

# Synthetic Studies Directed toward the Naturally Occurring Acyl Tetramic Acids. 1. Convergent Total Synthesis of ( $\pm$ )-Tirandamycin A

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**Abstract:** An efficient convergent synthetic approach to the structurally unusual tetramic acid antibiotic tirandamycin A is described. Among the key features is the use of a rigid substituted cyclohexanone derivative as a vehicle to assure control of the relative stereochemistry during construction of an acyclic precursor. A new  $\beta$  acyl vinyl anion equivalent was also utilized in the assembly of the key acyclic precursor. After homologation, this acyclic precursor was elaborated to ( $\pm$ )-tirandamycin A by use of a modified tetramic acid phosphonate reagent.

Recently, there have been reported a number of studies directed toward the preparation of the structurally unusual bicyclic ketal tetramic acid antibiotics tirandamycin A (**1**) and streptolydigin (**2**), which were the first members of this growing class of natural substances whose complete stereostructures became known<sup>1</sup> (Chart I). Prior efforts have resulted in the preparation of tirandamycin acid, a degradation product of **1**, by several groups.<sup>2</sup> Very recently, the first synthetic routes to **1** have been described by Schlessinger and DeShong.<sup>3</sup> In this paper, we describe our efforts in this area which have culminated in an efficient convergent synthesis of ( $\pm$ )-**1** via a quite different strategy than any employed previously.<sup>4</sup>

Our approach is based upon the recognition of a latent symmetry element in the stereochemical array represented by the four contiguous chiral centers C-6 through C-9 and the use of this symmetry in the assembly and manipulation of an acyclic precursor to the dioxabicyclic ring system as outlined in Chart II.

Our synthetic route to the monocyclic ketone **3**, which is outlined in Scheme I, was initiated from the readily available 2,6-dimethyl-1,4-cyclohexanedione (**4**)<sup>5</sup> which was converted to the monoethylene ketal **5** under standard conditions (95%). The remaining carbonyl group was then cleanly reduced to the axial alcohol **6** (mp 69.5–71 °C) with L-Selectride in THF at –78 °C (84%).<sup>6</sup> After protection of the relatively hindered axial alcohol with *tert*-butyldimethylsilyl (TBS) triflate<sup>7</sup> in CH<sub>2</sub>Cl<sub>2</sub> to afford TBS ether **7** (98%), removal of the ketal with *p*-TsOH in acetone provided ketone **8** in 97% yield.<sup>8</sup> Thus, the centers corresponding to C-6 through C-8 in **1** are in place. The installation of the oxygen center corresponding to C-9 was then initiated by treatment of

**8** with LDA/THF at –78 °C followed by quenching with trimethylsilyl chloride (Me<sub>3</sub>SiCl) to provide the related enol silyl ether **9**. Without purification, **9** was subjected to oxidation with catalytic OsO<sub>4</sub> and *N*-methylmorpholine *N*-oxide in aqueous THF to afford, after chromatographic purification, an essentially quantitative yield of ketol **10** (mp 50–52 °C).<sup>9</sup> Protection of the ketol **10** with TBSCl was straightforward under the usual conditions<sup>10</sup> and provided the protected ketone **3** (mp 48–49 °C) in 71% overall yield from **8**. Thus, the conformational bias imparted to the intermediates in this series by the *cis* 1,3-methyl groups permits completely stereoselective functionalization of these monocyclic intermediates.<sup>11</sup>

Our next objective was elaboration of an acyclic precursor suitable for closure to the required dioxabicyclo[3.3.1]nonane system. Direct conversion of monooxygenated ketones such as **3** to an olefin suitable for fragmentation to such a precursor was investigated (Chart III). We selected the dibromo ketal **11** as our precursor for the required  $\beta$  acyl anion equivalent. Ketal **11** was readily prepared from 1,1-dibromo-2-methyl-1-buten-3-one<sup>12</sup> by ketalization with CH(OCH<sub>3</sub>)<sub>3</sub>/methanol. Completely regioselective metalation of **11** (1.1 equiv) in Et<sub>2</sub>O at –78 °C with *sec*-BuLi (1.1 equiv) afforded the derived (*E*)-(1-bromovinyl)-lithium reagent **12**<sup>13</sup> (Chart IV). Addition of **12** to ketone **13**, prepared by a route analogous to that for **3**, proceeded smoothly to afford trimethylsilyl ether **14** in 65% yield. Direct in situ metalation of **14** by subsequent addition of *t*-BuLi (2.2 equiv) at –78 °C and quenching provided the desired (*Z*)-ketal trimethylsilyl ether **15** in ~80% yield.

Unfortunately, all attempts to effect dehydration of **15** were unsuccessful. For example, **15** was inert to mild reagents such as SO<sub>2</sub>Cl<sub>2</sub>/imidazole,<sup>14</sup> which has been shown to be effective in a hindered system.<sup>15</sup> Use of acidic conditions uniformly resulted in decomposition.<sup>16</sup> We attributed our failure to the acid sen-

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(3) Schlessinger, R. H.; Bebernitz, G. R.; Lin, P.; Poss, A. J. *J. Am. Chem. Soc.*, **1985**, *107*, 1777. DeShong, P.; Ramesh, S.; Elango, V.; Perez, J. J. *J. Am. Chem. Soc.* **1985**, *107*, 5219.

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(5) Teuber, H.-J.; Cornelius, D.; Wolcke, U. *Justus Liebig's Ann. Chem.* **1966**, *696*, 116. Mixtures of *cis* and *trans* **4** were employed without purification.

(6) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159. (7) Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.

(8) Caserio, F. F.; Roberts, J. D. *J. Am. Chem. Soc.* **1958**, *80*, 5837.

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(10) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(11) For a related system which exhibits a similar conformational bias, see: Eliel, E. L.; Nader, F. W. *J. Am. Chem. Soc.* **1970**, *92*, 3045.

(12) Prepared by the method utilized for 1,1-dichloro-1-buten-3-one except that 1,1-dibromo-1-propene and AlBr<sub>3</sub> were utilized: Heibron, I.; Jones, E. H. R.; Julia, M. *J. Chem. Soc.* **1949**, 1430. Banville, J.; Brassard, P. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1852.

(13) The high level of regioselectivity most probably arises as the result of chelation with the adjacent oxygens of the ketal: Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1. In this case, use of *sec*-BuLi (~100:0) is superior to use of *t*-BuLi (9:1) in terms of regioselectivity: Lau, S. Y. K.; Schlosser, M. *J. Org. Chem.* **1978**, *43*, 1595.

(14) Hanessian, S.; Vatele, J.-M. *Tetrahedron Lett.* **1981**, *22*, 3579.

(15) Rastetter, W. H.; Adams, J.; Bordner, J. *Tetrahedron Lett.* **1982**, *23*, 1319.

(16) The acidic conditions employed included (1) *p*-TsOH/CH<sub>3</sub>OH, (2) 5% HCl/THF, and (3) *pyr-p*-TsOH/CH<sub>2</sub>Cl<sub>2</sub>.

Chart I

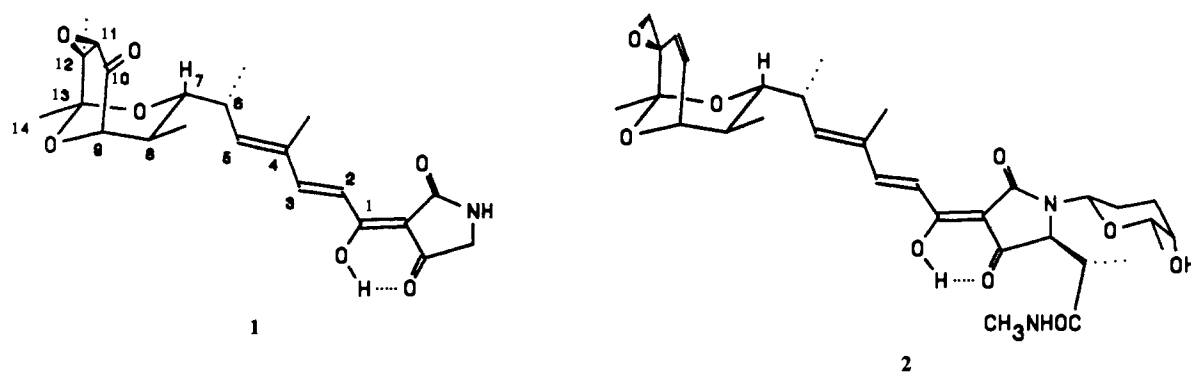


Chart II

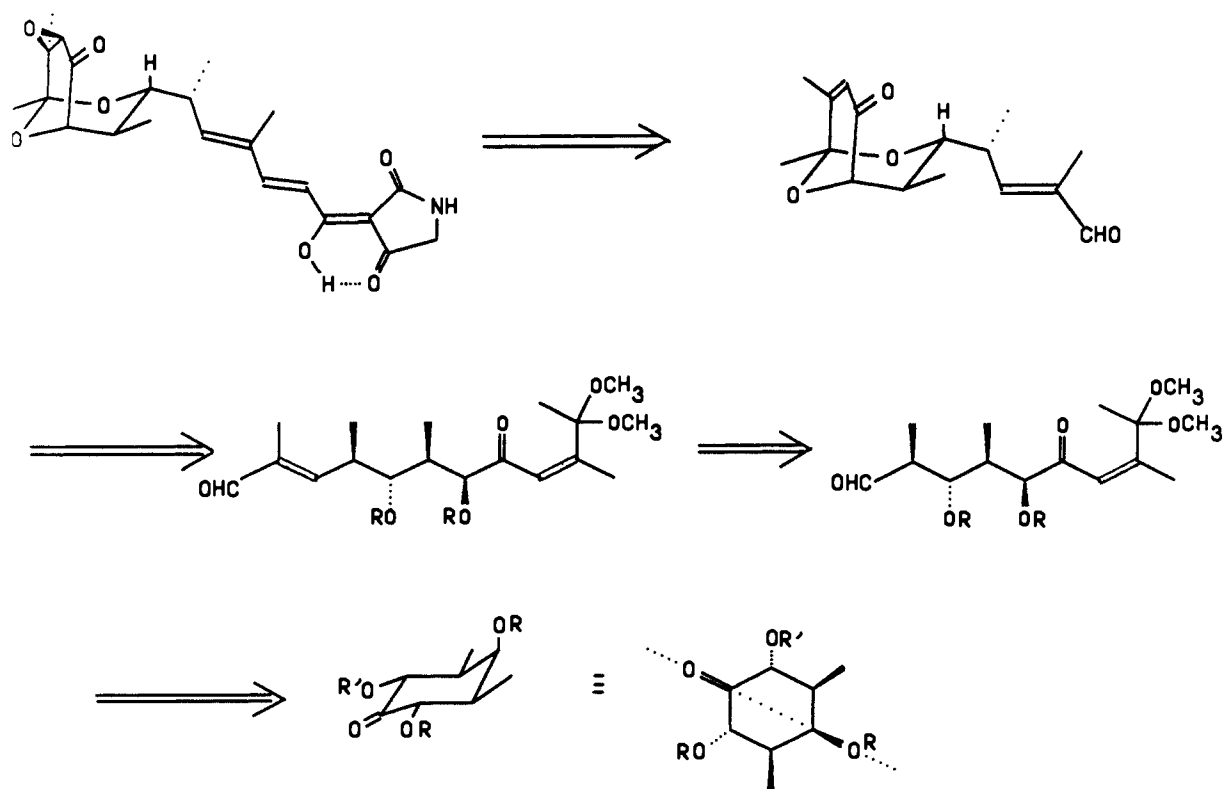
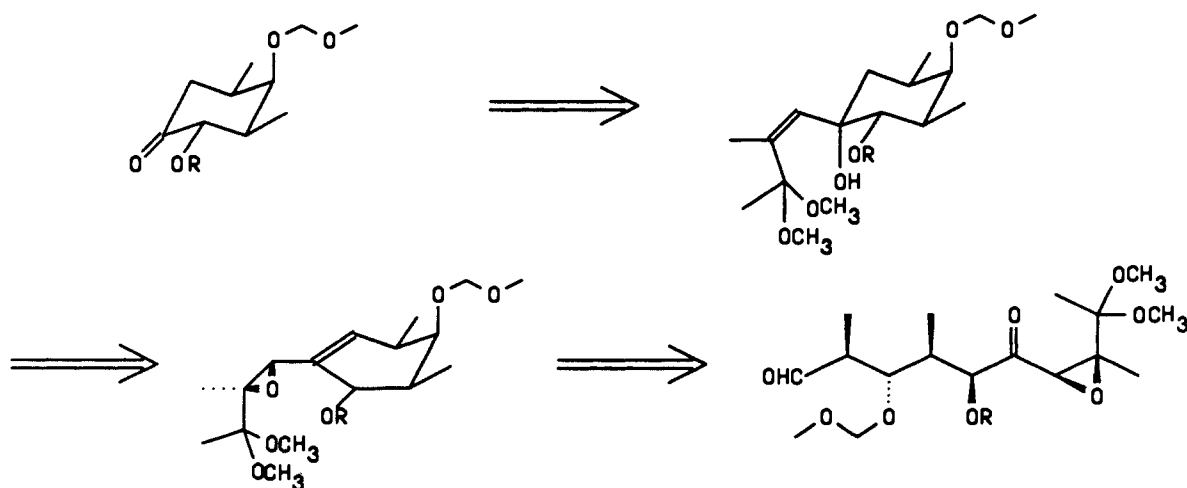


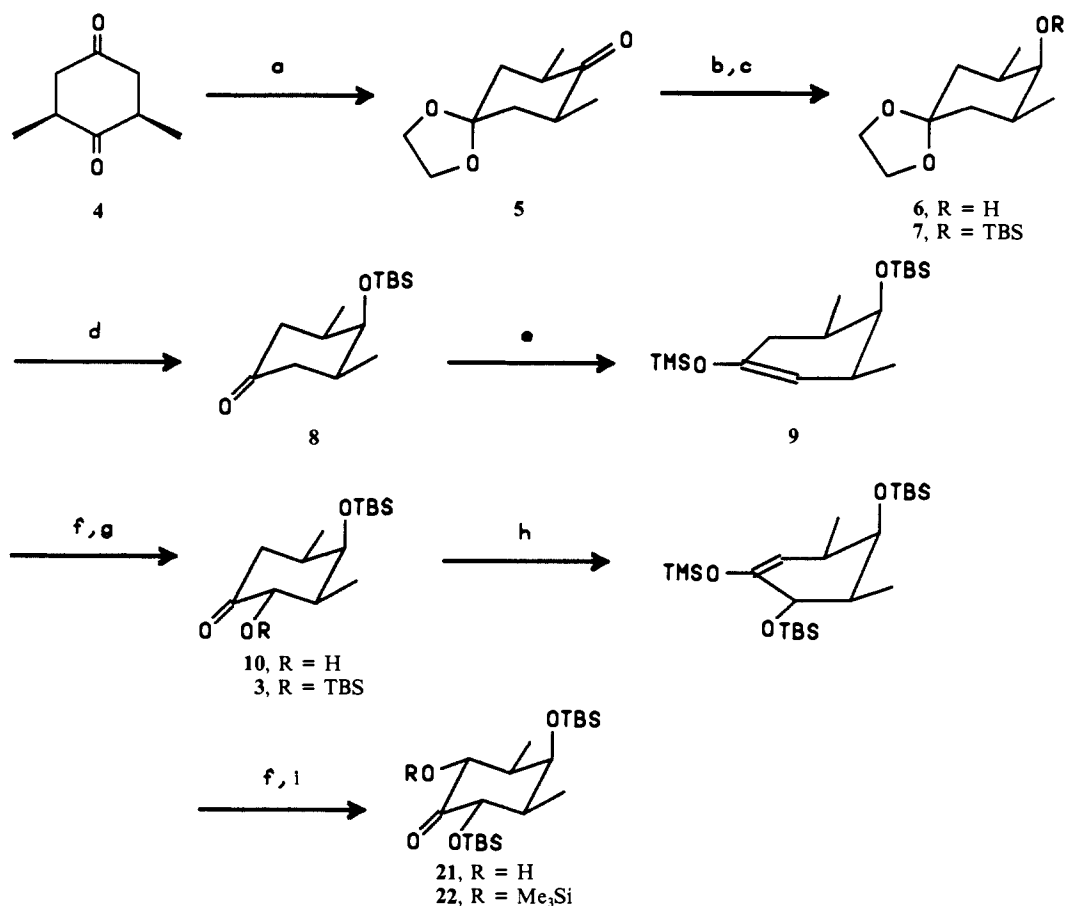
Chart III



sitivity of **15** and the extremely congested environment of the tertiary alcohol. Interestingly, no evidence of closure to the spirocyclic furanose derivative **16** (Chart V) was observed. This

failure to cyclize is undoubtedly due to stereoelectronic factors. Upon ionization of the ketal, the  $\pi$  system of the resulting allylic oxonium ion is orthogonal to the orbitals of the oxygen nonbonded

Scheme I<sup>a</sup>



<sup>a</sup> Reagents: (a) HOCH<sub>2</sub>CH<sub>2</sub>OH (0.95 equiv), *p*-TsOH (catalytic), PhH, reflux 24 h; (b) L-Selectride (1.25 Me<sub>3</sub>SiCl equiv), THF, -78 °C, 5 h; (c) *t*-Bu(CH<sub>3</sub>)<sub>2</sub>SiOTf (1.2 equiv), 2,6-lutidine (2 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 1 h; (d) *p*-TsOH (catalytic), acetone, reflux, ~48 h; (e) LDA (1.3 equiv), THF, -78 °C, 1 h, Me<sub>3</sub>SiCl (2 equiv), -78 °C, 1.5 h; (f) OsO<sub>4</sub> (catalytic), *N*-methylmorpholine *N*-oxide (2 equiv), THF-H<sub>2</sub>O (3:1), room temperature ~12 h; (g) *t*-Bu(CH<sub>3</sub>)<sub>2</sub>SiCl (3 equiv), imidazole (6 equiv), DMF, ~12 h; (h) LDA (3 equiv), THF, -30 °C, 1 h and then Me<sub>3</sub>SiCl (4 equiv), -30 °C, 1.5 h; (i) Me<sub>3</sub>SiCl (5 equiv), anhydrous Et<sub>3</sub>N (5.3 equiv), room temperature, ~2.4 h, nonaqueous workup.

Chart IV

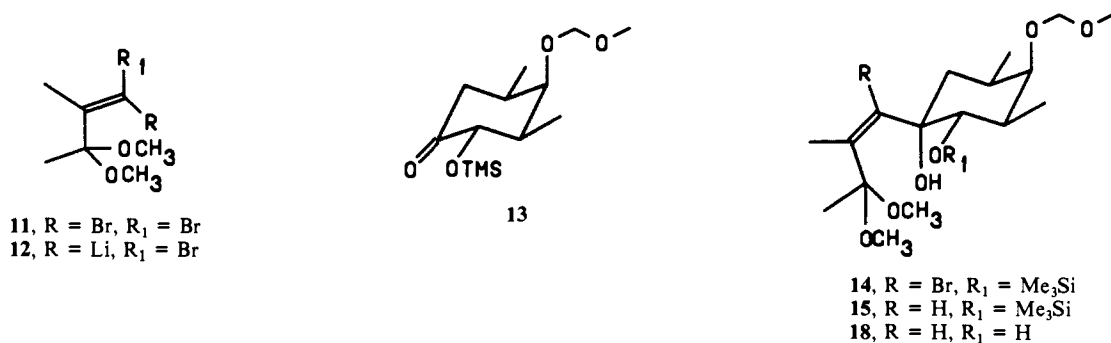
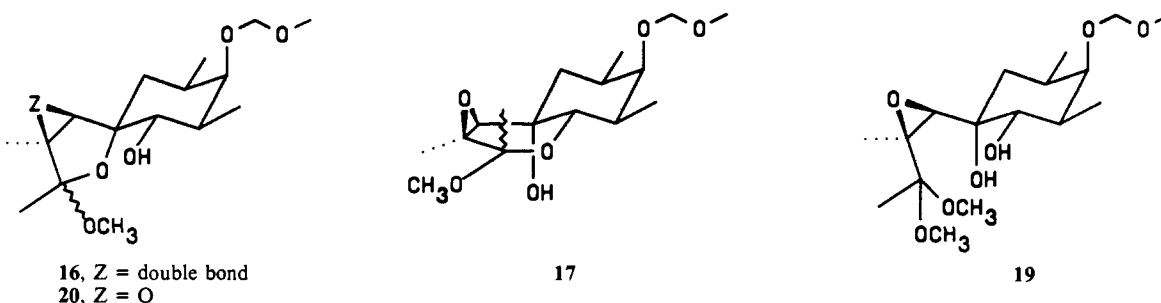


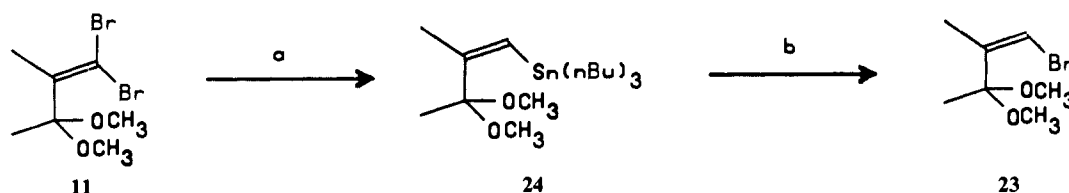
Chart V



electrons prohibiting ring closure.<sup>17</sup>

We also attempted to increase the accessibility of the tertiary

alcohol to external reagents and to effect stereocontrolled addition of the required epoxide by closure of 15 to pyranoside 17 prior

Scheme II<sup>a</sup>

<sup>a</sup> Reagents: (a) *sec*-BuLi (1.0 equiv), Et<sub>2</sub>O, -78 °C (0.33 h); *n*-Bu<sub>3</sub>SnCl (1.0 equiv), -78 °C (1 h) → room temperature (2 h); *t*-BuLi (2.0 equiv), -78 °C (0.25 h), aqueous NH<sub>4</sub>Cl; (b) NBS (1.0 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 0.5 h.

to dehydration. Thus, deprotection of **15** with fluoride produced the expected diol **18** (~100%). Hydroxyl-directed epoxidation of **18** with VO(AcAc)<sub>2</sub>/*t*-BuOH<sup>18</sup> sluggishly afforded the desired *syn*-epoxy diol **19** in ~70% yield. Alternatively, use of *p*-nitroperbenzoic acid<sup>19</sup> more rapidly afforded **19** (79% yield) but with somewhat lower stereoselectivity (9:1). Attempts to effect direct dehydration of **19** were similarly frustrated. Under mild conditions (SO<sub>2</sub>Cl<sub>2</sub>/imidazole), **19** was recovered unchanged. Under more vigorous or acidic conditions, rapid and clean cyclization to the furanose derivative **20** ensued. Attempts to equilibrate **20** to the desired pyranose **17** were also unrewarding as expected on the basis of the known propensity of ketoses to prefer the furanose form in nonaqueous media.<sup>20</sup> Upon treatment of **19** with HCl, we did isolate, in larger scale experiments, small amounts of a substance tentatively assigned structure **17** (on the basis of spectroscopic evidence), which was apparently formed under kinetic control. However, attempts to effect dehydration of this material also proved fruitless.

Therefore, we resorted to creation of a trigger for the fragmentation by further oxidation of **3** (Scheme I). Enolization of **3** with LDA at -30 °C in THF, trapping with Me<sub>3</sub>SiCl, and oxidation as before proceeded with complete regio- and stereo-control to afford the ketal bis(silyl) ether **21** (mp 95–96 °C).<sup>21</sup> This material was then silylated with Me<sub>3</sub>SiCl and triethylamine, providing the key protected ketone **22** (mp 64.5–66.5 °C) in 57% overall yield from **3**.

Surprisingly, ketone **22** proved to be inert when exposed to vinylolithium reagent **12** at temperatures where reagent **12** was stable (-78 → -50 °C). Therefore, we examined the related (*Z*)-vinylolithium reagent which is readily generated from vinyl bromide **23** by halogen-metal exchange. Bromide **23** is easily obtained from bromo ketal **11** in two steps via vinylstannane **24** by sequential selective metalations and reaction with NBS (Scheme II).

We were quite pleased to observe that exposure of **22** (1.0 equiv) to the vinylolithium reagent, generated from **23** (1.0 equiv) in Et<sub>2</sub>O at -78 °C (0.25 h), gave as the major diastereomer (97:3) alcohol **25** (79% total yield) (Scheme III).<sup>22,23</sup> The crucial fragmentation

was then achieved, after cleavage of the Me<sub>3</sub>Si group with excess Et<sub>3</sub>N-HF in CH<sub>2</sub>Cl<sub>2</sub> (room temperature, 3 h), by treatment of the resulting diol **26** (1 equiv) with Pb(OAc)<sub>4</sub> (1.5 equiv) in THF at 0 °C (5 min), affording the expected acyclic keto aldehyde **27** in 85% overall yield from **25**.

The required three-carbon homologation was then conveniently effected as shown in Scheme III by selective condensation of **27** with (*E*)-1-ethoxy-2-lithio-1-propene (1.5 equiv)<sup>24</sup> at -78 °C in Et<sub>2</sub>O followed by trapping with *p*-nitrobenzoyl chloride (2 equiv) at -78 °C → room temperature, and acidic treatment afforded ketal aldehyde **28** in 72% overall yield from **27**. Direct ring closure of **28** to the desired dioxabicyclo[3.3.1]nonane system was not possible due to our inability to effect removal of the TBS groups under sufficiently mild, nonbasic conditions. However, reduction of **28** with borohydride and acetylation of the resulting primary alcohol afforded ketal acetate **29** in 85% overall yield. Most gratifyingly, acetate **29** proved to be a suitable substrate for closure of the bicyclic ketal system. Treatment of **29** with tetrabutylammonium fluoride (0.5 M in THF, 6 equiv) in THF at room temperature (1.5 h) followed by direct treatment with BF<sub>3</sub>-Et<sub>2</sub>O (excess) in CH<sub>2</sub>Cl<sub>2</sub> at -78 °C (0.25 h) smoothly furnished the desired bicyclic ketal acetate **30** in 55% overall yield from **29**.<sup>25</sup>

The crucial ring closure (e.g., **29** → **30**) above proved to be extremely sensitive to substrate structure. One of the fundamental assumptions underlying our strategy, and generally the strategies employed to assemble a variety of naturally occurring polycyclic ketals, holds that the structure and stereochemistry of these substances result from thermodynamic control during the ring closures affording the most stable ketal.<sup>26</sup> We have observed that small changes in substrate structure apparently can alter the outcome, opening new domains of reactivity. For example, attempts to effect ring closure of **28** led to preferential reaction with the α,β unsaturated aldehyde unit. Attempts to effect protic acid catalyzed cyclization of several substrates resulted uniformly in mixtures of products or the production of δ lactones structurally similar to those reported by DeShong,<sup>3</sup> resulting from rearrangement. Thus the removal of the epoxide oxygen, a commonly employed retrosynthetic operation, apparently opens an undesired reaction manifold, although the natural substrate has not been examined to verify this conclusion. In some cases, we also noted the appearance of the desired cyclized material (e.g., **30**) which then underwent further reaction. The requirement for cyclization under kinetic control was verified by reexposure of **30** to the protic medium which resulted in conversion to a rearranged δ lactone. We have also noted that initial irreversible ring closure to a monocyclic mixed ketal appears to be a requirement for successful closure to the bicyclic ketal in our system. Attempts to effect closure of a diketone related to **28** afforded no bicyclic ketal products. This result may stem from reopening of the intermediate

(17) We observed formation of an unstable spiro epoxyvinyl ether from vinyl bromide **14** under mild acidic conditions. Rotation of the side chain, while restricted, is sufficient to permit closure in an overall S<sub>N</sub>2' sense. The analogous compound in the case of **15** is unstable to the reaction conditions. This effect is stereoelectronic in origin, as discussed by Deslongchamps: Deslongchamps, P. *Stereoelectronic Effects In Organic Chemistry*; Pergamon: Oxford, England, 1983; pp 1–53.

(18) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.

(19) Rastetter, W. H.; Richard, T. J.; Lewis, M. D. *J. Org. Chem.* **1978**, *43*, 3163.

(20) Stodder, J. F.; *Stereochemistry of Carbohydrates*; Wiley: New York, 1971; pp 158–232.

(21) For related studies of the effects of α oxygen functions on the regiochemistry of enolization, see: Wilson, S. R.; Walters, M. E.; Orbaugh, B. J. *Org. Chem.* **1976**, *41*, 378. Hirsch, J. A.; Wang, X. L. *Synth. Commun.* **1982**, *12*, 333. Eiden, F.; Wanner, K. T. *Liebigs Ann. Chem.* **1984**, 1759.

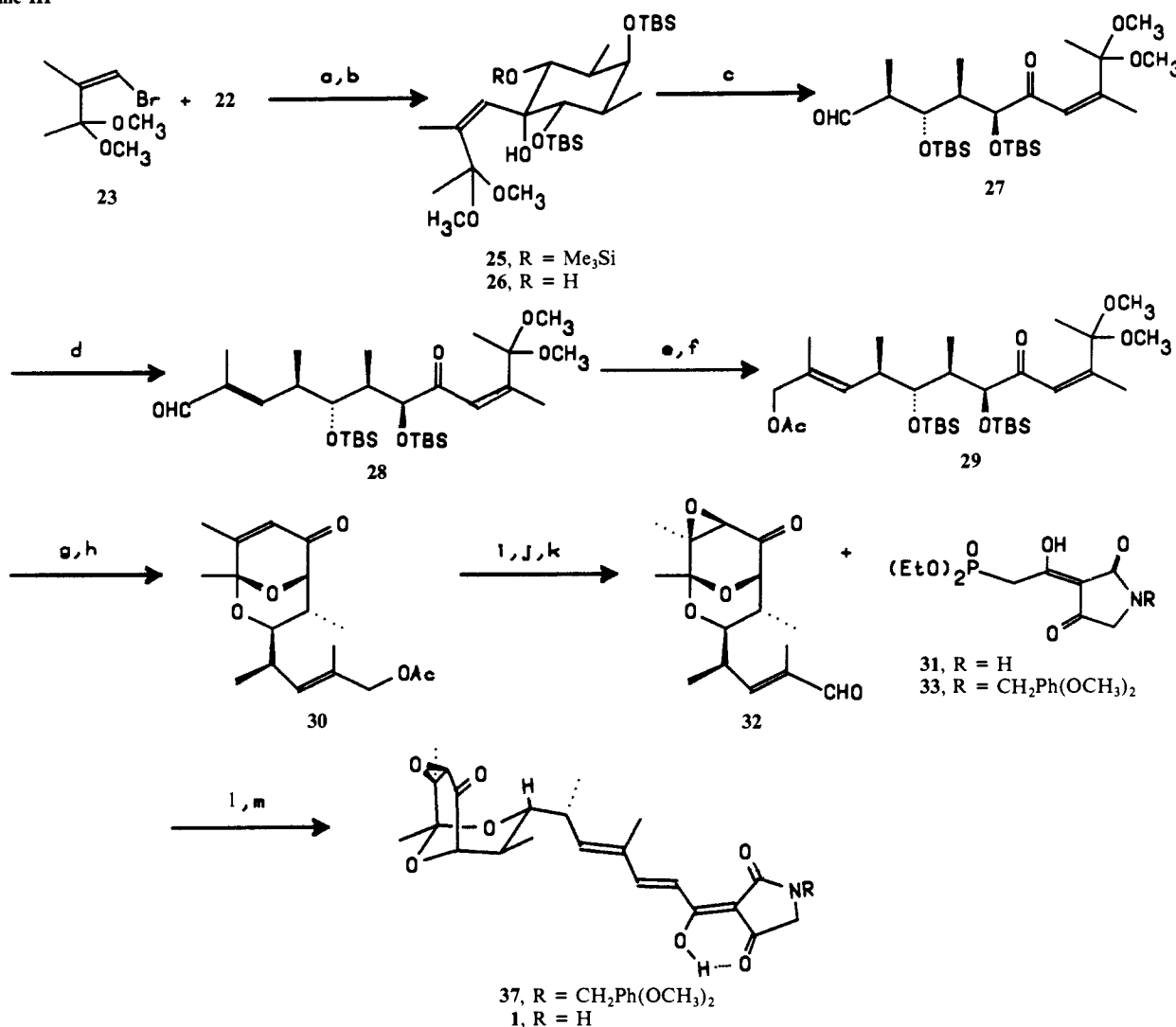
(22) It is interesting to note that the related α bromo lithium reagent **12** failed to add to ketone **22** at temperatures where reagent **12** was stable (-78 → -50 °C). Furthermore, the stereochemistry of addition of **23** to **22** could be essentially reversed by reaction of **23** (2 equiv) with ketone **22** in THF.

(23) Addition of the lithium reagent occurs nearly exclusively from the less sterically demanding equatorial direction due to the conformational bias exhibited by **12**, which undoubtedly reinforces the generally observed tendency for equatorial addition of organometallic reagents to cyclohexanones: Macdonald, T. R.; Still, W. C. *J. Am. Chem. Soc.* **1975**, *97*, 5280.

(24) Prepared from (*Z*)-2-bromo-1-ethoxy-1-propene<sup>27</sup> by halogen-metal exchange using *t*-BuLi (2 equiv) in THF at -78 °C (0.5 h): Neuman, H.; Seebach, D. *Chem. Ber.* **1978**, *111*, 2785.

(25) When **29** was treated with (*n*-Bu)<sub>4</sub>NF in THF under a variety of conditions, a complex mixture of products was produced, some of which appeared to arise via initial intramolecular Michael addition to the α,β unsaturated aldehyde unit.

(26) For example, see: Fukuyama, T.; Akasak, K.; Karanewsky, S.; Wang, C.-L. J.; Schmid, G.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 262. Evans, D. A.; Sacks, C. E.; Kleschick, W. A.; Taber, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 6789. Ireland, R. E.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1980**, *102*, 1155.

Scheme III<sup>a</sup>

<sup>a</sup> Reagents: (a) Bromide **23** (1.1 equiv), *t*-BuLi (2 equiv), Et<sub>2</sub>O, -78 °C → room temperature, 1.5 h; ketone **22** (1 equiv), Et<sub>2</sub>O, -78 °C, 0.25 h; (b) Et<sub>3</sub>N-HF (excess), CH<sub>2</sub>Cl<sub>2</sub>, room temperature, 3 h; (c) Pb(OAc)<sub>4</sub> (1.5 equiv), THF, 0 °C, 5 min; (d) (*Z*)-2-bromo-1-ethoxy-1-propene (1.5 equiv), *sec*-BuLi (1.5 equiv), Et<sub>2</sub>O, -78 °C, 0.33 h; aldehyde **27** (1 equiv), -78 °C, 0.25 h; *p*-nitrobenzoyl chloride (2 equiv), -78 °C → room temperature, 3 h; Et<sub>3</sub>N-HF, aqueous acetonitrile, 60 °C, 4 h; (e) NaBH<sub>4</sub> (1 equiv), EtOH, 0 °C, 1 h; (f) CH<sub>3</sub>COCl, pyridine, DMAR, CH<sub>2</sub>Cl<sub>2</sub>, room temperature, 0.25 h; (g) *n*-Bu<sub>4</sub>NF (0.5 M in THF, 6 equiv), THF, room temperature, 1.5 h; (h) BF<sub>3</sub>-Et<sub>2</sub>O (excess), CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 0.25 h; (i) DBU (6 equiv), *t*-BuOOH (6 equiv), THF, 60 °C, 12 h; (j) K<sub>2</sub>CO<sub>3</sub> (excess), methanol, room temperature, 0.5 h; (k) PDC (1.5 equiv), CH<sub>2</sub>Cl<sub>2</sub>, room temperature, 1 h; (l) tetramic acid **33** (2 equiv), KO-*t*-Bu (2.1 equiv), THF (0.4 M in **33**), 0 °C, 1 h, and then **31** (1 equiv), 0 °C, 12 h, quenched with 5% HCl; (m) CF<sub>3</sub>COOH (anhydrous), neat (0.1 M in **33**), room temperature, 0.33 h.

hemiketal and (or) preferential ionization of the exocyclic methoxy group in the mixed ketal. Thus, it appears necessary to at least question the validity of the commonly employed strategic assumption that natural polycyclic ketal systems are the result of thermodynamic control, when addressing new problems in this area.

Final conversion of the acetate **30** to (±)-**1** requires elaboration of the β epoxide and dienoyl tetramic acid units. Some time ago, we described methodology utilizing tetramic acid phosphonates such as **31**, designed to permit the required conversion.<sup>27</sup> We, thus, required the keto aldehyde **32** to implement this approach as outlined in Scheme III. Epoxidation of the acetate **30** was then accomplished by treatment with *t*-BuOOH/DBU in THF at 60 °C (12 h), affording the related β epoxy acetate in 89% yield.<sup>2,3</sup> Conversion of this intermediate to keto aldehyde **32** was straightforward. Exposure of the β epoxy acetate to K<sub>2</sub>CO<sub>3</sub> in methanol (room temperature, 0.5 h) followed by oxidation of the resulting alcohol with PDC (1.5 equiv) in CH<sub>2</sub>Cl<sub>2</sub> provided the keto aldehyde **32** in 81% yield.<sup>28</sup>

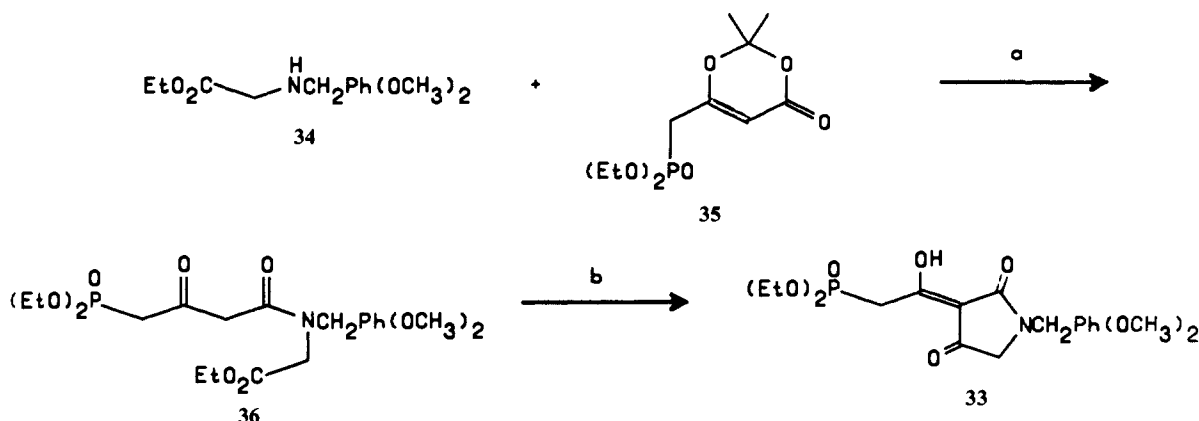
Preliminary experiments established that aldehyde **32** was not sufficiently stable to permit use of the strongly basic conditions employed for condensation of the dianions derived from **31** with tiglic aldehyde.<sup>27</sup> Therefore, the modified phosphonate reagent **33** bearing the acid-labile *N*-(2,4-dimethoxybenzyl) protecting group previously described by Schlessinger was utilized.<sup>3</sup> Phosphonate **33** was prepared, as described in Scheme IV, from ethyl *N*-(2,4-dimethoxybenzyl)glycinate **34**<sup>3</sup> via a modification of our previously described procedure.<sup>29</sup> Treatment of **34** with dioxolone phosphonate **35** in xylene at 130 °C provided the β keto amide **36** in 82% yield. This thermal process, which presumably proceeds via the intermediacy of the acylketene derived from **35**, is generally superior to the use of acid catalysis for most amino ester substrates except those prone to rapid dimerization.<sup>30</sup> Cyclization of **36** to the tetramic acid phosphonate **33** (65%) was

(28) This material was identical by comparison (NMR (300 MHz), TLC) with an authentic sample of aldehyde **32** (optically active) kindly provided by Prof. R. H. Schlessinger.

(29) Boeckman, R. K., Jr.; Perni, R. B.; MacDonald, J. E.; Thomas, A. J. *Org. Synth.*, in press.

(30) Hyatt, J. A.; Feldman, P. L.; Clemens, R. J. *J. Org. Chem.* **1984**, *49*, 5105.

(27) Boeckman, R. K., Jr.; Thomas, A. J. *J. Org. Chem.* **1982**, *47*, 2823.

Scheme IV<sup>a</sup>

<sup>a</sup> Reagents: (a) xylenes, 130 °C, 1 h; (b) KO-*t*-Bu (1.1 equiv), THF, room temperature, 16 h.

then effected by exposure of **36** to KO-*t*-Bu (1.1 equiv) in THF at room temperature.

Keto aldehyde **32** was elaborated to the penultimate precursor of (±)-tirandamycin A, dienoyl tetramic acid **37**, by treatment of a THF solution (0.05 M) of **33** (2.0 equiv) with KO-*t*-Bu (2.1 equiv), producing the related dianion which was condensed with **32** in THF (final concentration ~0.02 M) at 0 °C (6 h).<sup>3,27</sup> The reaction was quenched by addition of 5% HCl, and extractive workup and chromatography afforded the desired dienoyl tetramic acid **37** in 70% yield. Cleavage of the *N*-(2,4-dimethoxybenzyl) group was then effected by dissolving **37** in anhydrous trifluoroacetic acid (0.1 M in **37**) for 15 min at room temperature. Chromatography of the crude (±)-tirandamycin A (**1**), after conversion to the sodium salt, on silica gel in CH<sub>2</sub>Cl<sub>2</sub>/methanol (9:1) and acidification afforded synthetic (±)-tirandamycin A (**1**) in 83% yield.<sup>31</sup>

Studies directed toward the application of this strategy to streptolydigin (**2**) and toward the preparation of **1** and **2** in optically active form via advanced intermediates which possess meso symmetry are presently in progress.

### Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Beckman Acculab IR8 spectrophotometer and are reported in wavenumbers (cm<sup>-1</sup>) with polystyrene as standard. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM390 (90 MHz), a General Electric QE-300 (300 MHz), or a Bruker WH-400 (400 MHz) spectrometer. Chemical shifts are reported in ppm (δ) downfield relative to tetramethylsilane (Me<sub>4</sub>Si) as standard. Low-resolution mass spectra were obtained on either a Du Pont 490-B or a VG-7035 mass spectrometer. Exact mass measurements were made on the VG-7035 mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Louisville, KY.

All reactions were run under an inert atmosphere of Ar or N<sub>2</sub>, and reactions requiring anhydrous conditions were performed in a flame-dried or oven-dried (120 °C) apparatus. Vigorous stirring refers to mechanical overhead stirring. Temperatures below room temperature refer to bath temperatures unless otherwise stated. Solvents and anhydrous reagents were dried according to established procedures by distillation under N<sub>2</sub> from an appropriate drying agent: benzene, ether, THF, DME, toluene, hexanes (Na/benzophenone); 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), DMF, diisopropylamine, xylene (CaH); acetone, pyridine, triethylamine (BaO); CH<sub>2</sub>Cl<sub>2</sub> (P<sub>2</sub>O<sub>5</sub>); chlorotrimethylsilane (*N,N*-dimethylaniline); *tert*-butyl hydroperoxide (passed through anhydrous MgSO<sub>4</sub>, not distilled).

Analytical TLC was performed on E. Merck precoated silica gel plates (0.25 mm). Column chromatography was performed by the method of Still<sup>32</sup> with E. Merck silica gel 60 (230–400 mesh), and preparative LC

was performed with the Waters Prep 500 system on SiO<sub>2</sub>.

(**7R,9S**)-**7,9-Dimethyl-1,4-dioxaspiro[4.5]decan-8-one** (**5**). A solution of 2,6-dimethyl-1,4-cyclohexadione (**4**)<sup>5</sup> (37.26 g, 0.266 mol), ethylene glycol (15.67 g, 0.253 mol, 0.95 equiv), and 250 mg (1.3 mmol, 0.005 equiv) of *p*-toluenesulfonic acid monohydrate in 600 mL of benzene was heated at reflux for 24 h under a Dean-Stark separator. The mixture was allowed to cool, diluted with ether, and washed with saturated sodium bicarbonate solution. The organic layer was dried over anhydrous MgSO<sub>4</sub> and filtered, and the ether was removed under reduced pressure to give 48.8 g (99%) of a mixture of mono- and diketal, which was used without purification in the next synthetic transformation. The monoketal **5** had *R*<sub>f</sub> 0.34 (1:2 ether-hexanes) and bp 134 °C (aspirator pressure).

Pure monoketal **5** had the following spectral characteristics: NMR (400 MHz, CDCl<sub>3</sub>) 4.06–3.97 (m, 4 H), 2.76–2.73 (m, 2 H), 2.06 (dd, *J*<sub>1</sub> = 13, *J*<sub>2</sub> = 6 Hz, 2 H), 1.68 (dd, *J*<sub>1</sub> = 13, *J*<sub>2</sub> = 13 Hz, 2 H), 1.00 (d, *J* = 7 Hz, 6 H); IR (thin film) 1740 (s); MS (EI), *m/e* (relative intensity) 184 (M<sup>+</sup>, 6).

Anal. Calcd for C<sub>10</sub>H<sub>16</sub>O<sub>3</sub>: C, 65.19; H, 8.75. Found: C, 65.02; H, 8.66.

(**7R,8s,9S**)-**7,9-Dimethyl-1,4-dioxaspiro[4.5]decan-8-ol** (**6**). A solution of 11.5 g (62 mmol) of monoketal **5** in 600 mL of dry THF was cooled to –78 °C, and 78 mL of a THF solution of L-Selectride<sup>33</sup> (78 mmol, 1.25 equiv) was added slowly dropwise. The reaction mixture was stirred at –78 °C for 5 h, at which time 50 mL of 30% hydrogen peroxide was added. The solution was allowed to warm to 0 °C, and 5% HCl was added until the solution was slightly acidic. The reaction mixture was poured into 500 mL of ether, the layers were separated, and the organic phase was washed with saturated sodium bicarbonate solution. The combined aqueous layers were extracted twice with ether and the combined organic layers washed with brine and then dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give crude material which was purified by chromatography on silica gel (230–400 mesh) with elution by 1:3 ether-hexanes to provide the desired alcohol. Removal of the solvent from the combined product fractions under reduced pressure gave the alcohol **6** as a white solid, which upon recrystallization from ether-hexanes (1:10) gave 9.77 g (84%) of white crystalline **6**: (mp 69.5–71 °C; *R*<sub>f</sub> 0.14 (1:2 ether-hexanes); NMR (400 MHz, CDCl<sub>3</sub>) 3.92 (dd, *J*<sub>1</sub> = 3, *J*<sub>2</sub> = 3 Hz, 4 H), 3.50 (m, 12 H), 1.87–1.81 (m, 2 H), 1.58 (dd, *J*<sub>1</sub> = 13, *J*<sub>2</sub> = 13 Hz, 2 H), 1.43 (dd, *J*<sub>1</sub> = 13, *J*<sub>2</sub> = 3 Hz, 2 H), 1.19 (d, *J* = 2 Hz, 1 H), 0.98 (d, *J* = 7 Hz, 6 H); <sup>13</sup>C NMR (15.04 MHz) 109, 74, 64, 36, 35, 18; IR (CCl<sub>4</sub>) 3630 (w), 3510 (br w); MS (EI), *m/e* (relative intensity) 186 (M<sup>+</sup>, 1.4).

Anal. Calcd for C<sub>10</sub>H<sub>18</sub>O<sub>3</sub>: C, 64.49; H, 9.74. Found: C, 64.60; H, 9.78.

(**7R,8s,9S**)-**tert-Butyldimethyl[(7,9-dimethyl-1,4-dioxaspiro[4.5]decan-8-yl)oxy]silane** (**7**). A solution of 6.08 g (32.6 mmol) of ketal alcohol **6** in 100 mL of dry methylene chloride was cooled to 0 °C, and 7.6 mL (65.3 mmol, 2.0 equiv) of dry 2,6-lutidine followed by 9.0 mL (39.2 mmol, 1.2 equiv) of *tert*-butyldimethylsilyl triflate<sup>7</sup> were each added via syringe. The reaction mixture was stirred at 0 °C for 1 h, at which time monitoring by TLC showed no starting material remaining. The reaction was quenched by addition of saturated sodium bicarbonate solution; the mixture was warmed to room temperature and poured into 200 mL of ether. The layers were separated, and the organic phase was washed 2 times with 10% hydrochloric acid solution and once each with saturated

(31) Synthetic (±)-tirandamycin A (**1**) was identical in all respects except optical rotation (IR, NMR, MS, TLC) with samples of natural (+)-tirandamycin A and synthetic (+)-tirandamycin A. We thank Prof. Schlessinger for making copies of the spectral data for synthetic (+)-**1** available to us for comparison.

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

(33) L-Selectride (lithium tri-*sec*-butylborohydride) is available as a 1 M solution in THF from Aldrich Chemical Co., Milwaukee, WI.

sodium bicarbonate solution, water, and brine and then dried over anhydrous magnesium sulfate. Concentration in vacuo gave a yellow oil, which was chromatographed on 200–400-mesh silica gel eluting with 1:4 ether–hexanes ( $R_f$  0.49 (1:2 ether–hexanes)) to give 9.63 g (98%) of **7** as a clear oil: bp  $\sim 140$  °C/0.5 mm (Kugelrohr). NMR (400 MHz,  $\text{CDCl}_3$ ) 3.91 (dd,  $J_1 = 3.1$ ,  $J_2 = 3.7$  Hz, 4 H), 3.52 (m, 1 H), 1.83–1.71 (m, 2 H), 1.65 (dd,  $J_1 = 12.6$ ,  $J_2 = 12.6$  Hz, 2 H), 1.33 (br d,  $J = 13.2$ , 2 H), 0.89 (s, 9 H), 0.86 (d,  $J = 6.3$  Hz, 6 H), 0.03 (s, 6 H); IR (thin film) 2970 (s), 2945 (s), 2895 (s), 2870 (s), 1465 (s), 1430 (m), 1405 (w), 1385 (m), 1370 (s), 1345 (w), 1330 (m); MS (EI),  $m/e$  (relative intensity), 243 ( $M^+ - 57$ , 6).

Anal. Calcd for  $\text{C}_{16}\text{H}_{32}\text{O}_3\text{Si}$ : C, 63.95; H, 10.73. Found: C, 63.78; H, 10.83.

(**1s**, **2R**, **6S**)-*tert*-Butyldimethyl[(2,6-dimethyl-4-oxo-1-cyclohexyl)oxy]silane (**8**). A solution of 4.89 g (16.3 mmol) of *tert*-butyldimethylsilyl ether **7** in 700 mL of dry acetone and 100 mg (0.5 mmol, catalyst) of *p*-TsOH– $\text{H}_2\text{O}$  was heated at reflux for  $\sim 48$  h. Completion was monitored by TLC ( $R_f$  0.42 (1:2 ether–hexanes)). The reaction mixture was cooled to room temperature and the acid neutralized by addition of aqueous, saturated sodium bicarbonate solution. The acetone was removed in vacuo, the residue was diluted with ether, the layers were separated, and the organic phase was washed once with water and brine and then dried over anhydrous magnesium sulfate. The ether was removed under reduced pressure to give ketone **8** as a yellow oil, which was used without purification in the next reaction. An analytical sample of **8** (bp  $\sim 170$  °C, aspirator pressure (Kugelrohr)) was purified by distillation: NMR (400 MHz,  $\text{CDCl}_3$ ) 3.68 (br s, 1 H), 2.39 (dd,  $J_1 = 13.9$ ,  $J_2 = 13.9$  Hz, 2 H), 2.03 (dd,  $J_1 = 14.2$ ,  $J_2 = 3.7$  Hz), 2.00–1.88 (m, 2 H), 0.98 (d,  $J = 6.8$  Hz, 6 H), 0.93 (s, 9 H), 0.10 (s, 6 H); IR (film) 1750 (w), 1720 (s), 1665 (w), 1365 (s), 1255 (s), 1175 (s); MS (EI),  $m/e$  (relative intensity) 241 ( $M^+ - 15$ , 6).

Anal. Calcd for  $\text{C}_{14}\text{H}_{28}\text{O}_2\text{Si}$ : C, 65.57; H, 11.01. Found: C, 65.70; H, 11.01.

(**3R**\*, **4S**\*, **5S**\*)-[3,5-Dimethyl-4-((*tert*-butyldimethylsilyl)oxy)-1-cyclohexenyl]oxy]trimethylsilane (**9**). A solution of lithium diisopropylamide (LDA) in 75 mL of dry THF (21.2 mmol, 1.3 equiv) was prepared and cooled to  $-78$  °C.<sup>34</sup> To the LDA solution was added dropwise slowly via syringe 4.20 g (16.4 mmol) of **8** in 25 mL of dry THF with stirring. The resulting solution was stirred at  $-78$  °C for 1 h, and 4.16 mL (32.8 mmol, 2.0 equiv) of chlorotrimethylsilane was added via syringe. After the mixture stirred at  $-78$  °C for 1.5 h, the cold bath was removed, and the reaction was stirred for an additional 1 h at room temperature. A majority of the THF was removed under reduced pressure and the residue diluted with 200 mL of hexanes resulting in a white, flocculent precipitate, which was removed by vacuum filtration through a Florisil pad with the aid of more hexanes. Concentration of the filtrate under reduced pressure gave enol silyl ether **9** ( $R_f$  0.72 (1:2 ether–hexanes); bp  $\sim 110$  °C/0.1 mm (Kugelrohr)) as a clear oil, which was used without further purification in the subsequent synthetic transformation: NMR (400 MHz,  $\text{CDCl}_3$ ) 4.42 (br s, 1 H), 3.57 (d,  $J = 2.8$  Hz, 1 H), 2.37–2.31 (m, 1 H), 1.96–1.85 (m, 1 H), 0.94 (d,  $J = 2.6$  Hz, 3 H), 0.92 (d,  $J = 3.3$  Hz, 3 H), 0.88 (s, 9 H), 0.15 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H); IR (thin film) 2940 (s), 2910 (s), 2870 (s), 2840 (s), 1665 (m), 1465 (m), 1455 (m), 1250 (s), 1200 (s); MS (EI),  $m/e$  (relative intensity) 313 ( $M^+ - 15$ , 10).

(**1R**\*, **2S**\*, **3S**\*, **6R**\*)-*tert*-Butyldimethyl[(2,6-dimethyl-3-hydroxy-4-oxocyclohexyl)oxy]silane (**10**). A turbid well-stirred solution of enol silyl ether **11** (5.38 g, 16.4 mmol) and *N*-methylmorpholine *N*-oxide (4.43 g, 32.8 mmol, 2.0 equiv) in 200 mL of THF and 66 mL of deionized water was treated with 2 mL of a 4% (w/v) THF solution of  $\text{OsO}_4$  (0.3 mmol, 0.02 equiv). After stirring for  $\sim 1$  h, the resulting mixture lost its turbidity. The resulting yellow solution was stirred at room temperature overnight, followed by addition of  $\sim 1$  g of solid  $\text{NaHSO}_3$ , filtration, and removal of the THF in vacuo. The residual aqueous phase was extracted with 250 mL of  $\text{CH}_2\text{Cl}_2$ , the layers were separated, and the water was removed from the aqueous phase via freeze drying. The resulting solid residue was suspended in 250 mL of  $\text{CH}_2\text{Cl}_2$ , vigorously stirred for 1 h, and filtered, and the combined  $\text{CH}_2\text{Cl}_2$  extracts were dried over anhydrous  $\text{MgSO}_4$ . The solvent was removed under reduced pressure to give a dark-brown oil which was purified by chromatography (Prep 500 on  $\text{SiO}_2$ ; 1:6 ether–hexanes) to give 4.54 g ( $\sim 100\%$ ) of **10** as an off-white solid ( $R_f$  0.34 (1:2 ether–hexanes)). An analytical sample of **10** (mp 50–52 °C) was prepared by recrystallization from hot methanol and cooling to  $-20$  °C: NMR (400 MHz,  $\text{CDCl}_3$ ) 4.11 (dd,  $J_1 = 3.3$ ,  $J_2 = 11.4$  Hz, 1 H), 3.76 (br s, 1 H), 3.38 (d,  $J = 3.7$  Hz, 1 H), 2.62 (dd,  $J_1 = 12.6$ ,  $J_2 = 12.6$  Hz, 1 H), 2.24 (dd,  $J_1 = 13.6$ ,  $J_2 = 3.0$  Hz, 1H), 2.02–1.91 (m, 1 H), 1.73–1.61 (m, 1 H), 1.22 (d,  $J = 6.7$  Hz, 3 H), 1.01

(d,  $J = 6.8$  Hz, 3 H), 0.93 (s, 9 H), 0.13 (s, 3 H), 0.09 (s, 3 H); IR ( $\text{CH}_2\text{Cl}_2$ ) 3460 (br m), 1710 (s), 1455 (m), 1385 (m), 1105 (s), 1095 (s), 1075 (s), 1035 (s); MS (EI),  $m/e$  (relative intensity) 272 ( $M^+$ , 0.5), 216 (27).

Anal. Calcd for  $\text{C}_{14}\text{H}_{28}\text{O}_3\text{Si}$ : C, 61.72; H, 10.36. Found: C, 61.96; H, 10.36.

(**1R**\*, **2R**\*, **3S**\*, **6R**\*)-*tert*-Butyldimethyl[(3-((*tert*-butyldimethylsilyl)oxy)-2,6-dimethyl-4-oxo-1-cyclohexyl)oxy]silane (**3**). A solution of keto alcohol **10** (14.59 g, 53 mmol), 21.5 g (315 mmol, 6.0 equiv) of imidazole, and 23.8 g (157 mmol, 3.0 equiv) of *tert*-butyldimethylchlorosilane in 200 mL of dry DMF was stirred overnight at room temperature. The reaction mixture was poured into 1500 mL of ether and washed 4 times with 100 mL of water. The combined aqueous phases were extracted with 100 mL of ether, the combined organic layers washed sequentially with 100 mL of saturated  $\text{CuSO}_4$  and brine, dried over anhydrous  $\text{MgSO}_4$ , and filtered, and the solvent was removed under reduced pressure to provide crude **3** as a green oil. Purification by Prep 500 ( $\text{SiO}_2$ ; 1:20 ether–hexanes) afforded 15.49 g (71% yield from **8**) of pure **3** as a white solid ( $R_f$  0.37 (1:10 ether–hexanes)). An analytical sample of *tert*-butyldimethylsilyl ether **3** (mp 48–49 °C) was obtained by recrystallization from hot methanol and cooling to  $-20$  °C: NMR (400 MHz,  $\text{CDCl}_3$ ) 4.25 (d,  $J = 11.5$  Hz, 1 H), 3.78 (br s, 1 H), 2.52 (dd,  $J_1 = 13.6$ ,  $J_2 = 13.6$  Hz, 1 H), 2.10 (dd,  $J_1 = 13.6$ ,  $J_2 = 3.9$  Hz, 1 H), 2.01–1.84 (m, 2 H), 1.11 (d,  $J = 6.8$  Hz, 3 H), 0.97 (d,  $J = 6.8$  Hz, 3 H), 0.94 (s, 9 H), 0.89 (s, 9 H), 0.12 (s, 3 H), 0.11 (s, 3 H), 0.09 (s, 3 H),  $-0.03$  (s, 3 H); IR ( $\text{CH}_2\text{Cl}_2$ ) 2965 (s), 2950 (s), 1730 (s), 1475 (m), 1465 (m), 1265 (s), 1140 (s); MS (EI)  $m/e$  (relative intensity) 330 ( $M^+ - 56$ , 14), 329 (50).

Anal. Calcd for  $\text{C}_{20}\text{H}_{42}\text{O}_3\text{Si}$ : C, 62.12; H, 10.95. Found: C, 62.18; H, 10.95.

(**3R**\*, **4R**\*, **5R**\*, **6S**\*)-[3,5-Dimethyl-4,6-bis((*tert*-butyldimethylsilyl)oxy)-1-cyclohexenyl]oxy]trimethylsilane. A solution of LDA<sup>34</sup> (54.7 mmol, 3.0 equiv) in 175 mL of dry THF was cooled to  $-30$  °C, and a solution of ketone **3** (7.05 g, 18.2 mmol) in 35 mL of dry THF was added dropwise with good stirring. The resulting solution was stirred at  $-30$  °C for 1 h and 9.25 mL (72.9 mmol, 4.0 equiv) of chlorotrimethylsilane was added via syringe. After the mixture stirred at  $-30$  °C for 1.5 h, the cold bath was removed, and the reaction stirred for an additional 1 h at room temperature. After the THF was removed in vacuo, the residue was diluted with hexanes and the resulting white, flocculent precipitate was removed by vacuum filtration through a pad of Florisil with the aid of more hexanes. Concentration of the filtrate under reduced pressure gave the title compound as a yellow oil,  $R_f$  0.67 (1:10 ether–hexanes), which was used without purification in the next synthetic transformation. Distillation (Kugelrohr) at 0.1 mm afforded a purified sample of the title enol silyl ether: (bp  $\sim 130$  °C/0.1 mm; NMR (400 MHz,  $\text{CDCl}_3$ ) 4.61 (d,  $J = 3.6$  Hz, 1 H), 3.99 (dd,  $J_1 = 3.2$ ,  $J_2 = 1.9$  Hz, 1 H), 3.78 (d,  $J = 3.9$  Hz, 1 H), 2.45–2.38 (m, 1 H), 1.89–1.82 (m, 1 H), 0.97 (d,  $J = 2.8$  Hz, 3 H), 0.95 (d,  $J = 2.9$  Hz, 3 H), 0.88 (s, 9 H), 0.87 (s, 9 H), 0.19 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H), 0.03 (s, 3 H), 0.02 (s, 3 H); IR (film) 2970 (s), 2950 (s), 2900 (s), 2870 (s), 1665 (m), 1625 (w), 1475 (m), 1465 (m), 1265 (s), 1210 (s); MS (EI),  $m/e$  (relative intensity) 458 ( $M^+$ , 1.2), 402 (33), 401 (92).

(**1R**\*, **2S**\*, **3S**\*, **5R**\*, **6R**\*)-*tert*-Butyldimethyl[(3-((*tert*-butyldimethylsilyl)oxy)-2,6-dimethyl-5-hydroxy-4-oxo-1-cyclohexyl)oxy]silane (**21**). A solution of 8.37 g (18.2 mmol) of crude silyl enol ether obtained as described in the preceding procedure and 4.9 g (2.0 equiv, 36.5 mmol) of *N*-methylmorpholine *N*-oxide in 266 mL of 3:1 THF–water (deionized) was treated with 2.3 mL of a 4% (w/v) solution of  $\text{OsO}_4$  (0.02 equiv, 0.37 mmol) in THF. The cloudy, yellow solution was stirred at room temperature for 24 h. An additional 1 mL of  $\text{OsO}_4$  solution was then added, and the reaction mixture was stirred for an additional 12 h. TLC monitoring showed starting material still remaining; therefore, 1.23 g (0.5 equiv, 9.1 mmol) of *N*-methylmorpholine *N*-oxide and an additional 1 mL of the  $\text{OsO}_4$  solution were added. After 48 h, the reaction was complete. Excess solid sodium bisulfite was added to the reaction mixture, the resulting black mixture was filtered, and the THF was removed under reduced pressure. The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (200 mL) and the water removed via freeze drying. The resulting residue was extracted with an additional portion (100 mL) of  $\text{CH}_2\text{Cl}_2$ , and the combined organic extracts were dried over anhydrous  $\text{MgSO}_4$ . Filtration, concentration in vacuo, and purification by chromatography (Prep 500, silica gel, 1:6 ether–hexanes) gave **11** as an off-white solid ( $R_f$  0.21 (1:2 ether–hexanes)), which was used without further purification in the next step. An analytical sample of **11** (mp 50–52 °C) was prepared by recrystallization from hot  $\text{CH}_3\text{OH}$  with cooling to  $-20$  °C and had the following spectral characteristics: NMR (400 MHz,  $\text{CDCl}_3$ ) 4.40 (d,  $J = 11.5$  Hz, 1 H), 4.14 (dd,  $J_1 = 11.2$ ,  $J_2 = 3.6$  Hz, 1 H), 3.81 (br s, 1 H), 3.40 (d,  $J = 4.33$  Hz, 1 H), 1.94–1.81 (m, 1 H), 1.70–1.59 (m, 1 H), 1.30 (d,  $J = 6.8$  Hz, 3 H), 1.18 (d,  $J =$

6.7 Hz, 3 H), 0.93 (s, 9 H), 0.91 (s, 9 H), 0.13 (s, 3 H), 0.12 (s, 3 H), 0.10 (s, 3 H), -0.01 (s, 3 H); IR (CCl<sub>4</sub>) 3480 (br w), 1730 (s), 1475 (m), 1465 (m), 1260 (s); MS (EI), *m/e* (relative intensity) 345 (M<sup>+</sup> - 57, 35).

Anal. Calcd for C<sub>20</sub>H<sub>42</sub>O<sub>4</sub>Si<sub>2</sub>: C, 59.65; H, 10.51. Found: C, 59.68; H, 10.69.

**(1R\*,2R\*,3S\*,5R\*,6S\*)-tert-Butyldimethyl[3-((tert-butyltrimethylsilyloxy)-2,6-dimethyl-5-((trimethylsilyloxy)-4-oxo-1-cyclohexyl)oxy)silane (22).** A solution of 6.75 g (16.8 mmol) of crude keto alcohol **21** in 400 mL of anhydrous THF was treated sequentially with 12.38 mL (5.3 equiv, 88.8 mmol) of dry triethylamine and 10.63 mL (5.0 equiv, 83.8 mmol) of chlorotrimethylsilane. The resulting heterogeneous mixture was stirred at room temperature for 24 h. A majority of the THF was removed under reduced pressure, and the residue was diluted with hexanes. The resulting flocculent, white precipitate was removed by vacuum filtration through a pad of Florisil with the aid of additional hexanes. Concentration of the filtrates in vacuo gave a yellow oil, which was purified by column chromatography (Florisil, elution with 1:10 ether-hexanes) to afford 4.89 g (57% for three steps, 82% average yield) of trisilyl ketone **22** (*R<sub>f</sub>* 0.54 (1:2 ether-hexanes)) as a white solid: mp 64.5–66.5 °C; NMR (400 MHz, CDCl<sub>3</sub>) 4.26 (d, *J* = 11.6 Hz, 1 H), 4.19 (d, *J* = 11.5 Hz, 1 H), 3.82 (br s, 1 H), 1.89–1.74 (m, 2 H), 1.10 (d, *J* = 6.8 Hz, 3 H), 1.05 (d, *J* = 6.7 Hz, 3 H), 0.94 (s, 9 H), 0.89 (s, 9 H), 0.12 (s, 9 H), 0.09 (s, 9 H), -0.04 (s, 3 H); IR (CCl<sub>4</sub>) 2950 (s), 2920 (s), 2880 (s), 1735 (s), 1465 (m), 1455 (m).

Anal. Calcd for C<sub>23</sub>H<sub>50</sub>O<sub>4</sub>Si<sub>3</sub>: C, 58.17; H, 10.61. Found: C, 58.44; H, 10.60.

**(3RS)-4,4,4-Tribromo-3-methylbutan-2-one.** Aluminum bromide (10.0 g, 0.0375 mol) was cooled to ~0 °C in an ice-water bath, and 10.5 g (2.85 equiv, 0.0855 mol) of freshly distilled acetyl bromide was slowly added to the mechanically stirred solid. The resulting mixture was stirred for 15 min at 0 °C after all of the solid had dissolved. To the resulting dark colored, homogeneous solution was slowly added 6.0 g (0.030 mol) of freshly distilled 1,1-dibromopropene dropwise over a 15-min period. The reaction mixture was stirred for an additional 3 h, during which time the temperature was allowed to slowly rise to room temperature. The dark, homogeneous solution was then carefully poured onto crushed ice and extracted twice with 100-mL portions of CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were washed once with water and then dried over anhydrous MgSO<sub>4</sub> for 1 h. The solvent was removed in vacuo to provide 7.28 g of the crude tribromo ketone as a dark liquid.<sup>35</sup> which was used without purification in the subsequent transformation: NMR (90 MHz, CDCl<sub>3</sub>) 3.78 (q, *J* = 7 Hz, 1 H), 2.00 (s, 3 H), 1.46 (d, *J* = 7 Hz, 3 H).

**1,1-Dibromo-2-methyl-1-buten-3-one.** A solution of 7.28 g (0.0226 mol) of the crude tribromo ketone in 30 mL of dry methanol was treated with 2.21 g (0.0226 mol, 1.0 equiv) of solid potassium acetate. Upon addition of the potassium acetate, the dark color discharged. The stirred reaction mixture was heated at reflux for 5 h and cooled to room temperature, and the solids were removed via vacuum filtration with the aid of anhydrous ether. The solvent was removed from the combined filtrates in vacuo, and the residue was taken up in 100 mL of ether and washed successively with two portions (30 mL) of saturated NaHCO<sub>3</sub> solution and brine. After the mixture was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, the ether was removed in vacuo to give a brown liquid, which upon Kugelrohr distillation afforded 5.06 g (70% from 1,1-dibromo-1-propene) of the title dibromo enone as a light-green liquid: bp ~63 °C/5.5 mm; NMR (90 MHz, CDCl<sub>3</sub>) 2.4 (s, 3 H), 2.0 (s, 3 H).

Anal. Calcd for C<sub>5</sub>H<sub>8</sub>Br<sub>2</sub>O: C, 24.82; H, 2.50. Found: C, 24.76; H, 2.39.

**1,1-Dibromo-3,3-dimethoxy-2-methyl-1-butene (11).** A solution of 5.06 g (0.021 mol) of 4,4-dibromo-3-methyl-2-butenone in 50 mL of dry methanol was treated successively with 24.36 mL (23.5 g, 0.222 mol, 10.6 equiv) of trimethyl orthoformate (optimum concentration 1:2 CH<sub>3</sub>(OCH<sub>3</sub>)<sub>3</sub>-CH<sub>3</sub>OH) and 5 drops of concentrated H<sub>2</sub>SO<sub>4</sub>. The reaction mixture was heated at reflux for 1 h during which the reaction mixture became red-orange in color. After the mixture cooled to room temperature, excess solid NaHCO<sub>3</sub> was added, and the resulting mixture was allowed to stir until the color had changed from red-orange to light yellow or light green. The acid must be completely neutralized before proceeding further or decomposition occurs during purification. The volatiles were removed in vacuo, and the semisolid residue was dissolved in 50 mL of water. The resulting two-phase mixture was extracted 3 times with 50 mL of pentane, and the combined organic extracts were washed twice with brine and dried over anhydrous K<sub>2</sub>CO<sub>3</sub>. Concentration of the pentane extracts under reduced pressure provided a yellow oil, which upon careful Kugelrohr distillation gave 5.22 g (86%) of ketal **11** (bp 50 °C/1 mm) as a clear liquid: NMR (90 MHz, CDCl<sub>3</sub>) 3.14 (s, 6 H), 2.00

(s, 3 H), 1.46 (s, 3 H); IR (film) 3000 (m), 2950 (m), 2840 (m), 1625 (w), 1585 (w), 1385 (s), 1260 (s), 1200 (s).

**[1R\*(1Z),2R\*,3S\*,4S\*,5S\*]-1-(3,3-Dimethoxy-2-methyl-1-but-1-enyl)-4-(methoxymethoxy)-2-((trimethylsilyloxy)-3,5-dimethylcyclohexan-1-ol (15).** A solution of dibromo ketal **11** (10.34 g, 0.036 mol) in 150 mL of anhydrous ether was cooled to -78 °C, and 26.4 mL (0.037 mol) of a 1.40 M solution of *sec*-BuLi in cyclohexane was added. The resulting solution was stirred for 30 min at -78 °C followed by dropwise addition of a solution of ketone **13** (6.028 g, 0.022 mol) in 50 mL of anhydrous ether. After the resulting mixture stirred for 1 h at -78 °C, 34.3 mL (0.055 mol) of a 1.6 M solution of *t*-BuLi in pentane was added in one portion via syringe. After the mixture stirred an additional 15 min at -78 °C, saturated aqueous NaCl (50 mL) was added, and the mixture was allowed to warm to room temperature. The layers were separated, and the aqueous layer was extracted with ether (2 × 50 mL). The combined organic phases were dried over anhydrous MgSO<sub>4</sub> and concentrated in vacuo to afford 8.40 g of crude products. Purification by flash chromatography (40-mm column) with elution by hexanes-ether (5:1) afforded 7.20 g (81%) of alcohol **15**: NMR (400 MHz, CDCl<sub>3</sub>) 5.36 (s, 3 H), 4.66 (m, 2 H), 3.55 (d, *J* = 10 Hz, 1 H), 3.50 (m, 1 H), 3.46 (s, 3 H), 3.40 (s, 3 H), 2.10 (m, 2 H), 1.80–1.33 (m, 2 H), 1.75 (s, 3 H), 1.65 (s, 3 H), 1.50 (d, *J* = 2 Hz, 3 H), 1.00 (d, *J* = 7 Hz, 3 H), 0.90 (d, *J* = 7 Hz, 3 H); MS (EI), *m/e* (relative intensity) 389 (M<sup>+</sup> - 15, 0.5).

**[1R\*(1Z),2R\*,3R\*,4S\*,5S\*]-1-(3,3-Dimethoxy-2-methyl-1-but-1-enyl)-4-(methoxymethoxy)-3,5-dimethylcyclohexan-1,2-diol (18).** A stirred solution of trimethylsilyl ether **15** (4.04 g, 0.01 mol) in 20 mL of anhydrous THF was treated dropwise with 25 mL of a 1.0 M solution of *n*-Bu<sub>4</sub>NF in THF (0.025 mol) at room temperature. After 1.5 h at room temperature, TLC analysis indicated the reaction was complete. The reaction mixture was diluted with 60 mL of ether, and the resulting solution was washed successively with saturated aqueous NaHCO<sub>3</sub> (20 mL) and saturated aqueous NaCl (20 mL), dried over anhydrous MgSO<sub>4</sub>, and concentrated in vacuo to afford 3.25 g (97%) of crude diol which was sufficiently pure to be used as obtained in subsequent transformations.

**[1R\*(1S\*,2S\*),2S\*,3S\*,4R\*,5R\*]-1-(3,3-Dimethoxy-1,2-epoxy-2-methylbutyl)-4-(methoxymethoxy)-3,5-dimethylcyclohexan-1,2-diol (19).** A solution of diol **18** (40 mg, 0.12 mmol) in 5 mL of CH<sub>2</sub>Cl<sub>2</sub> was combined with 5 mL of pH 8 phosphate buffer (0.1 M NaH<sub>2</sub>PO<sub>4</sub> + sufficient 0.1 M Na<sub>2</sub>HPO<sub>4</sub> to bring the pH to 8), and a total of 180 mg (0.96 mmol) of *p*-nitroperbenzoic acid<sup>19</sup> was added at room temperature in 45-mg portions over a total of 24 h. At that time, TLC analysis indicated consumption of **18**. The reaction mixture was diluted with ether (20 mL), and the organic layer was washed with aqueous NaHSO<sub>3</sub> (5 mL) and aqueous Na<sub>2</sub>CO<sub>3</sub> (5 mL), dried over anhydrous MgSO<sub>4</sub>, and concentrated in vacuo to afford 33 mg (79%) of epoxy diol **19**: NMR (90 MHz, CDCl<sub>3</sub>) 4.85 (s, 1 H), 4.60 (s, 2 H), 4.40 (m, 2 H), 4.35 (s, 3 H), 4.25 (s, 6 H), 2.68 (s, 1 H), 2.50–1.50 (m, 6 H), 1.43 (s, 3 H), 1.32 (s, 3 H), 1.08 (d, *J* = 7.0 Hz, 3 H), 0.91 (d, *J* = 7.0 Hz, 3 H); MS (EI), *m/e* (relative intensity) 348 (M<sup>+</sup>, 0.5), 317 (5), 301 (12).

**[2(RS),3S\*,4S\*,5R\*,6S\*,7S\*,8R\*,9R\*]-3,4-Epoxy-8-(methoxymethoxy)-2,3,7,9-tetramethyl-1-oxaspiro[4.5]decan-6-ol (20).** A solution of epoxy diol **19** (0.922 g, 2.65 mmol) in 25 mL of CH<sub>2</sub>Cl<sub>2</sub> was treated with a catalytic amount of pyridinium *p*-toluenesulfonate (30 mg) and the resulting mixture stirred at room temperature for 18 h. The reaction mixture was diluted with 50 mL of ether, and the resulting solution was washed successively with saturated aqueous NaHCO<sub>3</sub> (10 mL) and saturated aqueous NaCl (20 mL), dried over anhydrous MgSO<sub>4</sub>, and concentrated in vacuo to afford 885 mg of crude material. Purification by flash chromatography (20-mm column) afforded 770 mg (89%) of a 4:1 epimeric mixture of spiro acetals **20**: NMR (400 MHz, CDCl<sub>3</sub>) 4.66 (m, 2 H), 3.79 (d, *J* = 10.0 Hz, 1 H), 3.45 (s, 3 H), 3.43 (s, 1 H), 3.39 (s, 3 H), 3.33 (s, 1 H), 2.05–1.85 (m, 3 H), 1.55 (s, 3 H), 1.51 (s, 3 H), 1.46 (s, 3 H), 1.40–1.16 (m, 4 H), 1.34 (d, *J* = 12 Hz, 1 H), 1.12 (d, *J* = 7 Hz, 3 H), 0.97 (d, *J* = 7 Hz, 3 H); MS (EI), *m/e* (relative intensity) 316 (M<sup>+</sup>, 1.5).

**(Z)-1-Bromo-3,3-dimethoxy-2-methyl-1-butene (23).** A solution of vinyltin **24** (738 mg, 1.77 mmol) in 20 mL of CH<sub>2</sub>Cl<sub>2</sub> was cooled to 0 °C, and *N*-bromosuccinimide (315 mg, 1.77 mmol) was added. The resulting mixture was stirred at 0 °C for 30 min and then poured into saturated Na<sub>2</sub>SO<sub>3</sub>. The aqueous layer was washed with 20 mL of CH<sub>2</sub>Cl<sub>2</sub>, and the combined organic layers were dried over anhydrous MgSO<sub>4</sub>. The solution was concentrated at 20 °C, and the residue was distilled in vacuo (Kugelrohr) to give 373 mg (54%) of bromo ketal **23** (bp 65–70 °C/20 mm) as a clear, colorless oil: NMR (300 MHz, CDCl<sub>3</sub>) 6.13 (s, 1 H), 3.20 (s, 6 H), 1.82 (s, 3 H), 1.50 (s, 3 H); IR (film) 2930, 1605, 1430, 1360, 1310, 1150, 1040, 870; MS (EI), *m/e* (relative intensity) 195, 193 (M<sup>+</sup> - 15, 7.7), 177, 179 (25), 153 (16), 129 (49), 89 (38), 67 (27), 43 (100).

(35) Mixtures of tribromo ketone and dibromo enone were sometimes obtained at this point depending upon the particular run.



(*Z*)-Tributyl(3,3-dimethoxy-2-methyl-1-butenyl)stannane (**24**). A solution of dibromo ketal **11** (1.00 g, 3.47 mmol) in 25 mL of anhydrous ether was cooled to  $-78^{\circ}\text{C}$ , and 2.50 mL (3.5 mmol) of a 1.40 M solution of *sec*-BuLi in cyclohexane was added. The resulting solution was stirred for 30 min at  $-78^{\circ}\text{C}$  followed by addition of 0.94 mL (3.45 mmol) of (*n*-Bu)<sub>3</sub>SnCl. The cooling bath was removed, and the solution was allowed to warm to room temperature. After 1 h at room temperature, the reaction mixture was recooled to  $-78^{\circ}\text{C}$  and treated with 1.84 mL of a 1.87 M solution of *t*-BuLi in pentane. After stirring 30 min at  $-78^{\circ}\text{C}$ , the reaction mixture was poured into 20 mL of a saturated NH<sub>4</sub>Cl solution and diluted with an additional 30 mL of ether. The organic layer was washed with 20 mL of water, dried over anhydrous MgSO<sub>4</sub>, and concentrated in vacuo. The residue was purified by flash chromatography (20-mm column) on SiO<sub>2</sub> with elution by hexanes-ethyl acetate (30:1) to afford 723 mg (50%) of stannane **24** as a colorless oil: NMR (300 MHz, CDCl<sub>3</sub>) 5.84 (s, 1 H), 3.13 (s, 6 H), 1.89 (s, 3 H), 1.50–1.30 (m, 12 H), 1.36 (s, 3 H), 0.90 (t,  $J = 7.8$  Hz, 9 H), 0.81 (t,  $J = 7.8$  Hz, 6 H); MS (EI),  $m/e$  (relative intensity) 387 ( $M^+ - 31$ , 0.7), 361 (2.1), 331 (100).

(**1R\*(1Z)**,**2S\***,**3R\***,**4R\***,**5S\***,**6R\***)-2,4-Bis((*tert*-butyldimethylsilyloxy)-1-(3,3-dimethoxy-2-methyl-1-butenyl))-3,5-dimethyl-6-((trimethylsilyloxy)cyclohexan-1-yl) (25). A stirred solution of **23** (40.0 mg, 0.189 mmol) in 8 mL of ether at  $-78^{\circ}\text{C}$  was treated with 0.23 mL (0.38 mmol) of a 1.65 M solution of *t*-BuLi in pentane. The resulting solution was stirred at  $-78^{\circ}\text{C}$  for 10 min, then the cooling bath was removed, and the reaction mixture was allowed to warm to room temperature. To the resulting solution was added a solution of ketone **22** (45.0 mg, 0.095 mmol) in 1 mL of ether dropwise. The resulting mixture was stirred for 20 min and poured into 20 mL of saturated NH<sub>4</sub>Cl. The organic layer was dried over MgSO<sub>4</sub> and evaporated to dryness in vacuo, and the residue was purified by flash column chromatography (20-mm column). Elution with hexane-EtOAc (10:1) afforded 42 mg (75%) of alcohol **25** ( $R_f$  0.46, 1:6 ether-hexanes) and 1.4 mg (2%) of the corresponding axial epimer. A purified sample of alcohol **25** had the following spectral characteristics: NMR (400 MHz, CDCl<sub>3</sub>) 6.78 (s, 1 H), 5.61 (s, 1 H), 3.68 (br s, 1 H), 3.60 (d,  $J = 12.0$  Hz, 1 H), 3.51 (d,  $J = 12.0$  Hz, 1 H), 3.24 (s, 3 H), 3.20 (s, 3 H), 1.80–1.66 (m, 1 H), 1.68–1.62 (m, 1 H), 1.49 (s, 3 H), 1.20 (s, 3 H), 0.98 (d,  $J = 7.4$  Hz, 3 H), 0.95–0.90 (m, 12 H), 0.86 (s, 9 H), 0.12 (s, 3 H), 0.11 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H), 0.03 (s, 3 H); IR (film) 3440 (br m).

Anal. Calcd for C<sub>30</sub>H<sub>64</sub>O<sub>6</sub>Si<sub>3</sub>: C, 59.55; H, 10.66. Found: C, 59.26; H, 10.43.

(**1R\*(1Z)**,**2R\***,**3R\***,**4R\***,**5R\***,**6S\***)-4,6-Bis((*tert*-butyldimethylsilyloxy)-1-(3,3-dimethoxy-2-methyl-1-butenyl))-3,5-dimethylcyclohexan-1,2-diol (**26**). A solution of alcohol **25** (36 mg, 0.059 mmol) in 5 mL of CH<sub>2</sub>Cl<sub>2</sub> was treated with 0.5 mL of Et<sub>3</sub>N-HF, and the reaction mixture was stirred for 4 h at room temperature. After dilution with 30 mL of CH<sub>2</sub>Cl<sub>2</sub>, the reaction mixture was washed with saturated NaHCO<sub>3</sub> solution and evaporated to dryness in vacuo. The crude oily residue was purified by flash chromatography (20-mm column). Elution with hexanes-EtOAc (4:1) provided 24 mg (80%) of diol **26**: NMR (400 MHz, CDCl<sub>3</sub>) 5.79 (s, 1 H), 5.73 (s, 1 H), 3.63 (br s, 1 H), 3.63 (d,  $J = 10.7$  Hz, 1 H), 3.58 (dd,  $J_1 = 11.4$ ,  $J_2 = 2.4$  Hz, 1 H), 3.31 (s, 3 H), 3.22 (s, 3 H), 1.80 (d,  $J = 0.8$  Hz, 3 H), 1.79–1.68 (m, 1 H), 1.47 (s, 3 H), 1.43–1.36 (m, 1 H), 1.00 (d,  $J = 6.2$  Hz, 3 H), 0.98 (d,  $J = 6.3$  Hz, 3 H), 0.90 (s, 9 H), 0.85 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 6 H), 0.01 (s, 3 H); MS (EI),  $m/e$  (relative intensity) 411 (15), 368 (18), 335 (17), 317 (19), 315 (25), 280 (11), 279 (11), 240 (25), 239 (100), 213 (17), 205 (19), 201 (20), 185 (17), 177 (11), 175 (12), 174 (16), 173 (96), 168 (22), 167 (69), 161 (18), 156 (31), 149 (12), 147 (20), 145 (22), 143 (33), 141 (11), 139 (17), 137 (13), 136 (10), 135 (18), 126 (35), 125 (82), 124 (15), 123 (19), 117 (19), 115 (54), 111 (12), 109 (33), 103 (10), 99 (17), 91 (11), 89 (96), 76 (12), 75 (100), 73 (100), 69 (19), 67 (13).

(**2R\***,**3R\***,**4S\***,**5R\***,**7Z**)-3,5-Bis((*tert*-butyldimethylsilyloxy)-9,9-dimethoxy-2,4,8-trimethyl-6-oxo-7-decanal (**27**). A solution of diol **26** (40 mg, 0.08 mmol) in 2 mL of anhydrous THF was cooled to  $0^{\circ}\text{C}$  in an ice-water bath and treated with 50 mg (0.11 mmol, 1.5 equiv) of Pb(OAc)<sub>4</sub> in small portions every 5 min until the addition was complete. TLC analysis showed complete consumption of **26** in most runs. The reaction mixture was diluted with ether, and the resulting suspension was filtered through a short pad of SiO<sub>2</sub> in ether. The filtrate was washed with cold 10% HCl (10 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated to afford 31 mg of aldehyde **27** (73%) as a yellow oil ( $R_f$  0.43 (1:6 ether-hexanes)): NMR (400 MHz, CDCl<sub>3</sub>) 9.77 (s, 1 H), 5.78 (d,  $J = 1.2$  Hz, 1 H), 4.68 (d,  $J = 2.2$  Hz, 1 H), 4.13 (dd,  $J_1 = 8.2$ ,  $J_2 = 1.8$  Hz, 1 H), 3.09 (s, 3 H), 3.07 (s, 3 H), 2.54–2.47 (m, 1 H), 2.18–2.10 (m, 1 H), 1.76 (s, 3 H), 1.40 (s, 3 H), 1.14 (d,  $J = 7.1$  Hz, 3 H), 0.90 (s, 9 H), 0.87 (s, 9 H), 0.11 (s, 3 H), 0.08 (s, 3 H); IR (film) 2930 (s),

2880 (s), 2850 (s), 2710 (m), 2690 (m), 1720 (s), 1710 (s), 1695 (m), 1625 (m), 1615 (m), 1460 (s), 1385 (s), 1365 (s), 1355 (s), 1255 (s), 1230 (s), 1195 (s); MS (EI),  $m/e$  (relative intensity) 483 ( $M^+ - 57$ , 1.5).

Aldehyde **27** is unstable to storage and was used without further purification in the next reaction.

(**2E,4R\***,**5R\***,**6R\***,**7S\***,**9Z**)-5,7-Bis((*tert*-butyldimethylsilyloxy)-11,11-dimethoxy-2,4,6,10-tetramethyl-8-oxo-2,9-dodecadienal (**28**). A solution of (*Z*)-2-bromo-1-ethoxy-1-propene<sup>37</sup> (30 mg, 0.18 mmol) in 5 mL of ether was cooled to  $-78^{\circ}\text{C}$ , and 0.22 mL (0.35 mmol) of a 1.61 M solution of *t*-BuLi was added dropwise with stirring. After 20 min at  $-78^{\circ}\text{C}$ , a solution of aldehyde **27** (78 mg, 0.15 mmol) in 2 mL of ether was added dropwise to the reaction mixture with good stirring. The resulting solution was stirred at  $-48^{\circ}\text{C}$  for 20 min, followed by dropwise addition of a solution of *p*-nitrobenzoyl chloride (55 mg, 0.30 mmol) in 1 mL of ether. The cooling bath was removed, the reaction mixture was allowed to warm to room temperature, and stirring was continued for 1 h at room temperature. The resulting reaction mixture was diluted with 20 mL of ether, and the resulting solution was washed with saturated aqueous NH<sub>4</sub>Cl (5 mL), dried over MgSO<sub>4</sub>, and evaporated to dryness in vacuo.

The residue (a mixture (~3:2) of diastereomeric allylic benzoates which could be isolated and purified at this point if desired) was dissolved in 3 mL of CH<sub>3</sub>CN and 0.15 mL of water. To this solution was added 105 mg (0.85 mmol) of Et<sub>3</sub>N-HF,<sup>36</sup> and the mixture was heated at  $60^{\circ}\text{C}$  (oil bath) for 3 h. The cooled reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL), and the organic layer was washed with water (5 mL), dried over anhydrous MgSO<sub>4</sub>, and concentrated in vacuo. The crude oily residue was purified by flash chromatography (20-mm column) by elution with hexanes-EtOAc (6:1), affording 52 mg (62%) of unsaturated aldehyde **28**: NMR (300 MHz, CDCl<sub>3</sub>) 9.41 (s, 1 H), 6.79 (d,  $J = 9.6$  Hz, 1 H), 5.88 (s, 1 H), 4.52 (d,  $J = 3.6$  Hz, 1 H), 3.79 (d,  $J = 7.3$  Hz, 1 H), 3.12 (s, 3 H), 3.11 (s, 3 H), 2.96 (m, 1 H), 1.94 (m, 1 H), 1.81 (s, 3 H), 1.79 (s, 3 H), 1.45 (s, 3 H), 1.11 (d,  $J = 7.0$  Hz, 3 H), 0.95 (s, 9 H), 0.93 (s, 9 H), 0.70 (d,  $J = 7.0$  Hz, 3 H), 0.16 (s, 3 H), 0.16 (s, 3 H), 0.15 (s, 3 H), 0.11 (s, 3 H); IR (film) 1710 (s), 1690 (m); MS (EI),  $m/e$  (relative intensity) 538 ( $M^+ - 32$ , 0.8), 481 (5.5), 441 (1.4), 341 (2.5), 297 (4.9), 269 (18.6), 241 (100), 157 (55.1), 143 (12.5), 73 (3).

(**2E,4R\***,**5R\***,**6R\***,**7S\***,**9Z**)-5,7-Bis((*tert*-butyldimethylsilyloxy)-11,11-dimethoxy-2,4,6,10-tetramethyl-8-oxo-2,9-dodecadienol. A solution of aldehyde **28** (70.0 mg, 0.123 mmol) in 6 mL of absolute ethanol was cooled to  $4^{\circ}\text{C}$  (ice water), and 7.2 mg (0.19 mmol) of NaBH<sub>4</sub> was added with stirring. The reaction mixture was stirred at  $4^{\circ}\text{C}$  for 1 h, diluted with ether (20 mL), and washed with saturated aqueous NH<sub>4</sub>Cl (5 mL) and water (5 mL). The organic layer was dried over anhydrous MgSO<sub>4</sub> and concentrated in vacuo to afford the oily title allylic alcohol (67 mg) of sufficient purity to be used in the subsequent reaction: NMR (300 MHz, CDCl<sub>3</sub>) 5.83 (s, 1 H), 5.60 (d,  $J = 9.2$  Hz, 1 H), 4.66 (d,  $J = 2.4$  Hz, 1 H), 4.01 (s, 2 H), 3.70 (d,  $J = 8.0$  Hz, 1 H), 3.12 (s, 3 H), 2.63 (m, 1 H), 1.95 (m, 1 H), 1.79 (s, 3 H), 1.71 (s, 3 H), 1.43 (s, 3 H), 1.01 (d,  $J = 6.9$  Hz, 3 H), 0.92 (s, 18 H), 0.69 (d,  $J = 6.8$  Hz, 3 H), 0.17 (s, 3 H), 0.14 (s, 3 H), 0.12 (s, 3 H), 0.11 (s, 3 H); IR (film) 3440 (m), 2900 (s), 1700 (s), 1470 (s), 1380 (s), 1250 (s), 1120 (s), 1050 (s); MS (EI),  $m/e$  (relative intensity) 540 ( $M^+ - 32$ , 0.5), 515 ( $M^+ - 57$ , 0.4), 483 (2.1), 441 (2.3), 409 (2.5), 341 (6.2), 309 (10.1), 269 (30.7), 243 (64.8), 225 (22.1), 157 (28.0), 73 (100).

(**2E,4R\***,**5R\***,**6R\***,**7S\***,**9Z**)-5,7-Bis((*tert*-butyldimethylsilyloxy)-11,11-dimethoxy-2,4,6,10-tetramethyl-8-oxo-2,9-dodecadienyl Acetate (**29**). A solution of crude allylic alcohol from the previous experiment (67 mg, 0.12 mmol), pyridine (0.10 mL, 1.24 mmol), and 4-(dimethylamino)pyridine (2 mg, 0.016 mmol) in 5 mL of CH<sub>2</sub>Cl<sub>2</sub> was treated with 20  $\mu\text{L}$  (0.28 mmol) of acetyl chloride. After 15 min, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL), washed with saturated aqueous NH<sub>4</sub>Cl (5 mL), dried over anhydrous MgSO<sub>4</sub>, and concentrated in vacuo. The residual oil was purified by flash chromatography (20-mm column) eluting with hexanes-EtOAc (10:1) to give 53 mg (78% over two steps) of acetate **29**: NMR (300 MHz, CDCl<sub>3</sub>) 5.84 (s, 1 H), 5.63 (d,  $J = 9.5$  Hz, 1 H), 4.64 (d,  $J = 2.9$  Hz, 1 H), 4.45 (s, 2 H), 3.68 (dd,  $J_1 = 8.0$ ,  $J_2 = 1.3$  Hz, 1 H), 3.12 (s, 3 H), 3.11 (s, 3 H), 2.6 (m, 1 H), 2.07 (s, 3 H), 1.94 (m, 1 H), 1.79 (s, 3 H), 1.68 (s, 3 H), 1.43 (s, 3 H), 1.01 (d,  $J = 7.0$  Hz, 3 H), 0.92 (s, 12 H), 0.91 (s, 12 H), 0.68 (d,  $J = 6.9$  Hz, 3 H), 0.20 (s, 3 H), 0.17 (s, 3 H), 0.14 (s, 3 H), 0.12 (s, 3 H); IR (film) 2960, 1735, 1700, 1455, 1370, 1250; MS (EI),  $m/e$  (relative intensity) 582 ( $M^+ - 31$ , 1.1), 525 (1.7), 425 (1.5), 285 (26.2), 225 (100), 157 (51.6), 73 (100).

[**4R\***(**1S\***,**5S\***,**6R\***,**7R\***),**2E**]-2-Methyl-4-(1,2,6-trimethyl-4-oxo-8,9-dioxabicyclo[3.3.1]non-2-en-7-yl)-2-penten-1-yl Acetate (**30**). A stirred

(36) Hunig, S.; Wehner, G. *Synthesis* **1975**, 180.

(37) Ahrens, J. F. *Recl. Trav. Chim. Pays-Bas* **1955**, 74, 271.

solution of acetate **29** (50 mg, 0.082 mmol) in 3 mL of anhydrous THF was treated with 0.26 mL (10.26 mmol) of a freshly prepared 1 M solution of (*n*-Bu)<sub>4</sub>NF in THF.<sup>38</sup> After stirring at room temperature for 1.5 h, the reaction mixture was diluted with ether (20 mL), washed successively with saturated aqueous NH<sub>4</sub>Cl (5 mL) and water (2 × 5 mL), dried over anhydrous MgSO<sub>4</sub>, and concentrated in vacuo.

A solution of the residual crude diol in 2 mL of CH<sub>2</sub>Cl<sub>2</sub> was cooled to -78 °C and treated with 50 μL (0.41 mmol) of BF<sub>3</sub>-Et<sub>2</sub>O. The reaction mixture was stirred at -78 °C for 20 min, followed by quenching with 5% of aqueous NaHCO<sub>3</sub> (0.1 mL), diluting with CH<sub>2</sub>Cl<sub>2</sub> (20 mL), and drying over anhydrous MgSO<sub>4</sub>. After concentration in vacuo, the residual oil was purified by flash chromatography (20-mm column) with elution by hexanes-EtOAc (4:1) to afford 14.5 mg (55% from **29**) of bicyclic acetate **30**: NMR (300 MHz, CDCl<sub>3</sub>) 6.13 (s, 1 H), 5.65 (d, *J* = 10.2 Hz, 1 H), 4.51 (d, *J* = 2.7 Hz, 2 H), 4.05 (d, *J* = 6.1 Hz, 1 H), 3.39 (dd, *J*<sub>1</sub> = 12.8 *J*<sub>2</sub> = 1.6 Hz, 1 H), 2.70 (m, 1 H), 2.12 (s, 3 H), 2.00 (m, 1 H), 1.94 (s, 3 H), 1.68 (s, 3 H), 1.55 (s, 3 H), 1.02 (d, *J* = 6.9 Hz, 3 H), 0.73 (d, *J* = 7.0 Hz, 3 H); IR (film) 2950, 1750, 1700, 1390, 1250, 1140, 1030, 910; MS (EI), *m/e* (relative intensity) 322 (M<sup>+</sup>, 1.0), 263 (5.0), 181 (10.0), 141 (89.0), 125 (31.6), 99 (38.9), 81 (31.3).

Anal. Calcd for C<sub>18</sub>H<sub>26</sub>O<sub>5</sub>: 322.1780. Found: 322.1765.

**[4R\*(1S\*,2S\*,4R\*,6S\*,7R\*,8R\*),2E]-2-Methyl-4-(1,2,7-trimethyl-5-oxo-3,9,10-trioxatricyclo[4.3.1.0<sup>2,4</sup>]dec-8-yl)-2-penten-1-yl Acetate.** A solution of acetate **30** (11.1 mg, 0.034 mmol) and 27 μL (0.18 mmol) of strictly anhydrous deoxygenated DBU in 0.5 mL of anhydrous THF under an argon atmosphere was treated with 18 μL (0.18 mmol) of strictly anhydrous *t*-BuOOH via syringe.<sup>39</sup> The flask was sealed with Parafilm, and the reaction mixture was heated (oil bath) at 60 °C for 15 h. After cooling, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (~15 mL) and washed with 5% aqueous HCl (5 mL). The aqueous layer was extracted again with CH<sub>2</sub>Cl<sub>2</sub> (10 mL). The combined organic layers were washed with water (5 mL). The aqueous layer was again back-extracted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL), and the combined organic layers were dried over anhydrous MgSO<sub>4</sub>. After concentration in vacuo, the residual oil was purified by flash chromatography (10-mm column) using hexanes-EtOAc (8:1) as eluant to afford 10.4 mg (89%) of the title β epoxy acetate: NMR (300 MHz, CDCl<sub>3</sub>) 5.60 (d, *J* = 10.1 Hz, 1 H), 4.51 (s, 2 H), 4.05 (d, *J* = 6.1 Hz, 1 H), 3.52 (dd, *J*<sub>1</sub> = 11.4, *J*<sub>2</sub> = 1.9 Hz, 1 H), 3.29 (s, 1 H), 2.60 (m, 1 H), 2.11 (s, 3 H), 2.00 (s, 1 H), 1.68 (d, *J* = 0.8 Hz, 3 H), 1.56 (s, 3 H), 1.48 (s, 3 H), 1.09 (d, *J* = 7.0 Hz, 3 H), 0.73 (d, *J* = 7.0 Hz, 3 H); IR (film) 2990 (s), 1750 (s), 1740 (s), 1250 (s); MS (EI), *m/e* (relative intensity) 338 (M<sup>+</sup>, 0.5), 197 (75), 69 (100), 43 (85).

**[4R\*(1S\*,2S\*,4R\*,6S\*,7R\*,8R\*),2E]-2-Methyl-4-(1,2,7-trimethyl-5-oxo-3,9,10-trioxatricyclo[4.3.1.0<sup>2,4</sup>]dec-8-yl)-2-pentenal (32).** A solution of β epoxy acetate (7.1 mg, 0.021 mmol) from the previous experiment in 1 mL of dry methanol was treated with 0.15 mL of a saturated solution of anhydrous K<sub>2</sub>CO<sub>3</sub> in dry methanol (supernatant of a suspension of 0.7 g of anhydrous K<sub>2</sub>CO<sub>3</sub> in 10 mL of anhydrous methanol). Consumption of **30** was monitored by TLC. The reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL), washed with water (2 mL), and dried over anhydrous MgSO<sub>4</sub>, and the solvent was removed in vacuo. The residual crude epoxy alcohol was utilized without purification in the subsequent transformation.

A solution of the crude alcohol above in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was treated with 24 mg (0.063 mmol) of PDC (added in one portion) and stirred at room temperature for 1.5 h. The reaction mixture was diluted with 10 mL of ether and filtered through anhydrous MgSO<sub>4</sub>. After removal of the solvent, the resulting crude alcohol was purified by flash chromatography (10-mm column) with elution by hexanes-EtOAc (2:1) to afford 4.8 mg (83% from **30**) of keto aldehyde **32**: NMR (300 MHz, CDCl<sub>3</sub>) 9.48 (s, 1 H), 6.68 (d, *J* = 10.0 Hz, 1 H), 4.06 (d, *J* = 6.0 Hz, 1 H), 3.65 (d, *J* = 10.7 Hz, 1 H), 3.32 (s, 1 H), 3.00 (m, 1 H), 2.00 (m, 1 H), 1.79 (s, 3 H), 1.61 (s, 3 H), 1.51 (s, 3 H), 1.20 (d, *J* = 6.9 Hz, 3 H), 0.76 (d, *J* = 7.0 Hz, 3 H).

Keto aldehyde **32** was identical with an authentic sample of optically active aldehyde **32** in all respects except optical rotation, including spectroscopic criteria (NMR (300 MHz), MS (low resolution)) and TLC mobility in several solvent systems.<sup>28</sup>

**Ethyl *N*-(2,4-Dimethoxybenzyl)glycinate.** A suspension of 4.10 g (0.029 mol) of ethyl glycinate hydrochloride in 10 mL of anhydrous CH<sub>3</sub>OH was combined with 4 mL (0.029 mol) of Et<sub>3</sub>N and the resulting mixture diluted with 50 mL of anhydrous EtOH containing 3.32 g (0.02 mol) of 2,4-dimethoxybenzaldehyde. The solvents were removed in va-

cuo, the residue was dissolved in 70 mL of anhydrous EtOH, and 1.1 g (0.029 mol) of NaBH<sub>4</sub> was added at room temperature with stirring. After 1 h at room temperature, the reaction was quenched with saturated NH<sub>4</sub>Cl (until gas evolution ceases), and the mixture was extracted with ether (3 × 50 mL). The combined organic layers were dried over anhydrous MgSO<sub>4</sub>, and the solvent was removed in vacuo. The residue was purified by flash chromatography (40-mm column) with elution by EtOAc to afford 3.0 g (59% based on 2,4-dimethoxybenzaldehyde) of ethyl *N*-(2,4-dimethoxybenzyl)glycinate which was used as obtained for the next transformation.

**Ethyl *N*-(4-(Diethoxyphosphinyl)-3-oxobutanoyl)-*N*-(2,4-dimethoxybenzyl)glycinate.** A solution of 6-((diethoxyphosphinyl)methyl)-2,2-dimethyl-1,3-diox-5-en-4-one<sup>29</sup> (4.9 g, 0.018 mol) and ethyl *N*-(2,4-dimethoxybenzyl)glycinate (3.0 g, 0.012 mol) in 50 mL of freshly distilled anhydrous xylene was heated from room temperature to 160 °C in an oil bath. After 1 h at 160 °C, the cooled reaction mixture was concentrated in vacuo. The resulting crude material was purified by using the Waters Prep 500 on SiO<sub>2</sub> with elution by EtOAc to afford 3.8 g (69%) of the title amino ester which was used as obtained for the next transformation.

**3-(1-Hydroxy-2-(diethoxyphosphinyl)ethylidene)-1-(2,4-dimethoxybenzyl)-2,4-pyrrolidinedione (33).** A solution of 280 mg (0.59 mmol) of the acyl glycinate from the previous experiment in 10 mL of anhydrous THF was treated dropwise with stirring with a solution of 73 mg (0.65 mmol) of KO-*t*-Bu (handled under N<sub>2</sub> in a glovebag) in 5 mL of anhydrous THF at room temperature. After 16 h at room temperature, the resulting reaction mixture was concentrated in vacuo, the residue was dissolved in 20 mL of CH<sub>2</sub>Cl<sub>2</sub>, and the resulting solution was extracted with saturated aqueous NaHCO<sub>3</sub> (2 × 20 mL). The aqueous layer was carefully acidified to pH 2 with 5% HCl and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 25 mL). The combined organic extracts were dried and concentrated in vacuo to afford 171 mg (65%) of tetramic acid **33**: NMR (300 MHz, CDCl<sub>3</sub>) 8.80 (br s, 1 H), 7.19 (d, *J* = 7.8 Hz, 1 H), 6.24 (m, 2 H), 4.60 (s, 2 H), 4.20 (s, 4 H), 3.82 (s, 6 H), 3.70 (s, 2 H), 3.55 (d, *J* = 23.4 Hz, 2 H), 1.37 (t, *J* = 6.0 Hz, 6 H).

Tetramic acid **33** was somewhat unstable and was utilized without further characterization in subsequent transformations.

**[1S\*,2S\*,4R\*,6S\*,7R\*,8R\*(1E,2E,4E,6R\*)]-1-(2,4-Dimethoxybenzyl)-3-[1-hydroxy-4-methyl-6-(1,2,7-trimethyl-5-oxo-3,9,10-trioxatricyclo[4.3.1.0<sup>2,4</sup>]dec-8-yl)-2,4-heptadienylidene]-2,4-pyrrolidinedione (37).** A solution of phosphonate **33** (25.1 mg, 0.0588 mmol) in 1.0 mL of anhydrous THF at 0 °C was treated with 1.52 mL of a 0.081 M solution of KO-*t*-Bu (0.123 mmol) in anhydrous THF.<sup>40</sup> After the resulting mixture was stirred at 0 °C for 30 min, 1.10 mL (0.0255 mmol) of this dianion solution was added dropwise with stirring to a solution of keto aldehyde **32** (2.5 mg, 0.0085 mmol) in 0.5 mL of THF at 0 °C. The resulting reaction mixture was stirred at 0 °C for 6 h, followed by dilution with CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and partitioning with pH 2 phosphate buffer. The organic layer was dried over anhydrous MgSO<sub>4</sub> and concentrated in vacuo. The oily residue was dissolved in CHCl<sub>3</sub> and filtered through a short column (pipet) of SiO<sub>2</sub> (Merck 7734) in CHCl<sub>3</sub> to provide 3.4 mg (72%) of dienoyl tetramic acid **37**: NMR (300 MHz, CDCl<sub>3</sub>) 7.80-7.10 (m, 3 H), 6.51 (br s, 2 H), 6.20 (d, *J* = 9.9 Hz, 1 H), 4.60 (s, 2 H), 4.05 (d, *J* = 6.0 Hz, 1 H), 3.83 (s, 3 H), 3.82 (s, 3 H), 3.68 (s, 2 H), 3.60 (d, *J* = 10.9 Hz, 1 H), 3.32 (s, 1 H), 2.80 (m, 1 H), 2.00 (m, 1 H), 1.90 (s, 3 H), 1.60 (s, 3 H), 1.48 (s, 3 H), 1.13 (d, *J* = 7.0 Hz, 3 H), 0.75 (d, *J* = 7.0 Hz, 3 H).

Tetramic acid **37** was sufficiently pure as obtained for conversion to (±)-tirandamycin A.

**[1S\*,2S\*,4R\*,6S\*,7R\*,8R\*(1E,2E,4E,6R\*)]-3-[1-Hydroxy-4-methyl-6-(1,2,7-trimethyl-5-oxo-3,9,10-trioxatricyclo[4.3.1.0<sup>2,4</sup>]dec-8-yl)-2,4-heptadienylidene]-2,4-pyrrolidinedione ((±)-Tirandamycin A) (1).** *N*-benzyltetramic acid **33** (3.1 mg, 0.0055 mmol) was dissolved in 0.5 mL of anhydrous CF<sub>3</sub>CO<sub>2</sub>H, and the resulting purple solution was stirred at room temperature for 15 min. The reaction was quenched by addition of ice, and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 5 mL). The combined organic extracts were washed with saturated aqueous NaHCO<sub>3</sub> (3 × 5 mL), dried over anhydrous MgSO<sub>4</sub>, and concentrated in vacuo. The residual oil was purified by flash chromatography (5-mm column) with elution by CH<sub>2</sub>Cl<sub>2</sub>-CH<sub>3</sub>OH (9:1) affording after concentration the sodium salt of (±)-tirandamycin A. This material was redissolved in CH<sub>2</sub>Cl<sub>2</sub> (20 mL), and the solution was acidified with HCl-CH<sub>3</sub>OH, washed with water (10 mL), dried over anhydrous MgSO<sub>4</sub>, and concentrated in vacuo to afford 2.0 mg (83%) of yellow amorphous solid (±)-tirandamycin A (**1**) which was identical in all respects except optical rotation with an authentic samples of (±)-tirandamycin A, including

(38) Fowler, D. L.; Loebenstein, W. V.; Pall, D. B.; Kraus, C. A. *J. Am. Chem. Soc.* **1940**, *62*, 1140.

(39) If strictly anhydrous conditions are not maintained throughout, deacetylation occurs, resulting in decomposition.

(40) The sample of commercial KO-*t*-Bu used was never exposed to air. The sample was opened and all manipulations were carried out in a glovebag under a N<sub>2</sub> atmosphere.

NMR (300 MHz, CDCl<sub>3</sub>) and TLC behavior in several solvent systems.<sup>31</sup>

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**Registry No.** 1, 85880-71-3; 1-Na, 97859-37-5; 3, 103367-77-7; 3 (enol silyl derivative), 103367-78-8; 4, 34958-43-5; 5, 103367-73-3; 6, 103367-74-4; 7, 103383-24-0; 8, 103367-75-5; 9, 103421-92-7; 10, 103367-76-6; 11, 103367-82-4; 13, 103421-25-6; 15, 103367-83-5; 18,

103367-84-6; 19, 103367-85-7; 20 (isomer 1), 103367-86-8; 20 (isomer 2), 103421-26-7; 21, 103383-25-1; 22, 103367-79-9; 23, 103367-88-0; 24, 103367-87-9; 25, 103367-89-1; 26, 103383-26-2; 27, 103367-90-4; 27 (allylic benzoate) (isomer 1), 103367-91-5; 27 (allylic benzoate) (isomer 2), 103421-27-8; 28, 103367-92-6; 28 (alcohol), 103367-93-7; 29, 103383-27-3; 29 (diol), 103367-94-8; 30, 103367-95-9; 30 (epoxide), 103383-28-4; 30 (epoxide, alcohol), 103383-29-5; 32, 97859-35-3; 33, 103367-98-2; 34, 95218-34-1; 35, 81956-28-7; 36, 103367-97-1; 37, 97859-87-5; acetyl bromide, 506-96-7; 1,1-dibromopropene, 13195-80-7; 4,4,4-tribromo-3-methylbutan-2-one, 103367-80-2; 1,1-dibromo-2-methyl-1-buten-3-one, 103367-81-3; (Z)-2-bromo-1-ethoxy-1-propene, 34600-12-9; *p*-nitrobenzoyl chloride, 122-04-3; ethyl glycinate hydrochloride, 623-33-6; 2,4-dimethoxybenzaldehyde, 613-45-6; ethyl *N*-(2,4-dimethoxybenzoyl)glycinate, 103367-96-0.

## Stereocontrolled Total Synthesis of (±)-Tirandamycin A

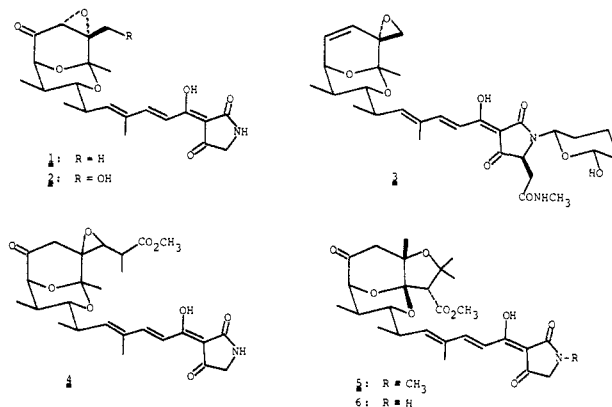
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**Abstract:** A total synthesis of the title compound which is fundamentally different from previously reported routes or approaches is presented. The key stereochemical intermediate, acetylenic lactone **16**, is prepared in a sequence involving diethylpropynylalane-induced epoxide displacement and iodolactonization/epoxidation. An important step in this sequence is the protection of an  $\alpha$ -hydroxy acid as its hexafluoroacetone (15). Methodology for introduction of the dienoyl tetramic acid side chain was developed with the ketal acetone **18** as a model substrate. The dienoyl ester **22** was prepared via addition of vinyl cuprate **21** to methyl propiolate, and the tetramic acid unit was introduced via acylation of silyl malonamide **25** followed by cyclization. Elaboration of the bicyclic ketal was accomplished via addition of lithio ketal **31** to lactone **32**. Direct cyclization of this material was not feasible, and a sequence involving stepwise ring closure was investigated. Intramolecular cycloaddition of an oxidopyrylium ylide (**41** → **43**) foiled one approach to generate enone ketal **9** after introduction of the double bond; the structure of the cycloadduct **43** was elucidated by crystallography. Enone **9** was eventually produced by cyclization of a reduced intermediate, via alcohol **45**, followed by oxidation and dehydrogenation of the alcohol, and the structure was verified by crystallography. From intermediate **45**, the methodology developed in the model systems was applied to the introduction of the dienoyl ester side chain (→ **48**), the enone functionality (→ **49**), and the tetramic acid moiety (→ **53**). (±)-Tirandamycin A was produced from trifluoroacetic acid catalyzed cleavage of the *N*-(2,4-dimethoxybenzyl) group, as reported previously.

Tirandamycin A (**1**)<sup>1</sup> and its congeners **2-6**<sup>2</sup> comprise a class of RNA polymerase inhibitors which contain stereochemically intriguing bicyclic ketal units wedged to planar and highly enolic dienoyl tetramic acids (Chart I). Tirandamycin A itself has been the focus of a number of synthetic efforts in recent years,<sup>6-15</sup>

Chart I



culminating in total syntheses reported by Schlessinger,<sup>16</sup> DeShong,<sup>17</sup> Boeckman,<sup>48</sup> and their co-workers. Since the pioneering work of the Rinehart<sup>6</sup> and Ireland<sup>8</sup> groups, a number of common themes have appeared in the published work in this area, namely, use of the Kishi aldehyde<sup>18</sup> (or an equivalent) as the

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