25b** revealed the presence of considerable olefinic material. Presumably this material arises via elimination of the vinylogously β-benzyloxy substituent. Fortunately, from an operational standpoint, the mixture of isoxazolines need not be separated but simply carried through the reaction sequence to afford pure aldehyde **7**.

Completion of the Northern Hemisphere: Application of the Ireland–Claisen Rearrangement. With an expedient approach to aldehyde **7** secure, we turned to introduction of the remaining six-carbon unit required to complete the northern hemisphere. The central feature of this operation was the proposed Ireland–Claisen rearrangement.[13] To initiate this sequence, aldehyde **7** was treated with isopropenylmagnesium bromide and the resulting alkoxide acylated with propionyl chloride. A 2:1 mixture of propionates **6b** and **6a** resulted. While at first the lack of stereochemical control would appear problematic, we reasoned that execution of a stereocontrolled Ireland–Claisen rearrangement employing the properly generated (*E*)- or (*Z*)-enolate with the appropriate propionate could, in theory at least, produce the requisite relative configuration at C(12). Such an operation would constitute a divergent–convergent maneuver to correct for the lack of stereocontrol in the isopropenyl Grignard addition.

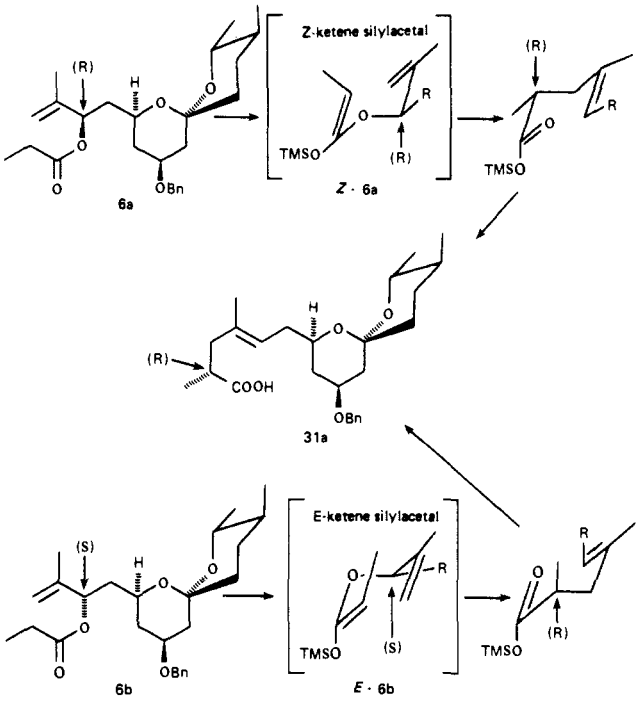
Toward this end, the mixture was separated and propionate **6a** subjected to the conditions first introduced by Ireland for the

(32) We are grateful to Dr. Yo Takiguchi, Group Director of the Fermentation Research Laboratories, Sankyo Company, Ltd., Tokyo, Japan, for providing the ^1H and ^{13}C NMR spectra of milbemycin β_3, as well as a generous sample of milbemycin β_1 utilized in our degradation studies.

(33) Reduction of isoxazoline **25a** (or **25b**) produced a 3:1 mixture (NMR) at the newly formed C(17) amine center in near quantitative yield. This level of stereoselectivity has been observed previously with LAH reductions of 5-substituted isoxazolines; see: Jager, V.; Schwab, W.; Buss, V. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 601.



(34) The relative stereochemistry at C(19) in isoxazolines **25a** and **25b** is based on the observation that only **25a** produces aldehyde **7**.

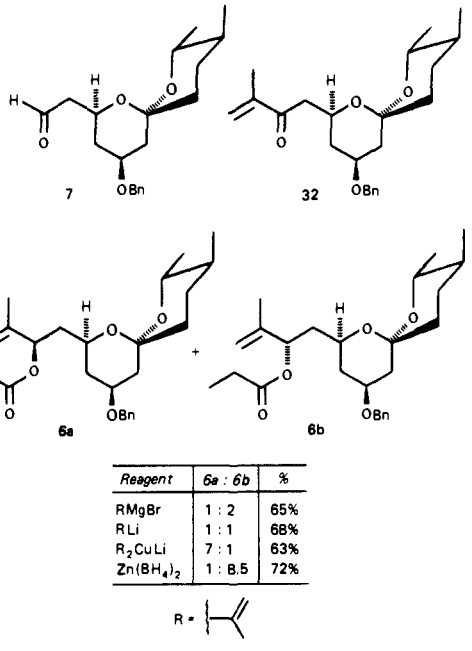


enolate Claisen rearrangement [i.e., (i) LDA/THF, (ii) Me_3SiCl in HMPA, and (iii) thermolysis].[13a] Surprisingly, only recovered ester resulted! After a number of unsuccessful experiments, we recognized that enolate formation was simply not occurring under the LDA/THF conditions. This observation, in conjunction with the related work of Ireland[35] and our laboratory,[36] suggested that with highly oxygenated systems, the lithium counterion coordinates with substrate oxygen atoms in such a fashion as to prevent deprotonation. Fortunately, this problem could be overcome by employing $KN(SiMe_3)_2$[37] in THF at −78 °C. Capture of the resulting (*Z*)-enolate, derived respectively from **6a** and **6b**, with trimethylsilyl chloride followed by warming to 55 °C resulted in rearrangement to the epimerically distinct acids **31a** and **31b**. The yield ranged from 52% to 57%, with a stereoselectivity of 6:1 in both cases (vide infra).

Well aware that the relative configuration at C(12) in **31a** and **31b** could only be established unambiguously after spectral comparisons were made between synthetic and natural milbemycin β_3, we carried both isomers (individually) through the entire synthetic sequence (vide infra). In this way, the *minor* propionate **6a** derived from the Grignard reaction was shown to be that required for the synthesis of β_3, while the *major* propionate **6b** produced epimilbemycin β_3.[38]

There remained at this point only the conversion of the major propionate **6b** via the (*E*)-enolate to acid **31a** to complete the proposed divergent–convergent operation. However, as with propionate **6a**, the LDA/THF conditions proved unsuccessful. More promisingly, treatment of **6b** with LDA in DME (a more dissociating solvent) afforded a 3:1 mixture of **31a** and **31b**. The yield in this case was 78%. Unfortunately, all attempts to increase production of **31a** at the expense of **31b** proved unsuccessful.

A More Direct Solution: The Stereocontrolled Construction of Propionate 6a. While in 1982 we had succeeded in executing the proposed divergent–convergent maneuver, the operation in practice left much to be desired. A more direct solution would entail the stereoselective conversion of aldehyde **7** to propionate **6a**. Although stereocontrolled addition of organometallic reagents to



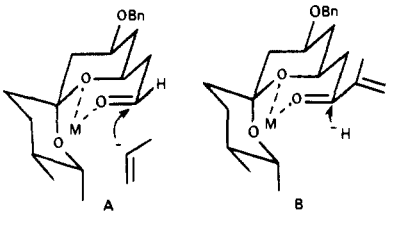
Reagent	*6a : 6b*	*%*
RMgBr	1 : 2	65%
RLi	1 : 1	68%
R_2CuLi	7 : 1	63%
$Zn(BH_4)_2$	1 : 8.5	72%

R =

aldehydes lacking α-substitutents is rare,[39] we reasoned that the asymmetry present in the spiro ketal unit would provide the needed stereochemical bias to direct the addition. Particularly attractive here was Still's observation[40] on the chelation-controlled addition of cuprates to β-alkoxy aldehydes. Toward this end, treatment of aldehyde **7** with isopropenyl cuprate afforded a 7:1 mixture of esters **6a** and **6b** (63%) after acylation.

Additional insight into the nature of this chelation-controlled process derived from enone **32**, available from **6a** and **6b** via ester hydrolysis and Collins[24] oxidation. In particular, reduction of this enone with $Zn(BH_4)_2$[41] in ether led, after acylation, to an 8.5:1 mixture of esters **6b** and **6a** in 72% yield.

These observations are explicable in terms of models A and B, wherein the aldehyde and spiro ketal oxygens coordinate with the copper or zinc to form a six-membered transition state; nucleophilic



attack from the pseudoaxial direction would then afford the derived products.[42] The change in stereochemistry when the cuprate or hydride is employed is simply a matter of reversing the order of introduction of the substituents.

With a stereoselective protocol for the preparation of either acid **31a** or **31b** in hand, completion of the northern hemispheres (i.e., **4a** and **4b**) proceeded as illustrated below. The overall yield for the four-step sequence was 47–59%.

Construction of the Southern Hemisphere: A Novel S_N2' Reaction. Synthesis of Horner–Emmons reagent, **5**, required as the southern hemisphere of milbemycin β_3, began with anisic acid **11**.

(35) Ireland, R. E.; Thompson, W. *J. Org. Chem.* **1979**, *44*, 3041 and references cited therein.

(36) Smith, A. B., III; Richmond, R. E. *J. Am. Chem.* Soc. **1983**, *105*, 575.

(37) Brown, C. A. *J. Org. Chem.* **1972**, *39*, 3913. Potassium hexamethyldisilizide was used by Ireland in his chlorothricolide synthesis to overcome the inability of lithium cation bases to effect deprotonation.[35]

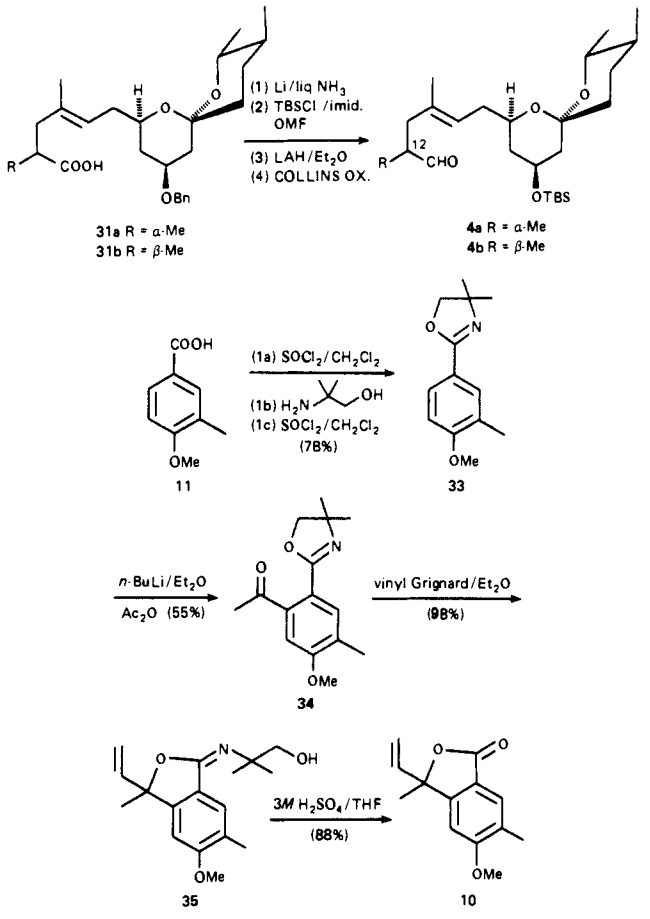
(38) Assignment of stereochemistry for esters **6a** and **6b** was based on the assumption that $KN(SiMe_3)_2$ yields the thermodynamic (*Z*)-enolate. Professor Robert Ireland, private communication.

(39) For examples of stannic chloride-catalyzed allylsilane addition to a β-alkoxyaldehyde lacking an α-substituent, see: Heathcock, C. H.; Kiyooka, S.-I. *Tetrahedron Lett.* **1983**, 4765. Also see: Reetz, M. T.; Kessler, K.; Jung, A. *Tetrahedron Lett.* **1984**, 729.

(40) Still, W. C.; McDonald, J. H., III. *Tetrahedron Lett.* **1980**, 1031. Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, 1035.

(41) Highly stereoselective reductions (30:1) of aryl or vinyl ketones, containing β'-alkoxy substituents have been obtained with $Zn(BH_4)_2$. T. Oishi and M. Fukui, The Institute of Physical and Chemical Research Tokyo, Japan, private communication.

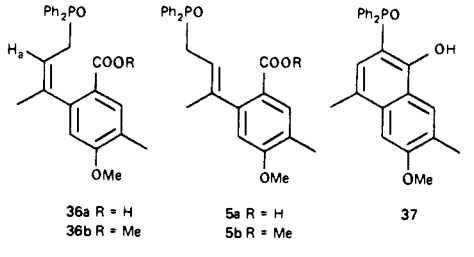
(42) A similar chelation-controlled addition of allylzinc involving pseudoaxial attack was exploited by Kishi in his rifamycin synthesis; see: Nagaoka, N.; Rutsch, W.; Schmid, G.; Iio, H.; Johnson, M. R.; Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7965.



Conversion to oxazoline **33** via the Meyers protocol[43] followed by metalation[44] with *sec*-BuLi in ether and then inverse addition to acetic anhydride afforded methyl ketone **34** in 55% yield as the sole product; the remainder of material was recovered oxazoline. Efforts to improve this procedure by using metal salts ($MgBr_2$ or $ZnCl_2$) and/or normal addition provided little encouragement. Apparently, ketone **34**, once formed, acts as a proton source, quenching a portion of the lithiated species prior to acylation.

Continuing with this sequence, ketone **34** was condensed with vinylmagnesium bromide to afford in near quantitative yield iminolactone **35**; acid hydrolysis then led to lactone **10**, substrate for the S_N2' process. In practice, both the Grignard and hydrolysis operations were carried out without purification; the yield in this case was 88%.

Lactone **10** was next subjected to the proposed S_N2' process via treatment with lithium diphenylphosphide in THF at −78 °C. Initial isolation of the derived phosphine proved difficult due to partial oxidation to the corresponding phosphine oxide. This problem was easily circumvented by completing the oxidation process (i.e., air oxidation). The result was a 3:1 mixture (69%) of phosphine oxides **36a** and **5a**, which were converted to the corresponding methyl esters **36b** and **5b** with diazomethane. Both the esters and acids proved readily separable by flash chromatography.

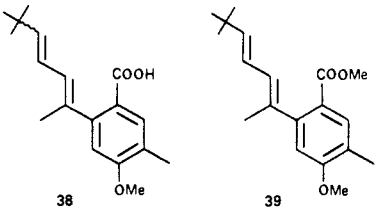


(43) Meyers, A. I.; Temple, D. L.; Haidukewych, D.; Mihelich, E. D. *J. Org. Chem.* **1974**, *39*, 2787.
(44) Gschwend, H. W.; Handan, A. *J. Org. Chem.* **1975**, *40*, 2008.

Assignment of the olefinic configuration derived from a combination of NMR and chemical evidence. First, a 27% NOE enhancement[45] was observed in **36b** for the vinyl hydrogen (H_a) upon irradiation of the vinyl methyl protons. Similar irradiation of **5b** produced no enhancement. Second, **36b**, possessing the (*Z*)-olefin, underwent a facile intramolecular cyclization upon treatment with NaH in THF to yield naphthol **37**. The *E* isomer **5b** remained unchanged under these conditions.

Given that **5a** was required for the milbemycin synthesis, we explored the feasibility of converting acid **36a** to **5a**. Best results were obtained when the mixture of acids was treated with potassium hydroxide in ethylene glycol at 140 °C for 12 h. Under these conditions the 3:1 mixture was converted to a 1:1 mixture. Separation by flash chromatography permitted recycling of the *Z* isomer.[46]

Union of the Northern and Southern Hemispheres. Before executing the coupling operation, we considered it prudent to explore the use of Horner–Emmons reagents **5a** and **5b** in olefination. Toward this end, acid **5a** was converted to the corresponding dianion by using NaH (excess) in THF. Addition of pivaldehyde resulted in a mixture of (*E*)- and (*Z*)-olefins **38** at



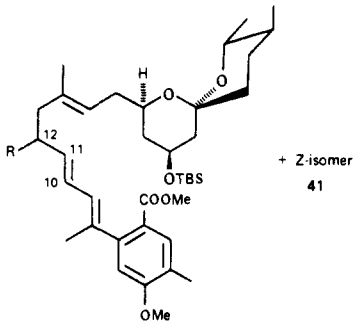
the newly formed olefinic linkage. The configuration at the trisubstituted olefin remained unchanged. Alternatively, treatment of ester **5b** with NaH led to a single *trans*-olefin **39** at the newly formed olefinic linkage. We concluded from these experiments that collapse of the betaine derived from the less stabilized Horner–Emmons reagent **5a** occurs rapidly to give a mixture of (*E,E*)- and (*E,Z*)-dienes, while the betaine resulting from the more stabilized ester can undergo equilibration and thereby afford only the (*E,E*)-diene.[12] Thus, phosphine oxide **5b** appeared to be the Horner–Emmons reagent of choice.

Turning to the union of the northern and southern hemispheres, the anion of **5b** was generated with NaH and aldehyde **4a** added. That olefination had proceeded was apparent by examination of the NMR spectrum of the derived product. While the *E*:*Z* ratio was 7:1, there were two major problems! First, the C(12) methyl center had undergone epimerization. Second, the yield of the coupling was only 15%. In an effort to improve the coupling process, we explored the use of $KN(SiMe_3)_2$. With this base, a 74% yield of diene was obtained; the C(10,11) *E*:*Z* ratio, however, was 3:2.

Olefin geometries and ratios were determined by inspection of the 250-MHz ^1H NMR spectrum, in particular the resonance for the C(11) proton. In **40a** (the (*E,E*)-isomer) a doublet of doublets was observed at δ 6.33 (J = 15.0, 11.0 Hz). A similar pattern is present in milbemycin β_3. The (*Z,E*)-diene **41**, on the other hand, displays the C(11) resonance as an apparent triplet at δ 5.90 (J = 11.0 Hz). Presumably the nearly equal *E,Z* mixture at C(10,11) indicates that the initially derived potassium alkoxide collapses too rapidly to result in good *E* selectivity.

Noting that sodium hydride gave high *E* selectivity, albeit in low yield, we conjectured that a possible problem was incomplete anion formation, possibly due to the insolubility of NaH in THF. We therefore sought a soluble base possessing sodium as the counterion. The most convenient source appeared to be $NaN(SiMe_3)_2$. Indeed, when ester **5b** was treated with $NaN(SiMe_3)_2$ in THF at −78 °C, a brilliant red solution resulted (i.e., anion

(45) Kotovych, G.; Aarts, G. H. M. *Can. J. Chem.* **1980**, *53*, 2649. Also see: Noggle, J. H.; Schirmer, R. E. *The Nuclear Overhauser Effect: Chemical Applications*; Academic: New York, 1971.
(46) A number of other methods ($I_2/h\nu$, *p*-TsOH/THF, toluene/Δ, $RhCl_3 \cdot 3H_2O$) to isomerize the phosphine oxides were explored with only limited success.

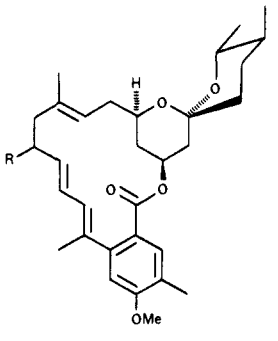


40a R = α-Me
40b R = β-Me

BASE	E : Z	%
NaH	7 : 1	15%
$KN(TMS)_2$	3 : 2	74%
$NaN(TMS)_2$	7 : 1	>90%

formation). Addition of aldehyde **4a** followed by warming the solution to room temperature then led to a diene in 85–95% yield after chromatography. NMR analysis revealed the C(10,11) *E*:*Z* ratio to be 7:1. Equally important, the C(12) methine center had not undergone epimerization.

Completion of the Milbemycin Synthetic Venture. At this point all that remained to complete a synthesis of milbemycin β_3 and its epimer (**1b**) was macrolide formation, followed by removal of the anisole methyl group. Toward this end, the silyl group was removed from **40a** with tetrabutylammonium fluoride[47] in THF. The resultant alcohol was then treated without purification with excess KH to yield milbemycin β_3 methyl ether (**42a**). The yield



42a R = α-Me
42b R = β-Me

for the two steps was 79%. Strong support that we had indeed effected macrolide formation derived from examination of the 250-MHz ^{1}H NMR spectra. In particular, only a single methoxy resonance (δ 3.82) for the anisole methyl group was observed. Furthermore, the resonance for the C(19) methine hydrogen had undergone a significant downfield shift (ca. 1.4 ppm) relative to the corresponding resonance in diene **40a**, indicative that the C(19) hydroxyl was now part of a lactone system. An identical sequence of Horner–Wittig coupling, desilylation, and macrocyclization provided **42b** from **40b**.[48] Significant here is the fact that both macrolactonizations were effected without resort to either ester or alcohol activation or use of extremely high dilution (e.g., syringe pump) techniques.[49]

Removal of the aryl methyl group was then accomplished by treatment of **42a** with sodium ethanethiolate in hot DMF for 1 h, according to the method of Feutrill and Mirrington.[50] The result was (±)-milbemycin β_3 (**1**), available in 86% yield after purification by preparative TLC (mp 153–156 °C). The same sequence employing methyl ether **42b** provided (±)-12-epimilbemycin β_3 in 83% yield (mp 205 °C dec).

Comparison of the ^{1}H and ^{13}C NMR spectra of synthetic milbemycin β_3 with spectra provided by Prof. Takiguchi[32] confirmed that β_3 was in hand. Interestingly, the ^{1}H and ^{13}C NMR of C(12)-epimilbemycin were distinctly different from the spectra of the natural epimer.

In summation, the total synthesis of both (±)-milbemycin β_3 and (±)-epimilbemycin β_3 has been achieved. Central to the successful strategy are a [3 + 3] buildup of the spiro ketal unit by a nitrile oxide dipolar addition, an introduction of the requisite C(12) methyl center via a chelation-controlled cuprate addition in tandem with a stereocontrolled Ireland–Claisen rearrangement, and a novel S_N2' construction of the southern hemisphere. This approach proved short (longest linear sequence, 16 steps), convergent, and for the most part highly stereocontrolled.

Experimental Section

Tetrahydro-2-methoxy-2-propenyl-2*H*-pyran (13b). A solution of δ-valerolactone (10.1 g, 0.101 mol) in 150 mL of dry tetrahydrofuran was cooled to −78 °C and treated with 80 mL of a 1.2 M solution of allylmagnesium chloride in THF. The mixture was stirred for 4 h at −78 °C, and then 200 mL of saturated ammonium chloride solution was added. The organic layer was separated and the aqueous layer extracted twice with 100 mL of ether. The combined organic extracts were dried (magnesium sulfate) and then evaporated to afford a residue which was stirred with 65 mL of trimethyl orthoformate and 250 mg of cerium(III) chloride heptahydrate at room temperature for 48 h. The excess trimethyl orthoformate was then removed by distillation through a 15-cm Vigreux column (oil bath 120 °C), followed by distillation of the residue at water aspirator pressure (oil bath 150 °C) to afford 5.6 g (36%) of ketal **13b** as a colorless liquid: bp 85–90 °C/20 mm; IR (CCl_4) 1610 (w), 1228 (m), 1110 (s), 1068 (s), 1035 (s), 915 (m) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.36–1.86 (m, 6 H), 2.26 (dd, *J* = 15, 6 Hz, 1 H), 2.50 (dd, *J* = 15, 6 Hz, 1 H), 3.24 (s, 3 H), 3.65 (m, 2 H), 5.08 (m, 1 H), 5.14 (m, 1 H), 5.78 (m, 1 H).

Anal. Calcd for $C_9H_{16}O_2$: C, 69.18; H, 10.34. Found: C, 69.29; H, 10.41.

Tetrahydro-2-methoxy-2*H*-pyranylacetaldehyde (14). A stirred solution of ketal **13b** (2.63 g, 16.8 mmol) in 60 mL of methylene chloride at −78 °C was treated with ozone until a blue color persisted. Triphenylphosphine (4.72 g, 18.0 mmol) was then added and the mixture stirred for 2 h at room temperature. The methylene chloride was evaporated and the residue subjected to flash chromatography [gradient elution, hexane–ethyl acetate, 20:1, 5:1 (v/v)][52] to afford 2.08 g (78%) of aldehyde **14** as a colorless liquid. This aldehyde was observed to undergo decomposition on storage at 0 °C. IR (CCl_4) 2735 (w), 1720 (s), 1290 (s), 1215 (s), 1140 (s), 1095 (s), 1080 (s), 1060 (s), 1035 (s) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.42–1.62 (m, 4 H), 1.70–1.86 (m, 2 H), 2.51 (dd, *J* = 13, 5 Hz, 1 H), 2.65 (dd, *J* = 13, 3 Hz, 1 H), 3.22 (s, 3 H), 3.64 (m, 2 H), 9.68 (dd, *J* = 5, 3 Hz, 1 H); chemical ionization mass spectrum, *m/e* 159.1014 (MH^+, calcd for $C_8H_{15}O_3$, 159.1020).

Spiro Ketals 16a and 17a. A stirred solution of diisopropylamine (3.6 mL, 25.3 mmol) in 60 mL of tetrahydrofuran at −78 °C under argon was treated with *n*-butyllithium (1.45 M, 17.46 mL, 25.23 mmol).[51] After 0.5 h ethyl acetoacetate (1.55 mL, 12.2 mmol) was added. After an additional 0.5 h at −78 °C, a solution of aldehyde **14** (1.75 g, 11.0 mmol) in 20 mL of tetrahydrofuran was added rapidly via cannula. The mixture was then stirred for 7 min at −78 °C, quenched with saturated NH_4Cl, and extracted with ether. The ether extracts were combined, washed with brine, and dried with $MgSO_4$. The solvent was removed in vacuo to afford 3.18 g of adduct **15**. This compound was used immediately since it underwent decomposition on storage at 0 °C or on flash chromatography.

A stirred solution of adduct **15** (3.18 g, 11.0 mmol) in 30 mL of methanol was cooled to 0 °C under argon and treated with excess sodium borohydride (550 mg) for 20 min. The reaction was quenched with saturated NH_4Cl and extracted with ether. The solvent was then re-

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(48) Comparison of the high-field 250-MHz ^{1}H NMR spectra indicated a clear difference for macrolides **42a** and **42b**, thereby permitting an accurate analysis of ratios of the C(12) epimers. Measurement of the peak heights for the C(9) proton indicate a 6:1 ratio in both cases. This provided a lower limit for the selectivity of the Ireland–Claisen rearrangement as well as all subsequent transformations.

(49) For other examples of macrocyclizations without resort to high dilution techniques, see: Kurihara, T.; Nakajima, Y.; Mitsunobu, O. *Tetrahedron Lett.* **1976**, 2455. Stelliou, K.; Szcygielska-Nowosielska, A.; Favre, A.; Poupart, M. A.; Hanessian, S. *J. Am. Chem. Soc.* **1980**, *102*, 7578. Stelliou, K.; Poupart, M. *J. Am. Chem. Soc.* **1983**, *105*, 7130 and references cited therein.

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moved in vacuo to afford 2.58 g of a residue (gum) which was dissolved in 100 mL of dry benzene and stirred under argon with 200 mg of *p*-TsOH for 3.5 h. The benzene was evaporated and the residue subjected to flash chromatography [hexane–ethyl acetate, 1:1 (v/v)]. First to elute was ketal **16a** (0.875 g, 31%) followed by ketal **17a** (0.220 g, 8%), both as colorless liquids.

Ketal 16a: IR (CCl_4) 3520 (m), 2940 (s), 1630 (s), 1270 (s), 1220 (s), 1185 (s), 1160 (s), 1080 (s), 1055 (s), 1035 (s), 990 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.25 (t, J = 6 Hz, 3 H), 1.30–1.85 (m, 10 H), 2.40 (dd, J = 15, 5 Hz, 1 H), 2.48 (dd, J = 15, 7 Hz, 1 H), 3.55–3.65 (m, 1 H), 3.74–3.88 (m, 1 H), 3.96–4.25 (m, 4 H), 4.35–4.46 (m, 1 H).

Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.43; H, 8.60. Found: C, 60.23; H, 8.44.

Ketal 17a: IR (CCl_4) 1720 (s), 1260 (s), 1215 (m), 1185 (m), 1030 (m), 990 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.28 (t, J = 6 Hz, 3 H), 1.15–1.80 (m, 9 H), 1.94–2.05 (m, 2 H), 2.44 (dd, J = 15, 3 Hz, 1 H), 2.55 (dd, J = 15, 7 Hz, 1 H), 3.49–3.60 (m, 1 H), 3.65–3.78 (m, 1 H), 4.04–4.25 (m, 4 H); electron impact mass spectrum, m/e 258.1483 (M^+, calcd for $C_{13}H_{22}O_5$, 258.1466).

Ketone 18. To a stirred solution of dry pyridine (1.3 mL, 16.1 mmol) in 15 mL of methylene chloride was added chromium trioxide (720 mg, 7.20 mmol) followed 15 min later by a solution of ketal **16a** (148 mg, 0.573 mmol) in 20 mL of methylene chloride. The reaction mixture was stirred a further 15 min and then quenched with ether (100 mL) followed by saturated $NaHCO_3$ (15 mL). The organic layer was removed and the aqueous phase extracted with ether. The ether extracts were combined and dried ($MgSO_4$). The solvent was removed and the residue subjected to flash chromatography [methylene chloride–ethyl acetate, 20:1 (v/v)] to afford 106 mg (72%) of the ketone **18** as a colorless oil: IR (CCl_4) 2940 (s), 1720 (s), 1375 (s), 1310 (s), 1260 (s), 1215 (s), 1170 (s), 1125 (s), 1095 (s), 1070 (s), 1045 (s), 1025 (s), 980 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.26 (t, J = 6 Hz, 3 H), 1.35–1.65 (m, 4 H), 1.70–1.90 (m, 2 H) 2.15–2.48 (m, 4 H), 2.53 (dd, J = 15, 5 Hz, 1 H), 2.65 (dd, J = 15, 10 Hz, 1 H), 3.52–3.80 (m, 2 H), 4.18 (q, J = 6 Hz, 2 H), 4.35–4.50 (m, 1 H); chemical ionization mass spectrum, m/e 257.1385 (MH^+, calcd for $C_{13}H_{21}O_5$, 257.1388).

Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.91; H, 7.88. Found: C, 60.84; H, 7.99.

In a similar manner, ketal **17a** (108 mg, 0.418 mmol) was oxidized with chromium trioxide–pyridine to afford 75 mg (70%) of the ketone **18**, which displayed the identical spectral properties as ketone **18** prepared above.

L-Selectride Reduction of Ketone 18. A stirred solution of ketone **18** (90 mg, 0.351 mmol) in 5 mL of tetrahydrofuran was cooled to 0 °C under argon and treated with L-Selectride in THF (1 M, 1.05 mL, 1.05 mmol). The mixture was stirred at 0 °C for 20 min and quenched with saturated NH_4Cl (25 mL) and ether (50 mL). The aqueous layer was then extracted with ether, and the ether fractions were combined and dried ($MgSO_4$). Removal of the solvent in vacuo and flash chromatography [hexane–ethyl acetate, 1:1 (v/v)] afforded 68 mg (75%) of ketal **16a**.

2-Methoxy-3-methylcyclopentenone (ii).[53] A solution of cyclotene (75 g, 670 mmol) in 600 mL of reagent grade methanol was cooled to 0 °C with a dry ice–acetone bath. Dry HCl gas was passed through the solution for 1 h. A small aliquot was withdrawn and the solvent removed. NMR analysis of the residue indicated conversion to the enol ether. The excess methanol was removed under aspirator pressure and the residue distilled with a 6-in. Vigreux column to afford 53.2 g (63.0%) of ketone ii as a pale yellow oil: bp 45–48 °C/1 mm; NMR (60 MHz, CCl_4) δ 1.90 (s, 3 H), 2.00–2.50 (m, 4 H), 3.90 (s, 3 H).

2-Methylcyclopentenone (iv).[53] To a vigorously stirred suspension of $LiAlH_4$ (8.1 g, 211 mmol) in ether at 0 °C was added ketone ii (53.2 g, 422 mmol) dropwise over a 30-min period. The mixture was allowed to stir in additional 2 h followed by the addition of 13 mL of H_2O, 13 mL of 15% aqueous NaOH, and 45 mL of H_2O. The ether layer was separated and the residue extracted thoroughly with ether. The ether fractions were combined, dried over $MgSO_4$, and concentrated in vacuo to afford enol ether iii, suitable for the next step. Alternatively, distillation afforded 43.7 g (81%) of iii as a colorless liquid (bp 75–80 °C/4 mm).

Enol ether iii was then dissolved in 150 mL of 1 N H_2SO_4 and brought to a gentle reflux for 3.5 h. After cooling, the solution was saturated with NaCl, the resulting slurry was extracted with ether, and the combined organic extracts were washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo (bath temperature $\leq$ 10 °C). The resultant yellow oil was purified by distillation with a 6-in. Vigreux column to afford 29 g (71.5%) of iv as a volatile mobile oil: bp 56–60 °C/15 mm; NMR (60 MHz, CCl_4) δ 1.75 (m, 3 H), 2.10–2.70 (m, 4 H), 7.15 (br s, 1 H).

2,3-Dimethylcyclopentanone (v).[54] To copper(I) iodide (30 g, 158 mmol) in 200 mL of Et_2O at −20 °C under argon was added methyllithium (1.6 M, 200 mL, 320 mmol). After the mixture was stirred an additional 15 min, a solution of enone iv (10 g, 104 mmol) in 200 mL of Et_2O was added dropwise over a 30-min period. The reaction mixture was stirred an additional 20 min at −20 °C and then quenched with saturated NH_4Cl. The organic layers were washed with concentrated NH_4OH and brine and dried over $MgSO_4$. Analysis of an aliquot by capillary gas chromatography indicated a 3:1 mixture of trans to cis isomers. The ether solution (ca. 300 mL) was then treated with 5 mL of an ether solution which had been saturated with HCl gas. The resulting solution was stirred for 24–48 h until analysis by capillary gas chromatography indicated a 10:1 mixture of isomers. At this point the reaction mixture was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo (bath temperature $\leq$ 10 °C). The resulting yellow oil was purified by distillation with a 6-in. Vigreux column to afford 9.5 g (81.5%) of a 10:1 mixture of *trans*:*cis*-2,3-dimethylcyclopentenone (v): bp 44–46 °C/15 mm; ^1H NMR (60 MHz, CCl_4) δ 0.70–1.80 (m, 3 H), 1.00 (d, J = 6.8 Hz, 3 H), 1.10 (d, J = 5.5 Hz, 3 H), 1.80–2.30 (m, 3 H).

Tetrahydro-5,6-dimethyl-2*H*-pyran-2-one (9).[17] Ketone v (10.0 g, 0.089 mmol) was dissolved in 200 mL of CH_2Cl_2. To this solution was added at room temperature *m*-chloroperbenzoic acid (23.1 g, 107 mmol), and the reaction mixture was stirred for 18 h. The excess per acid was quenched with 5% Na_2SO_3, and the reaction mixture was extracted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by simple distillation to afford 10.5 g (92%) of lactone **9** as a clear oil (bp 63–65 °C/0.5 mm) which solidified after cooling in the freezer: ^1H NMR (60 MHz, CCl_4) δ 1.00 (d, J = 6 Hz, 3 H), 1.30 (d, J = 7 Hz, 3 H), 1.10–2.20 (m, 3 H), 2.30–2.60 (m, 2 H), 3.95 (m, 1 H).

2-(2-Nitroethyl)-1,3-dioxolane (24). To bromide **23** (20 g, 0.1105 mmol) in 240 mL of Me_2SO at room temperature was added $NaNO_2$ (13 g, 0.188 mmol). After stirring for 3 h, the reaction mixture was dilted with 200 mL of H_2O, extracted with CH_2Cl_2, washed with H_2O, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by simple distillation to give 9 g (56%) of a clear colorless oil: bp 68–70 °C/0.3 mm; ^1H NMR (60 MHz, CCl_4) δ 2.34 (dt, J = 7, 4 Hz, 2 H), 3.90 (m, 4 H), 4.36 (t, J = 7 Hz, 2 H), 4.92 (t, J = 4 Hz, 1 H); chemical ionization mass spectrum, m/e 148.0606 (MH^+, calcd for $C_5H_{10}NO_4$, 148.0576).

Mixed Ketal 21. To lactone **9** (3.5 g, 27 mmol) in 100 mL of THF at −78 °C was added allylmagnesium chloride (1.2 M, 21.7 mL, 26.0 mmol) in THF over a 4-min period. The reaction mixture was stirred at −78 °C for 3 h, quenched with saturated NH_4Cl, and extracted with ether. The ether extracts were combined, washed with brine, and dried with $MgSO_4$. The solvent was removed in vacuo, and the remaining residue was taken up in 13 mL (3 equiv) of trimethyl orthoformate. The resulting solution was then treated with 200 mg of $CeCl_3 \cdot 7H_2O$ for 16 h, after which time the reaction mixture was taken up in pentane and filtered through Celite to remove the cerium salts, and the pentane was removed in vacuo. The residue was then carefully distilled through a 6-in. Vigreux column at atmospheric pressure until the $CH(OMe)_3$ was removed. Aspirator pressure was then applied and the product distilled to afford 3.5 g (71%) of **21** as a colorless liquid: bp 87–90 °C/25 mm; IR (CCl_4), 3060 (w), 2925 (br s), 1095 (s), 1055 (s), 995 (s), 915 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.83 (d, J = 6 Hz, 3 H), 1.15 (d, J = 6 Hz, 3 H), 1.10–1.29 (m, 1 H), 1.39–1.45 (m, 3 H), 1.66–1.78 (m, 1 H), 2.13–2.24 (dd, J = 13.0, 7.0 Hz, 1 H), 2.43–2.57 (dd, J = 14.0, 7.0 Hz, 1 H), 3.20 (s, 3 H), 3.22–3.33 (m, 1 H), 4.97–5.12 (m, 2 H), 5.60–5.80 (m, 1 H).

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.80; H, 10.92.

Isoxazolines 25a and 25b. To ketal **21** (1.0 g, 5.4 mmol) in 10 mL of benzene were added acetal **24** (1.2 g, 8.2 mmol) and 100 μL of triethylamine. To this solution was added methyl isocyanate (5 mL, 85 mmol), and the mixture was heated to 75 °C for 48 h. After the solution cooled, the methyl isocyanate and benzene were removed in vacuo. The residue was taken up in benzene, washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting yellow oil was purified by flash chromatography [gradient elution, hexane–etyl acetate, 4:1, 3:1, 2:1 (v/v)] to afford 1.2 g (71%) of a 60:40 mixture (by NMR) of isoxazolines **25a** and **25b** suitable for further use. The diastereomers can be separated by HPLC [semipreparative, μ Porasil, hexane–ethyl acetate–triethylamine, 75:25:1, one recycle] to afford pure isoxazolines.

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Isoxazoline 25a: IR (CCl_4) 2940 (br s), 1385 (m), 1140 (s), 1095 (s), 1065 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.81 (d, J = 6.5 Hz, 3 H), 1.12 (d, J = 6.7 Hz, 3 H), 1.20 (m, 1 H), 1.40–1.74 (m, 4 H), 1.84 (dd, J = 13.5, 7.0 Hz, 1 H), 2.08 (dd, J = 13.5, 5.0 Hz, 1 H), 2.66–2.82 (m, 3 H), 3.08 (dd, J = 16.0, 9.0 Hz, 1 H), 3.18 (s, 3 H), 3.26 (dq, J = 9.8, 5.5 Hz, 1 H), 3.82–4.10 (m, 4 H), 4.62 (m, 1 H), 5.04 (t, J = 5.0 Hz, 1 H); chemical ionization mass spectrum, m/e 314.1927 (MH^+, calcd for $C_{16}H_{28}O_5N$, 314.1960).

Isoxazoline 25b: IR (CCl_4) 2935 (br s), 1380 (m), 1135 (s), 1090 (s), 1055 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.80 (d, J = 6.4 Hz, 3 H), 1.15 (d, J = 6.3 Hz, 3 H), 1.25 (m, 1 H), 1.36–1.70 (m, 3 H), 1.86–2.04 (m, 3 H), 2.62–2.78 (m, 3 H), 3.04–3.15 (m, 1 H), 3.13 (s, 3 H), 3.28 (dq, J = 9.8, 6.5 Hz, 1 H), 3.80–4.06 (m, 4 H), 4.62 (m, 1 H), 5.02 (t, J = 4.8 Hz, 1 H); chemical ionization mass spectrum, m/e 314.1949 (MH^+, calcd for $C_{16}H_{28}O_5N$, 314.1960).

Amino Alcohols 26a–d. To an ether solution of LAH (Aldrich) (1 M, 32 mL, 32 mmol) at room temperature under argon were added the isoxazolines **25a,b** (5.0 g, 16 mmol) in three 10-mL portions of Et_2O. The reaction was heated to reflux for 3 h, cooled, and quenched with 1.2 mL of H_2O, 1.2 mL of 20% aqueous KOH, and 3.6 mL of H_2O. After stirring for an additional 40 min, the resulting solution was filtered through Celite and washed thoroughly with dry Et_2O, followed by concentration in vacuo to afford 4.8 g (95%) of a mixture of amino alcohols **26a–d** as a clear oil. This mixture is suitable for use in subsequent reactions: IR (CCl_4) 3500 (br), 3300 (br), 2925 (br s), 1140 (br s), 1100 (s), 1055 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.72–0.98 (m, 1.0 H), 0.85 (d, J = 7 Hz, 3 H), 1.00–1.24 (m, 1.0 H), 1.18 (app t, J = 7 Hz, 3 H), 1.32–1.98 (m, 11 H), 4.18 (m, 4.0 H), 4.30 (m, 1 H), 4.74–5.18 (m, 6.0 H), 5.95 (m, 1 H); chemical ionization mass spectrum, m/e 318.2256 (MH^+, calcd for $C_{16}H_{32}O_5N$, 318.2272).

Pure diastereomeric isoxazolines **25a** and **25b** were also reduced with LAH to afford ca. 3:1 mixture (NMR) of amino alcohols **26a,b** and **26c,d**, respectively, at the newly formed amine center.

Amino alcohol 26a,b: ^1H NMR (250 MHz, $CDCl_3$) δ 0.74–0.95 (m, 1 H), 0.82 (d, J = 7.0 Hz, 3 H), 1.02–1.24 (m, 1 H), 1.16 (d, J = 7.0 Hz, 3 H), 1.30–1.95 (m, 11 H), 3.08–3.24 (m, 4.0 H), 3.30 (m, 1 H), 3.76–4.18 (m, 6.0 H), 4.92 (m, 1 H).

Amino alcohol 26c,d: ^1H NMR (250 MHz, $CDCl_3$) δ 0.81 (d, J = 6.5 Hz, 3 H), 1.05–1.24 (m, 2 H), 1.12 (d, J = 6.5 Hz, 3 H), 1.34–2.05 (m, 11 H), 3.15 (m, 4.0 H), 3.30 (m, 1 H), 3.76–4.16 (m, 6.0 H), 4.93 (t, J = 4.8 Hz, 1 H).

Aldehyde 7. To a slurry of KH (10.8 g, 270 mmol) in 150 mL of THF was added a mixture of benzyl iodide (3.38 g, 15.5 mmol) and amino alcohols **26a–d** (4.9 g, 15.5 mmol) in 10 mL of THF. The slurry was stirred at room temperature for 3 h, and then methyl iodide (20 mL, 320 mmol) was added and the stirring continued for 48 h. The excess methyl iodide was removed in a stream of argon, and the residue was quenched with aqueous THF. The pH of the mixture was then brought to 5 with TsOH in THF (ca. 0.5 g/mL). The solution then was stirred at 25 °C for 24 h under argon, and the product was extracted with ether. The ether extracts were combined and dried over $MgSO_4$, and the solvent was removed in vacuo to afford a residue which was subjected to flash chromatography [gradient elution, hexane–ethyl acetate 20:1, 15:1, 10:1 (v/v)]. The resulting product was crystallized from hexane to yield 1.4 g (24.7%) of aldehyde **7** (mp 58–59 °C): IR (CCl_4) 2920 (br s), 1725 (s), 1095 (br s), 995 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.82 (d, J = 7.5 Hz, 3 H), 1.10 (d, J = 7.5 Hz, 3 H), 1.14–1.72 (m, 7 H), 2.10 (m, 2 H), 2.45 (ddd, J = 16.2, 4.4, 2.0 Hz, 1 H), 2.62 (ddd, J = 16.2, 8.6, 2.4 Hz, 1 H), 3.19–3.34 (m, 1 H), 3.87–4.03 (m, 1 H), 4.03–4.16 (m, 1 H), 4.55 (s, 2 H), 7.24–7.33 (m, 5 H), 9.83 (t, J = 2 Hz, 1 H).

Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.24; H, 8.51. Found: C, 72.39; H, 8.55.

Diol 28a. To a stirred solution of benzyl ether **7** (230 mg, 0.691 mmol) in 5 mL of tetrahydrofuran and 40 mL of liquid ammonia was added excess (ca. 100 mg) lithium. The solution was stirred for 20 min and quenched by the addition of NH_4Cl, and then the ammonia was allowed to evaporate. The residue was treated with 10 mL of saturated $NaHCO_3$ and the mixture extracted with ether. The combined ether fractions were dried ($MgSO_4$), the solvent was removed in vacuo, and the residue was subjected to flash chromatography [hexane–ethyl acetate, 3:7 (v/v)] to yield 98 mg (58%) of the alcohol **29**: IR ($CHCl_3$) 3600 (m), 3450 (m), 1720 (s), 1235 (br s), 1100 (s), 1030 (s), 995 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.80 (d, J = 7 Hz, 3 H), 1.11 (d, J = 7 Hz, 3 H), 1.00–2.05 (m, 10 H), 2.47 (ddd, J = 17.5, 5, 1 Hz, 1 H), 2.64 (ddd, J = 17.5, 9, 1 Hz, 1 H), 3.15–3.32 (m, 1 H), 4.03–4.33 (m, 2 H), 9.80 (br s, 1 H).

To a stirred solution of the aldehyde **29** (49 mg, 0.202 mmol) in 5 mL of methanol at 0 °C was added excess sodium borohydride (ca. 100 mg). The mixture was stirred at 0 °C for 0.5 h, the methanol removed in vacuo, and the residue treated with 5 mL of saturated sodium bicarbonate solution. The resultant mixture was extracted with ether, the combined ether fractions were dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was subjected to flash chromatography [hexane–ethyl acetate, 4:6 (v/v)] to afford 44 mg (89%) of diol **28a** as a colorless crystalline solid (mp 95–95.5 °C) after recrystallization from ether: IR ($CHCl_3$) 3600 (m), 3500 (m), 1075 (s), 998 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.82 (d, J = 6 Hz, 3 H), 1.12 (d, J = 7 Hz, 3 H), 1.16–2.05 (complex m, 12 H), 2.83 (br s, 1 H, OH), 3.24 (dq, J = 8, 6 Hz, 1 H), 3.72–3.88 (m, 3 H), 4.02–4.22 (m, 1 H); electron impact mass spectrum, m/e 244.1675, (M^+, calcd for $C_{13}H_{24}O_4$, 244.1513).

Anal. Calcd for $C_{13}H_{24}O_4$: C, 63.89; H, 9.92. Found: C, 63.95; H, 9.84.

Diacetate 28b. To a stirred solution of the diol **28a** (40 mg, 0.164 mmol), triethylamine (0.69 mL, 5 mmol), and a few crystals of DMAP was added acetic anhydride (0.31 mL). The solution was stirred at 20 °C for 20 h, and then the solvents were removed in vacuo. The residue was treated with 10 mL of saturated $NaHCO_3$ and the resulting solution extracted with ether. The residue from the dried ($MgSO_4$) ether extracts was subjected to flash chromatography [hexane–ethyl acetate, 10:1 (v/v)] to afford 43 mg (80%) of diacetate **28b** as a colorless gum: IR ($CHCl_3$) 1720 (s), 1250 (br s), 1105 (s), 1030 (s), 990 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.75 (d, J = 7 Hz, 3 H), 1.03 (d, J = 6 Hz, 3 H), 0.82–2.28 (complex m, 11 H), 1.92 (s, 3 H), 1.96 (s, 3 H), 3.13 (dq, J = 9, 6 Hz, 1 H), 3.67–3.82 (m, 1 H), 4.05–4.30 (m, 2 H), 5.08–5.26 (m, 1 H); electron impact mass spectrum, m/e 328.1889 (M^+, calcd for $C_{17}H_{28}O_6$, 328.1892).

Diol 28a via Degradation of Milbemycin β_1. A stirred solution consisting of milbemycin β_1 (40 mg, 0.073 mmol) and 10 mL of dichloromethane was cooled to −78 °C and ozone was passed through until a blue color developed. Excess dimethyl sulfide (1 mL) was then added, and the temperature of the solution was allowed to rise slowly to 20 °C over a 1-h period. The solvents were then removed in vacuo, and 5 mL of methanol was added. The resultant mixture was cooled to 0 °C and excess sodium borohydride added. This mixture was stirred at 0 °C for 1 h, and then the methanol was removed in vacuo. The residue was then stirred with 5 mL of saturated $NaHCO_3$ for 1 h at 20 °C. The mixture was extracted with ether, and the residue obtained from the dried ($MgSO_4$) ether extracts was subjected to flash chromatography [ethyl acetate] to yield 5 mg (28%) of diol **28a**. This diol was identical (TLC, IR, ^1H NMR) with the diol prepared from the benzyl ether **7**.

Acetylation of 28 mg of diol **28a** derived from milbemycin β_1 in the same manner as described for synthetic diol **28a** afforded 26 mg (60%) of diacetate **28b**, which was identical in all aspects (TLC, IR, ^1H NMR) with that derived from the synthetic diol.

Propionate 6a. To 2 mL of Et_2O at −78 °C under argon was added t-BuLi in pentane (1.63 M, 1.0 mL, 1.63 mmol) followed by addition of neat propenyl bromide (72 μL, 0.81 mmol), which was filtered through neutral alumina just prior to use. The reaction mixture was stirred at −75 °C for 40 min. A separate flask was charged with CuBr·DMS complex (84 mg, 0.410 mmol) which was dried azeotropically with benzene (2×) just prior to use. The CuBr·DMS complex was dissolved in 1 mL of dimethyl sulfide (freshly distilled over CaH_2) and transferred via syringe to the solution of propenyllithium. The resulting yellow-orange solution was stirred for 20 min at −78 °C, and then neat benzaldehyde (10 μL, 100 μmol) was added. After a minimum of 5 min, aldehyde **7** (20 mg, 0.060 mmol) was added in 3 × 0.25 mL portions of dry Et_2O. The reaction mixture was stirred for 20 min and quenched at −78 °C with saturated NH_4Cl, followed by warming to room temperature. The aqueous layer was extracted with Et_2O, and the combined organic fractions were washed with NH_4OH and brine. The resulting clear solution was dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography [gradient elution, hexane–ethyl acetate 20:1, 15:1, 10:1, 5:1 (v/v)] afforded 15.7 mg (70%) of a 7:1 mixture (NMR) of alcohols. To this mixture of alcohols, dissolved in 1 mL of dry CH_2Cl_2 at 0 °C, was added pyridine (0.2 mL, 2.48 mmol), followed by propionyl chloride (0.18 mL, 2.07 mmol) and a catalytic amount of DMAP. After 1 h at 0 °C, (dimethylamino)propylamine (0.5 mL, 4 mmol) was added to the reaction to quench the excess propionyl chloride. The reaction mixture was extracted with Et_2O, and the combined organic fractions were washed with 5% HCl, H_2O, and a brine–$NaHCO_3$ mixture. Purification by preparative thin-layer chromatography [hexane–ethyl acetate 10:1 (v/v)], three developments (20 × 20 cm plate), 0.5 mm) afforded 13 mg (72%) of β-propionate **6a** and 2 mg (11%) of the α-propionate **6b**.

6a: IR (CCl_4) 3050 (w), 3015 (w), 2930 (br s), 1735 (s), 1650 (w), 1198 (br s), 1100 (br s), 995 (s), 910 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.81 (d, J = 7 Hz, 3 H), 0.90–1.85 (m, 9 H), 1.06 (d, J = 6 Hz, 3 H), 1.13 (t, J = 7 Hz, 3 H), 1.73 (s, 3 H), 1 94–2.20 (m, 2 H), 2.31 (q, J = 7 Hz, 2 H), 3.08 (dq, J = 10.8, 7 Hz, 1 H), 3.55–3.72 (m, 1 H), 3.86–4.02 (m, 1 H), 4.54 (s, 2 H), 4.86 (s, 1 H), 4.96 (s, 1 H), 5.40 (m, 1 H), 7.24–7.33 (m, 5 H); chemical ionization mass spectrum, m/e

431.2781 (MH^+, calcd for $C_{26}H_{39}O_5$, 431.2787).

6b: IR (CCl_4) 3065 (w), 3030 (w), 2940 (br s), 1740 (s), 1650 (w), 1195 (br s), 1090 (br s), 995 (s), 910 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.82 (d, J = 7 Hz, 3 H), 1.04–2.18 (m, 11 H), 1.07 (d, J = 6 Hz, 3 H), 1.14 (t, J = 8 Hz, 3 H), 1.73 (s, 3 H), 2.33 (q, J = 8 Hz, 2 H), 3.22–3.36 (dq, J = 10.8, 7.0 Hz, 1 H), 3.48–3.62 (m, 1 H), 3.82–3.96 (m, 1 H), 4.53 (s, 2 H), 4.93 (s, 1 H), 5.00 (s, 1 H), 5.39 (t, J = 7 Hz, 1 H), 7.24–7.33 (m, 5 H); chemical ionization mass spectrum, m/e 431.2736 (MH^+, calcd for $C_{26}H_{39}O_5$, 431.2787.

Enone 32. To 3 mL of CH_2Cl_2 under argon at room temperature was added pyridine (0.2 mL, 2.48 mmol) followed by CrO_3 (127 mg, 1.27 mmol). After the mixture stirred at room temperature for 15 min, the above alcohols (39 mg, 0.105 mmol) were added in 3 × 1 mL portions of dry CH_2Cl_2. After 1 h the reaction was diluted with Et_2O, and the organic layers were washed consecutively with 5% NaOH, H_2O (until clear), 5% HCl, H_2O, and saturated $NaHCO_3$. The organic phase was dried over $MgSO_4$ and concentrated in vacuo to give a yellow oil. Purification by flash chromatography [gradient elution, hexane–ethyl acetate, 20:1, 15:1, 10:1, 5:1 (v/v)] afforded 32.7 mg (84.5%) of enone **32**: IR ($CHCl_3$) 2935 (br s), 1680 (s), 1630 (w), 1090 (s), 1060 (s), 990 (s), 940 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.76 (d, J = 6.4 Hz, 3 H), 1.04–1.74 (m, 7 H), 1.09 (d, J = 6.3 Hz, 3 H), 1.91 (s, 3 H), 2.04–2.22 (m, 2 H), 2.63 (dd, J = 15.0, 5.1 Hz, 1 H), 3.05 (dd, J = 8.0, 7.2 Hz, 1 H), 3.24 (dq, J = 9.8, 6.5 Hz, 1 H), 3.87–4.15 (m, 2 H), 4.56 (s, 2 H), 5.83 (s, 1 H), 6.02 (s, 1 H), 7.20–7.28 (m, 5 H); chemical ionization mass spectrum, m/e 373.2384 (MH^+, calcd for $C_{23}H_{33}O_4$, 373.2370).

Propionate 6b. To enone **32** (32 mg, 0.086 mmol) in 5 mL of Et_2O at 0 °C was added an ether solution of $Zn(BH_4)_2$ (0.25 M, 0.50 mL, 0.125 mmol). The reaction mixture was stirred at 0 °C for 2 h and then carefully quenched with 5% HCl. The resultant mixture was then extracted with Et_2O, and the organic phase was washed with a saturated $NaHCO_3$–brine mixture. After drying over $MgSO_4$ and concentration in vacuo, the resulting clear oil was purified by flash chromatography [gradient elution, hexane–ethyl acetate, 15:1, 10:1, 5:1 (v/v)] to afford 28 mg (87%) of an 8.5:1 mixture (NMR) of alcohols. The mixture was treated with propionyl chloride as described above to afford 19 mg (59%) of propionate **6b** and 2.5 mg (7.7%) of propionate **6a**.

Acid 31a. To a solution of $KN(SiMe_3)_2$ (0.305 M, 5.06 mL, 1.54 mmol) in THF at −78 °C was added ester **6a** (83 mg, 0.193 mmol) in 2 mL of THF. The reaction mixture was stirred for 10 min, HMPA (0.30 mL, 0.175 mmol) was added, and then after an additional 10 min, 0.35 mL of 75% Me_3SiCl-TEA solution (v/v) was added. The reaction mixture was then warmed to 25 °C, stirred for 1 h, and then heated at 40–50 °C for 1 h. After cooling, the solution was diluted with excess 5% HCl and extracted with ether. The ether extracts were washed with water and brine and concentrated in vacuo. The resulting oil was purified by flash chromatography [hexane–ether, 2:1, 1:1 (v/v)] to yield acid **31a** (45.5 mg, 55%) as a colorless oil: IR (CCl_4) 3400–2450 (br), 2925 (s), 1705 (s), 1205 (m), 1085 (s), 995 (s), 950 (m), 825 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.82 (d, J = 7 Hz, 3 H) 0.96–1.71 (m, 7 H), 1.14 (app t, J = 7 Hz, 6 H), 1.62 (s, 3 H), 1.91–2.28 (m, 5 H), 2.28–2.50 (m, 1 H), 2.50–2.68 (m, 1 H), 3.20 (dq, J = 9.8, 7.5 Hz, 1 H), 3.40–3.55 (m, 1 H), 3.72–3.97 (m, 1 H), 4.53 (s, 2 H), 5.27 (t, J = 7 Hz, 1 H), 7.24–7.33 (m, 5 H), OH not specified; chemical ionization mass spectrum, m/e 431.2773 (MH^+, calcd for $C_{21}H_{39}O_5$, 431.2787).

In a similar manner ester **6b** (60 mg, 0.140 mmol) was converted into acid **31b** (34.0 mg, 57%): IR (CCl_4) 3400–2450 (br), 2920 (s), 1703 (s), 1205 (m), 1085 (s), 995 (s), 950 (m), 825 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.82 (d, J = 7 Hz, 3 H), 0.95–1.73 (m, 7 H), 1.14 (app t, J = 7 Hz, 6 H), 1.62 (s, 3 H), 1.92–2.28 (m, 5 H), 2.28–2.50 (m, 1 H), 2.50–2.68 (m, 1 H), 3.26 (dq, J = 9.8, 7.0 Hz, 1 H), 3.39–3.52 (m, 1 H), 3.72–3.97 (m, 1 H), 4.53 (s, 2 H), 5.30 (t, J = 7.0 Hz, 1 H), 7.24–7.33 (m, 5 H), OH not specified; chemical ionization mass spectrum, m/e 431.2763 (MH^+, calcd for $C_{26}H_{39}O_5$, 431.2787).

Northern Hemisphere 4a. A solution of acid **31a** (93 mg, 0.216 mmol) in 2 mL of THF was added to excess lithium (~100 mg) in 15 mL of liquid ammonia. The reaction mixture was stirred for 20 min and quenched with NH_4Cl, and the excess ammonia was evaporated. The residue was then diluted with 5% HCl and extracted with ether; the ether extracts were washed with brine, dried with $MgSO_4$, and concentrated in vacuo.

The resultant alcohol was then dissolved in 10 mL of DMF and treated with TBDMSCl (250 mg, 1.66 mmol) and 600 mg (8.8 mmol) of imidazole for 24 h at 25 °C. The reaction mixture was diluted with ether and washed with saturated $NaHCO_3$, water, and brine, and the ether was reduced in vacuo to ~20 mL, whereupon excess LAH (~500 mg) was added. The reaction mixture was then heated at reflux for 1 h, quenched with $Na_2SO_4 \cdot 10H_2O$, and filtered, and the ether was removed in vacuo. The resulting product was purified by flash chromatography [gradient elution, hexane–ethyl acetate, 20:1, 15:1, 10:1 (v/v)] to afford 62 mg (65%) of a pure alcohol: IR (CCl_4) 3640 (w), 3510 (br), 2945 (br s), 1260 (m), 1080 (br s), 995 (m), 838 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.06 (s, 6 H), 0.75–1.92 (m, 15 H), 0.80 (d, J = 7 Hz, 3 H), 0.88 (s, 9 H), 1.10 (d, J = 7 Hz, 3 H), 1.64 (s, 3 H), 1.96–2.24 (m, 3 H), 3.24 (dq, J = 9.8, 7.0 Hz, 1 H), 3.36–3.56 (m, 3 H), 3.96–4.14 (m, 1 H), 5.26 (t, J = 7 Hz, 1 H); chemical ionization mass spectrum, m/e 441.3401 (MH^+, calcd for $C_{25}H_{49}O_4Si$, 441.3387.

In a similar manner acid **31b** (55 mg, 0.130 mmol) was converted into the C(12) epi alcohol (32 mg, 58%): IR (CCl_4) 3630 (w), 3500 (br), 2935 (br s), 1260 (m), 1080 (br s), 995 (m), 838 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.06 (s, 6 H), 0.75–1.70 (m, 15 H), 0.80 (d, J = 7 Hz, 3 H), 0.88 (s, 9 H), 1.10 (d, J = 7 Hz, 3 H), 1.64 (s, 3 H), 2.06–2.24 (m, 3 H), 3.24 (dq, J = 9.8, 7.0 Hz, 1 H), 3.36–3.56 (m, 3 H), 3.96–4.14 (m, 1 H), 5.26 (t, J = 7 Hz, 1 H); chemical ionization mass spectrum, m/e 441.3405 (MH^+, calcd for $C_{25}H_{49}O_4Si$, 441.3387).

To 3 mL of CH_2Cl_2 containing pyridine (0.2 mL, 2.5 mmol) was added CrO_3 (125 mg, 1.25 mmol). After the mixture was stirred at room temperature for 15 min, the alcohol derived from acid **31a** (50 mg, 0.136 mmol) was added in three 0.75-mL portions of CH_2Cl_2. After 0.5 h, the reaction mixture was diluted with Et_2O, and the organic layers were washed with 5% NaOH, H_2O (until clear), 5% HCl, and saturated NH_4Cl–brine mixture. After the organic phase was dried ($MgSO_4$) and concentrated in vacuo, the product was purified by flash chromatography [gradient elution, hexane–ethyl acetate 30:1, 20:1 (v/v)] to afford 52 mg (87%) of aldehyde **4a** as a colorless oil: IR (CCl_4) 2925 (br s), 2680 (w), 1720 (s), 1080 (s), 990 (m), 835 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.04 (s, 6 H), 0.72–2.26 (m, 12 H), 0.80 (d, J = 7 Hz, 3 H), 0.88 (s, 9 H), 1.06 (d, J = 7 Hz, 3 H), 1.10 (d, J = 7 Hz, 3 H), 1.62 (s, 3 H), 2.38–2.58 (m, 2 H), 3.20 (dq, J = 9.8, 7.0 Hz, 1 H), 3.40–3.54 (m, 1 H), 3.98–4.12 (m, 1 H), 5.28 (t, J = 7 Hz, 1 H), 9.58 (d, J = 2 Hz, 1 H).

Anal. Calcd for $C_{25}H_{46}O_4Si$: C, 68.44; H, 10.56. Found: C, 68.62; H, 10.41.

In a similar manner the alcohol derived from acid **31b** (36 mg, 0.082 mmol) was converted into aldehyde **4b** (26 mg, 72%): IR (CCl_4) 2930 (br s), 2690 (w), 1725 (s), 1085 (br s), 995 (s), 840 (m) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 0.06 (s, 6 H), 0.75–2.05 (m, 12 H), 0.80 (d, J = 7 Hz, 3 H), 0.86 (s, 9 H), 1.03 (d, J = 7 Hz, 3 H), 1.08 (d, J = 7 Hz, 3 H), 1.64 (s, 3 H), 2.38–2.58 (m, 2 H), 3.20 (dq, J = 9.8, 6 Hz, 1 H), 3.38–3.54 (m, 1 H), 3.98–4.12 (m, 1 H), 5.28 (t, J = 7 Hz, 1 H), 9.60 (d, J = 1 Hz, 1 H).

Anal. Calcd for $C_{25}H_{46}O_4Si$: C, 68.44; H, 10.56. Found: C, 68.29; H, 10.49.

4-Methoxy-3-methylbenzoic Acid (11).[55] Commercially available 3-methyl-*p*-anisaldehyde (10.0 g, 0.067 mol) was dissolved in 250 mL of acetone. Jones reagent[56] (65 mL, prepared from 15.4 g of CrO_3 and 12 mL of concentrated H_2SO_4 diluted to 100 mL with H_2O) was added, and the mixture was stirred overnight at 25 °C. The mixture was filtered through Celite, the volume was reduced by 50% in vacuo, and the remaining solution was poured into water. The aqueous mixture was extracted twice with ether, the ether fractions were combined, washed with water and brine, and dried over $MgSO_4$, and the solvent was removed in vacuo. The residual yellow solid was recrystallized (EtOH–H_2O 3:1) to afford a yellow-white crystalline solid: 7.6 g, 68%; mp 192–194 °C; ^1H NMR (60 MHz, $CDCl_3$) δ 2.20 (s, 3 H), 3.85 (s, 3 H), 6.80 (d, J = 9 Hz, 1 H), 7.75–7.95 (m, 2 H), *OH* not specified.

4,5-Dihydro-2-(4-methoxy-3-methylphenyl)-4,4-dimethyloxazole (33). Acid **11** (3.5 g, 21 mmol) was stirred with $SOCl_2$ (9 mL, 123 mmol) at 25 °C for 24 h. The excess $SOCl_2$ was removed in vacuo and the residue distilled (70–73 °C/0.1 mm) to give the corresponding acid chloride (3.5 g, 90%) which was then dissolved in 30 mL of CH_2Cl_2 and added to 2-methyl-2-aminopropanol (3.2 g, 36 mmol) in 15 mL of CH_2Cl_2. The mixture was stirred for 2 h at 25 °C and filtered, and the filtrate was concentrated in vacuo to afford an amide as a colorless oil.

Thionyl chloride (15 mL, 0.205 mol) was then slowly added, and the resulting solution was stirred at 25 °C for 30 min. The thionyl chloride was removed in vacuo, dilute HCl (5%, ca. 300 mL) was added to the residue, and the resultant solution was washed with ether. The aqueous fraction was made basic with 25% NaOH and extracted 3 times with ether. The ether solution was washed with water and brine, dried over K_2CO_3, and concentrated. The resulting oil was distilled (95–100 °C/0.15 mm) to afford a colorless viscous oil which solidified upon cooling (3.45 g, 88% based on acid chloride). Recrystallization from ether–hexane gave a white crystalline solid, **33**: mp 45–46.5 °C; IR ($CHCl_3$)

(55) Schall, C. *Chem. Ber.* **1879**, *12*, 816. Also see: Quelet, R. *Bull. Soc. Chim. Fr.* **1940**, *7*, 205.

(56) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. L. L. *J. Chem. Soc.* **1946**, 39. Also see: Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; Vol. 1, pp 142–144.

2960 (br s), 1630 (s), 1605 (s), 1270 (br s), 1145 (s), 1040 (s), 822 (s) cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 1.12 (s, 6 H), 2.20 (s, 3 H), 3.78 (s, 3 H), 4.0 (s, 2 H), 6.7 (d, J = 9 Hz, 1 H), 7.60–7.70 (m, 2 H).

Anal. Calcd for $C_{13}H_{17}O_2N$: C, 71.19; H, 7.83; N, 6.39. Found: C, 71.38; H, 7.79; N, 6.31.

1-[2-(4,5-Dihydro-4,4-dimethyl-2-oxazolyl)-5-methoxy-4-methylphenyl]ethanone (34). Oxazoline **33** (1.63 g, 7.434 mmol) was dissolved in 30 mL of ether and cooled to 0 °C. To this mixture was added *sec*-butyllithium (1.3 M, 6.8 mL, 8.84 mmol), and the mixture was stirred at 0 °C for 4 h. The contents of the flask were transferred to a second flask containing acetic anhydride (0.91 mL, 9.63 mmol) in 10 mL of ether at −78 °C. This mixture was stirred at −78 °C for 15 min and then allowed to warm to 25 °C. Saturated NH_4Cl was added and the mixture extracted with ether; the ether solution was washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue purified by flash chromatography [4:1 hexane–ethyl acetate (v/v)] to afford 1.00 g (51%) of **34** as a pale yellow oil: IR (thin film) 2975 (br s), 1710 (s), 1660 (s), 1160 (s), 990 (s) cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.12 (s, 6 H), 2.2 (s, 3 H), 2.46 (s, 3 H), 3.86 (s, 3 H), 4.03 (s, 2 H), 6.8 (s, 1 H), 7.6 (s, 1 H); chemical ionization mass spectrum, m/e 262.1434 (MH^+, calcd for $C_{15}H_{20}O_3N$, 262.1438).

Iminolactone 35. Ketone **34** (1.85 g, 7.08 mmol) was dissolved in 35 mL of ether, the solution was cooled to 0 °C, and vinylmagnesium bromide (1.1 M, 8.8 mL, 9.7 mmol) was added. The mixture was stirred at 0 °C for 15 min, allowed to warm to 25 °C, and then quenched with saturated NH_4Cl. The resultant solution was extracted with ether, and the ether fractions were washed with brine and dried over $MgSO_4$. Removal of solvents in vacuo gave 2.00 g (98%) of a yellow solid suitable for further use. Recrystallization from ether–hexane afforded a pure sample of **35** as a white crystalline solid: mp 105–106 °C, IR ($CHCl_3$) 3610 (m), 3450 (br), 2990 (br s), 1690 (s), 1260 (s), 1225 (s), 1050 (s) cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 1.35 (s, 6 H), 1.72 (s, 3 H), 2.36 (s, 3 H), 3.00 (br, 1 H), 3.40 (br s, 2 H), 3.92 (s, 3 H), 5.0–5.5 (m, 2 H), 6.06 (dd, J = 17, 10 Hz, 1 H), 6.55 (s, 1 H), 7.46 (s, 1 H); electron impact mass spectrum, m/e 289.1688 (M^+, calcd for $C_{17}H_{23}O_3N$, 289.1672).

3-Ethenyl-5-methoxy-3,6-dimethyl-1(3*H*)-isobenzofuranone (10). The iminolactone **35** (0.98 g, 3.39 mmol) was dissolved in 25 mL of THF, 2.5 mL of 3 M H_2SO_4 was added. The mixture was stirred for 12 h at 25 °C, whereupon the mixture was poured into water and extracted with ether. The ether fractions were washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$. Removal of the solvent in vacuo afforded 0.60 g (88%) of an off-white solid, suitable for further use. Recrystallization from CH_2Cl_2–ether yielded a pure sample of **10** as a white crystalline solid: mp 135–136 °C; IR ($CHCl_3$) 2970 (br s), 1750 (s), 1601 (s), 1050 (s) cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.85 (s, 3 H), 2.25 (s, 3 H), 3.90 (s, 3 H), 5.00–5.55 (m, 2 H), 6.00 (dd, J = 17, 10 Hz, 1 H), 6.65 (s, 1 H), 7.60 (s, 1 H).

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.53; H, 6.48. Found: C, 71.47; H, 6.50.

2-[3-(Diphenylphosphinyl)-1-propenyl]-4-methoxy-5-methyl-(*E*)-benzoic Acid (5a) and Its *Z* Isomer 36a. Diphenylphosphine (1.53 mL, 8.81 mmol) was dissolved in 25 mL of THF under an argon atmosphere and the solution cooled to −22 °C (dry ice–CCl_4). *n*-Butyllithium (1.59 M) was then added until a yellow color persisted; an additional 5.5 mL (8.75 mmol) was then added. To the resultant red solution lactone **10** (1.6 g, 7.34 mmol) in 25 mL of THF was added; the mixture was stirred at −22 °C for 30 min and then allowed to warm to 25 °C and stir for an additional 3-h period. Ether saturated with HCl gas was added until the mixture turned wet litmus paper red. All solvents were then removed in vacuo, the resulting green gel was dissolved in 100 mL of $CHCl_3$ containing 5 mL of AcOH, and air was bubbled through the solution for 12 h. The solvent was removed in vacuo and the AcOH removed as an azeotrope with heptane. Ethylene glycol (40 mL) and 2 g of sodium hydroxide were added, and the mixture was heated at 140 °C for 12 h. The resultant brown mixture was poured into water and washed with ether, and the aqueous solution was acidified to pH 1 with 5% HCl and extracted with ether. The combined ether fractions were washed with brine and dried over $MgSO_4$, and the solvent was removed in vacuo to afford a residue which was purified by flash chromatography [gradient elution, hexane–EtOAc–AcOH; 25:10:1, 20:10:1, 15:10:1] to afford the (*Z*)-acid **36a** (1.31 g, 36%) as a pale orange solid and the (*E*)-acid **5a** (1.03 g, 33%) as an off-white foam. Treatment of the acids with diazomethane afforded the corresponding methyl esters.

5b: IR ($CHCl_3$) 2990 (br s), 1705 (s), 1370 (s), 1280 (br s), 1180 (br s), 1015 (m), 915 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.00 (d, J = 3 Hz, 3 H), 2.22 (s, 3 H), 2.80–2.95 (m, 2 H), 3.75 (s, 3 H), 3.80 (s, 3 H), 5.45 (m, 1 H), 6.60 (s, 1 H), 7.30–7.65 (m, 10 H), 7.76 (s, 1 H); chemical ionization mass spectrum, m/e 435.1735 (MH^+, calcd for $C_{26}H_{28}O_4P$, 435.1717).

36b: IR ($CHCl_3$) 2970 (br s), 1705 (s), 1370 (s), 1270 (s), 1170 (s), 1010 (m), 910 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.84 (d, J = 1.8 Hz, 3 H), 2.14 (s, 3 H), 3.25–3.36 (dd, J = 14.8, 7.5 Hz, 2 H), 3.75 (s, 6 H), 5.35 (m, 1 H), 6.29 (s, 1 H), 7.45 (m, 6 H), 7.65 (s, 1 H), 7.78 (m, 4 H).

Anal. Calcd for $C_{26}H_{27}O_4P$: C, 71.87; H, 6.28. Found: C, 71.89; H, 6.45.

Naphthol 37 and Diene 39. Sodium hydride (214 mg, 60% oil dispersion) was washed with pentane under argon and dried. To this was added 20 mL of THF, and the resulting slurry was cooled to 0 °C. A mixture (1:3, respectively) of esters **5b** and **36b** (200 mg, 0.46 mmol) in 10 mL of THF was added. The resultant mixture was stirred at 0 °C for 10 min and then at 25 °C for 50 min and at 55 °C for 2.5 h. To the reaction mixture was added neat pivaldehyde (0.14 mL, 1.29 mmol), and the reaction mixture was cooled, quenched with saturated NH_4Cl, and extracted with Et_2O. The organic phase was washed once with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography [gradient elution, hexane–ether, 5:1, 3:1, 2:1 (v/v)] to afford 36.9 mg (26.5%) of diene **39** and 99.6 mg (53.8%) of naphthol **37**.

39: IR ($CHCl_3$) 3010 (w), 2980 (s), 1710 (s), 1260 (s), 1160 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.06 (s, 9 H), 2.04 (s, 3 H), 2.20 (s, 3 H), 3.80 (s, 3 H), 3.84 (s, 3 H), 5.74 (d, J = 15.0 Hz, 1 H), 5.92 (br d, J = 10.75 Hz, 1 H), 6.30 (dd, J = 15.0, 10.75 Hz, 1 H), 6.64 (s, 1 H), 7.66 (s, 1 H).

37: IR ($CHCl_3$) 3575 (w), 3020 (w), 2960 (s), 1375 (s), 1260 (s), 1175 (s), 1055 (s), 848 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.36 (s, 3 H), 2.40 (s, 3 H), 3.92 (s, 3 H), 6.66 (d, J = 12.5 Hz, 1 H), 7.00 (s, 1 H), 7.40–7.80 (m, 10 H), 8.14 (s, 1 H), 9.18 (s, 1 H).

Anal. Calcd for $C_{25}H_{23}PO_3$: C, 74.61; H, 5.77. Found: C, 74.64; H, 5.78.

Diene 38. Sodium hydride (20 mg, 60% oil dispersion) was washed with pentane under argon and dried. To this was added 3 mL of THF followed by acid **5a** (20 mg, 0.046 mmol) in 4 mL of THF at 25 °C. The mixture was stirred for 1 h at 25 °C and then for 2 h at 65 °C. To this mixture was added neat pivaldehyde (0.02 mL, 0.183 mmol). The reaction mixture was allowed to stir at 65 °C for 18 h. It was cooled, quenched with saturated NH_4Cl, extracted with Et_2O, washed once with H_2O and brine, and dried over $MgSO_4$. The organic phase was concentrated in vacuo and purified by flash chromatography [hexane–ethyl acetate, 2:1 (v/v)] to afford 6.9 mg (52%) of (*E*,*E*)- and (*E*,*Z*)-dienes **38**: IR ($CHCl_3$) 2950–2450 (br s), 1690 (s), 1610 (m), 1375 (m), 1355 (s), 1270 (s), 1045 (w), 970 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.84 (s, 4.5 H), 1.06 (s, 4.5 H), 2.06 (s, 3 H), 2.20 (m, 3 H), 3.88 (br s, 3 H), 5.66 (d, J = 5.0 Hz, 1 H), 5.72 (d, J = 15.5 Hz, 0.5 H), 5.94 (d, J = 10.5 Hz, 0.5 H), 6.02 (br t, J = 5 Hz, 0.5 H), 6.26 (dd, J = 15.5, 10.5 Hz, 0.5 H), 5.56 (s, 0.5 H), 5.62 (s, 0.5 H), 7.80 (s, 0.5 H), 7.86 (s, 0.5 H), O*H* not specified.

Diene 40a. Phosphine oxide **5b** (26.0 mg, 60 μmol) was dissolved in 2 mL of dry THF under argon. The solution was cooled to −78 °C, and saodium hexamethyldisilazide in THF (0.36 M) was added until an orange color persisted. An additional 142 μL of the base (51 μmol) was then added, producing a brilliant red mixture. To this mixture was added aldehyde **4a** (13.1 mg, 30 μmol) in 1.5 mL of dry THF; a slight fading of the color resulted. The mixture was stirred at −78 °C for 10 min, and then the cold bath was removed whereupon the color discharged rapidly. The reaction mixture was stirred an additional 1 h, quenched with saturated NH_4Cl, and extracted with ether. The ether fractions were washed with brine, dried ($MgSO_4$), and concentrated. The resulting oil was purified by flash chromatography [hexane–EtOAc 25:1 (v/v)] to yield 18.8 mg (95%) of diene **40a**.

40a: IR (CCl_4) 2925 (br s), 1720 (s), 1600 (w), 1550 (w), 1270 (s), 1170 (s), 1080 (m), 995 (m), 840 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.04 (s, 6 H), 0.78–2.28 (m, 13 H), 0.78 (d, J = 6.6 Hz, 3 H), 0.84 (s, 9 H), 0.96 (d, J = 6.3 Hz, 3 H), 1.10 (d, J = 6.3 Hz, 3 H), 1.62 (s, 3 H), 2.08 (s, 3 H), 2.18 (s, 3 H), 2.45 (m, 1 H), 3.24 (dq, J = 9.8, 7.0 Hz, 1 H), 3.47 (m, 1 H), 3.78 (s, 3 H), 3.84 (s, 3 H), 4.05 (m, 1 H), 5.22 (t, J = 7 Hz, 1 H), 5.64 (dd, J = 15.0, 6.9 Hz, 1 H), 5.90 (d, J = 11.0 Hz, 1 H), 6.33 (dd, J = 15.0, 11.0 Hz, 1 H), 6.60 (s, 1 H), 7.64 (s, 1 H); chemical ionization mass spectrum, m/e 655.4376 (MH^+, calcd for $C_{39}H_{63}O_6Si$, 655.4377).

In a similar manner phosphine oxide **5b** (111 mg, 0.256 mmol) was reacted with aldehyde **4b** (56 mg, 0.128 mmol) to afford diene **40b** (70 mg, 83%): IR (CCl_4) 2940 (br s), 1720 (s), 1600 (w), 1555 (w), 1270 (s), 1165 (s), 1080 (s), 995 (m), 840 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.04 (s, 6 H), 0.75–2.28 (m, 16 H), 0.89 (d, J = 6.6 Hz, 3 H), 0.84 (s, 9 H), 1.07 (d, J = 6.3 Hz, 3 H), 1.62 (s, 3 H) 2.05 (s, 3 H), 2.18 (s, 3 H), 2.43 (m, 1 H), 3.21 (m, 1 H), 3.45 (m, 1 H), 3.78 (s, 3 H), 3.84 (s, 3 H), 4.05 (m, 1 H), 5.22 (br t, J = 7 Hz, 1 H), 5.65 (dd, J = 15.1, 6.8 Hz, 1 H), 5.90 (d, J = 10.9 Hz, 1 H), 6.3 (dd, J = 15.1, 10.9 Hz,

1 H), 6.60 (s, 1 H), 7.64 (s, 1 H); chemical ionization mass spectrum, *m/e* 655.4347 (MH^+, calcd for $C_{39}H_{63}O_6Si$, 655.4377).

2,5,6,7-Tetradehydro-7,28-dideoxy-25-methyl-(25*R*)-(±)-milbemycin B (42a). Diene **40a** (65 mg, 0.098 mmol) was dissolved in 5 mL of THF and excess (ca. 2 mL, 1 M) Bu_4NF-THF (Aldrich) solution added. The orange solution was stirred for 4 h at 25 °C. Water was then added and the mixture extracted with ether; the ether fractions were washed with brine, dried over $MgSO_4$, and evaporated. The resultant alcohol was dissolved in 10 mL of THF and added to five drops (excess) of a 35% KH-oil dispersion (previously, washed with ether) in 10 mL of THF. The mixture was stirred at 25 °C for 3 h. Saturated NH_4Cl was then added and the mixture extracted with ether; the ether solution was washed with brine, dried over $MgSO_4$, and evaporated. Purification by flash chromatography [hexane–ethyl acetate, 30:1 (v/v)] afforded 38 mg (76%) of macrolide **42a** as a colorless viscous oil: IR (CCl_4) 2940 (br s), 1715 (s), 1605 (m), 1550 (w), 1265 (br s), 1170 (s), 1105 (s), 1055 (s), 1005 (s), 970 (m), 855 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.70–2.38 (m, 13 H), 0.82 (d, *J* = 6.3 Hz, 3 H), 1.02 (d, *J* = 6.6 Hz, 3 H), 1.12 (d, *J* = 6.3 Hz, 3 H), 1.62 (s, 3 H), 2.09 (s, 3 H), 2.17 (s, 3 H), 2.48 (m, 1 H), 3.27 (m, 1 H), 3.67 (m, 1 H), 3.82 (s, 3 H), 4.88 (br d, *J* = 8.8 Hz, 1 H), 5.24 (dd, *J* = 14.9, 9.4 Hz, 1 H), 5.50 (m, 1 H), 5.70 (d, *J* = 10.7 Hz, 1 H), 6.12 (dd, *J* = 14.9, 10.7 Hz, 1 H), 6.60 (s, 1 H), 7.32 (s, 1 H); chemical ionization mass spectrum, *m/e* 509.3237 (MH^+, calcd for $C_{32}H_{45}O_5$, 509.3255).

In a similar manner diene **40b** (89 mg, 0.135 mmol) was converted into macrolide **42b** (54 mg, 79%): IR (CCl_4) 2930 (br s), 1700 (s), 1600 (m), 1265 (br s), 1170 (s), 1050 (m), 1000 (m), 960 (w), 850 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.75–2.32 (m, 13 H), 0.82 (d, *J* = 6.6 Hz, 3 H), 1.06 (d, *J* = 6.6 Hz, 3 H), 1.12 (d, *J* = 6.2 Hz, 3 H), 1.60 (s, 3 H), 2.02 (s, 3 H), 2.16 (s, 3 H), 2.50 (m, 1 H), 3.22 (dq, *J* = 9.8, 7.0 Hz, 1 H), 3.73 (m, 1 H), 3.80 (s, 3 H), 5.16 (br d, *J* = 10.6 Hz, 1 H), 5.28 (m, 1 H), 5.42 (dd, *J* = 15.1, 8.9 Hz, 1 H), 5.80 (d, *J* = 10.8 Hz, 1 H), 6.15 (dd, *J* = 15.1, 10.8 Hz, 1 H), 6.58 (s, 1 H), 7.32 (s, 1 H); chemical ionization mass spectrum, *m/e* 509.3231 (MH^+, calcd for $C_{32}H_{45}O_5$, 509.3255).

Milbemycin β_3 (1a) and Its Epimer, Epimilbemycin β_3 (1b). Sodium hydride (400 mg, 60% oil dispersion) was washed with ether under argon and dried. Distilled DMF (5 mL) was added, followed by careful addition of sufficient 1:1 EtSH-DMF to consume all of the hydride. Methyl ether **42a** (37 mg, 0.073 mmol) in 5 mL of DMF was then added to the clear yellow solution and the mixture heated at reflux for 1 h. The reaction mixture was cooled, poured into saturated NH_4Cl, and extracted with ether. The ether extract was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography [hexane–ethyl acetate, 5:1 (v/v)] afforded 31 mg (84%) of milbemycin β_3 (**1**) as a colorless hard glass. Crystallization from methylene chloride–hexane afforded 29 mg of crystalline solid: mp 153–156 °C; IR (CCl_4), 3600 (w), 3470 (br), 2940 (br s), 1675 (s), 1605 (m), 1285 (s), 1170 (s), 995 (s), 965 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.65–2.35 (m, 13 H), 0.82 (d, *J* = 6.6 Hz, 3 H), 1.00 (d, *J* = 6.6 Hz, 3 H), 1.12 (d, *J* = 6.3 Hz, 3 H), 1.61 (s, 3 H), 2.04 (s, 3 H), 2.20 (s, 3 H), 2.45 (m, 1 H), 3.26 (dq, *J* = 9.8, 7 Hz, 1 H), 3.68 (m, 1 H), 4.87 (br d, *J* = 9.5 Hz, 1 H), 5.13 (s, 1 H), 5.23 (dd, *J* = 15.1, 9.5 Hz, 1 H), 5.49 (m, 1 H), 5.69 (d, *J* = 11.1 Hz, 1 H), 6.12 (dd, *J* = 15.1, 11.1 Hz, 1 H), 6.59 (s, 1 H), 7.30 (s, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 15.19, 16.10, 17.83, 18.01, 19.39, 21.63, 27.83, 33.89, 35.83, 36.30, 36.62, 41.27, 48.74, 67.68, 68.21, 71.24, 97.73, 114.23, 121.52, 122.38, 124.11, 125.49, 128.79, 131.93, 134.05, 135.78, 140.26, 144.20, 155.55, 169.52.

Anal. Calcd for $C_{31}H_{42}O_5$: C, 75.27; H, 8.56. Found: C, 75.09; H, 8.77.

In a similar manner macrolide **42b** (50 mg, 0.098 mmol) was converted into **1b** (42.7 mg, 88%): mp 221–224 °C dec; IR (CCl_4), 3600 (w), 3470 (br), 2940 (br s), 1670 (s), 1601 (m), 1290 (s), 1175 (s), 1005 (s), 965 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.75–2.30 (m, 13 H), 0.80 (d, *J* = 6.6 Hz, 3 H), 1.04 (d, *J* = 7.0 Hz, 3 H), 1.09 (d, *J* = 6.3 Hz, 3 H), 1.58 (s, 3 H), 1.98 (s, 3 H), 2.20 (s, 3 H), 2.47 (m, 1 H), 3.23 (dq, *J* = 10.0, 7.5 Hz, 1 H), 3.75 (br d, *J* = 10.7 Hz, 1 H), 5.15 (br d, *J* = 12.9 Hz, 1 H), 5.25 (m, 1 H), 5.40 (dd, *J* = 15.3, 9.2 Hz, 1 H), 5.52 (s, 1 H), 5.76 (d, *J* = 10.7 Hz, 1 H), 6.12 (dd, *J* = 15.3, 10.7 Hz, 1 H), 6.53 (s, 1 H), 7.28 (s, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 15.13, 15.92, 17.86, 18.86, 19.33, 21.86, 27.92, 32.60, 34.27, 35.45, 35.77, 36.62, 40.83, 48.48, 66.12, 69.50, 71.18, 97.53, 114.85, 121.58, 122.20, 124.41, 125.17, 128.64, 131.52, 134.87, 135.29, 140.05, 144.87, 155.61, 168.75; chemical ionization mass spectrum, *m/e* 495.3070 (MH^+, calcd for $C_{31}H_{43}O_5$, 495.3099).

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Photocycloaddition of Anthracene to *trans,trans*-2,4-Hexadiene

Jack Saltiel,* Reza Dabestani, Kirk S. Schanze, Deanna Trojan, David E. Townsend, and Virgil L. Goedken

Contribution from the Department of Chemistry, The Florida State University, Tallahassee, Florida 32306. *Received October 10, 1985*

Abstract: Irradiation of anthracene (A) in the presence of *trans,trans*-2,4-hexadiene (D) gives A dimer (A_2), two adducts corresponding to [4 + 4] addition of D to the 9,10 positions of A, an adduct corresponding to [2 + 4] addition, and several unidentified minor adducts. A-^{14}C and isotopic dilution based analyses were used to establish that D reduces rather than enhances anthracene photodimerization quantum yields. A thermal Diels–Alder reaction between the strained trans double bond of the major anthracene/diene adduct (*t*-[4,4]Ad) and A is shown to account quantitatively for high A losses previously attributed to A dimerization. The structure of the 2:1 A/D adduct (A_2d) and, by inference, the structure of *t*-[4,4]Ad are established unequivocally by X-ray crystallography. These observations confirm Kaupp's qualitative results and conclusions. The singlet A/D exciplex is not an intermediate leading to either anthracene dimer or to A_2d. The singlet pathway for adducts gives *t*-[4,4]Ad (81%), *c*-[4,4]Ad (<5%), and the [2 + 4] adduct ([2,4]Ad) (14%). Triplet quenching, sensitization, and CH_3I experiments show that [2,4]-Ad and a fourth unknown minor adduct (x-Ad) derive from triplet-state precursors.

Suzuki was the first to propose that a termolecular interaction may enhance the efficiency of anthracene (A) photodimer (A_2) formation in solution.[1] In modern notation,[2,3] he proposed that interaction between the singlet anthracene excimer, $^1(AA)^*$, and anthracene gives A_2.

$$^1(AA)^* + A \rightarrow A_2 + A \quad (1)$$

Although eq 1 has been shown not to explain Suzuki's observations[4] which furthermore were not borne out by recent experi-

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