A Total Synthesis of (±)-Tirandamycin B

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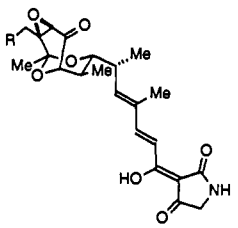
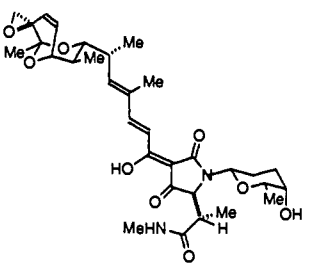
Abstract: The total synthesis of the dienoyl tetramic acid antibiotic (±)-tirandamycin B is described. The key transformations of the strategy include (1) cyclization of pyranone **14** with fluorosilicic acid to provide the 2,6-dioxabicyclo[3.3.1]nonane system of the natural product, (2) reductive removal of the benzyl ether from enone **15**, and (3) attachment of the tetramic acid moiety by using the Schlessinger phosphonate protocol. Protection of the primary hydroxyl function of tirandamycin B as the triisopropylsilyl (TIPS) ether was crucial to the success of the strategy.

Tirandamycin B (**1**)[1] is a member of the 3-dienoyl tetramic acid family of antibiotics. This family includes several structurally related substances such as tirandamycin A (**2**),[2] streptolydigin (**3**),[3] nocamycin,[4] and Bu-2313 A and B.[5] These substances display a diversity of biological activities. For example, tirandamycin B has been shown to possess antimicrobial activity by interfering with the function of bacterial DNA-directed RNA polymerase.[6] It is also a potent inhibitor of terminal transferase found in leukemia cell lines.[6a]



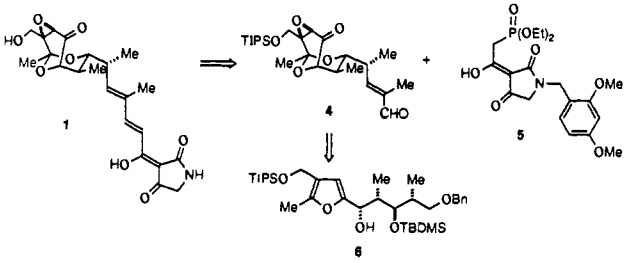
Tirandamycin B (1): R = OH
Tirandamycin A (2): R = H



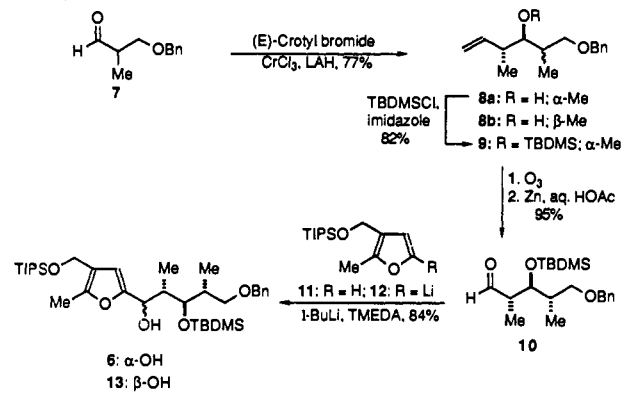
Streptolydigin (3)

A number of research groups have been involved in developing methodology for the synthesis of the dienoyl tetramic acid antibiotics.[7] Development of methodology has progressed to the point that total syntheses of tirandamycin A (**2**), the simplest member of this family, have been reported from this laboratory[8] and by Schlessinger,[9] Martin,[10] Boeckman,[11] and Bartlett.[12] In

Scheme I



Scheme II



(1) Hagenmaier, H.; Jaschke, K. H.; Santo, L.; Scheer, M.; Zähner, H. *Arch. Microbiol.* **1976**, *109*, 65.

(2) (a) Isolation: Reusser, F. *Infect. Immun.* **1970**, *2*, 77, 82. Meyer, C. E. *J. Antibiot.* **1971**, *24*, 558. Reusser, F. *Antibiotics V-1; Mechanism of Action of Antibacterial Agents*; Springer-Verlag: Berlin, 1979; Vol. 1, Part 1, p 361. (b) Gross structure: MacKellar, F. A.; Grostic, M. F.; Olson, E. C.; Wnuk, R. J.; Branfman, A. R.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1971**, *93*, 4943. (c) Absolute stereochemistry: Duchamp, D. J.; Branfman, A. R.; Button, A. C.; Rinehart, K. L., Jr. *Ibid.* **1973**, *95*, 4077.

(3) (a) Isolation: Eble, T. E.; Large, C. M.; DeVries, W. H.; Crum, G. F.; Shell, J. W. *Antibiot. Ann.* **1955–1956**, 893. (b) Gross structure: Rinehart, K. L., Jr.; Beck, J. R.; Epstein, W. W.; Spicer, L. D. *J. Am. Chem. Soc.* **1963**, *85*, 4035. Rinehart, K. L., Jr.; Borders, D. B. *Ibid.* **1963**, *85*, 4037. Rinehart, K. L., Jr.; Beck, J. R.; Borders, D. B.; Kinstle, T. H.; Krauss, D. *Ibid.* **1963**, *85*, 4038. Stevens, C. L.; Blumbergs, P.; Wood, D. L. *Ibid.* **1964**, *86*, 3592. Lee, V. J.; Rinehart, K. L., Jr. *J. Antibiot.* **1980**, *33*, 408. (c) Biosynthesis: Rinehart, K. L., Jr.; Weller, D. D.; Pearce, C. J. *J. Nat. Prod.* **1980**, *43*, 1. Pearce, C. J.; Ulrich, S. E.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 2510. Pearce, C. J.; Rinehart, K. L., Jr. *J. Antibiot.* **1983**, *36*, 1536.

(4) Horváth, G.; Brazhnikova, M. G.; Konstantinova, N. V.; Tolstykh, I. V.; Potapova, N. P. *J. Antibiot.* **1979**, *32*, 555.

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(6) (a) DiCioccio, R. A.; Sahai Srivastava, B. I. *Biochem. Biophys. Res. Commun.* **1976**, *72*, 1343. (b) Reusser, F. *Antimicrob. Agents Chemother.* **1976**, *10*, 618.

(7) (a) Ireland, R. E.; Wuts, P. G. M.; Ernst, B. *J. Am. Chem. Soc.* **1981**, *103*, 3205. (b) Ziegler, F. E.; Thottathil, J. K. *Tetrahedron Lett.* **1981**, *22*, 4883. (c) DeShong, P.; Ramesh, S.; Perez, J. J.; Bodish, C. *Ibid.* **1982**, *23*, 2243. (d) DeShong, P.; Ramesh, S.; Perez, J. J. *J. Org. Chem.* **1983**, *48*, 2117. (e) Bartlett, P. A. In *Selectivity- a Goal for Synthetic Efficiency*; Bartmann, W., Trost, B. M. Eds.; Verlag Chemie: Weinheim, Germany, 1984; p 1. (f) Ziegler, F. E.; Wester, R. T. *Tetrahedron Lett.* **1984**, *25*, 617. (g) Kelly, T. R.; Chandrakumar, N. S.; Cutting, J. D.; Goehring, R. R.; Weibel, F. R. *Ibid.* **1985**, *26*, 2173. (h) Danishefsky, S.; Harvey, D. F. *J. Am. Chem. Soc.* **1985**, *107*, 6647. (i) DeShong, P.; Lin, M.-T.; Perez, J. J. *Tetrahedron Lett.* **1986**, *27*, 2091. (j) Martin, S. F.; Gluchowski, C.; Campbell, C. L.; Chapman, R. C. *Tetrahedron* **1988**, *44*, 3171. (k) Ikegami, S.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1988**, *29*, 5285. (l) Ireland, R. E.; Smith, M. G. *J. Am. Chem. Soc.* **1988**, *110*, 854. (m) Taschner, M. J.; Aminbhavi, A. S. *Tetrahedron Lett.* **1989**, *30*, 1029. (n) DeShong, P.; Simpson, D. M.; Lin, M.-T. *Ibid.* **1989**, *30*, 2885. (o) Paterson, I.; Lister, M. A.; Ryan, G. R. *Ibid.* **1991**, *32*, 1749.

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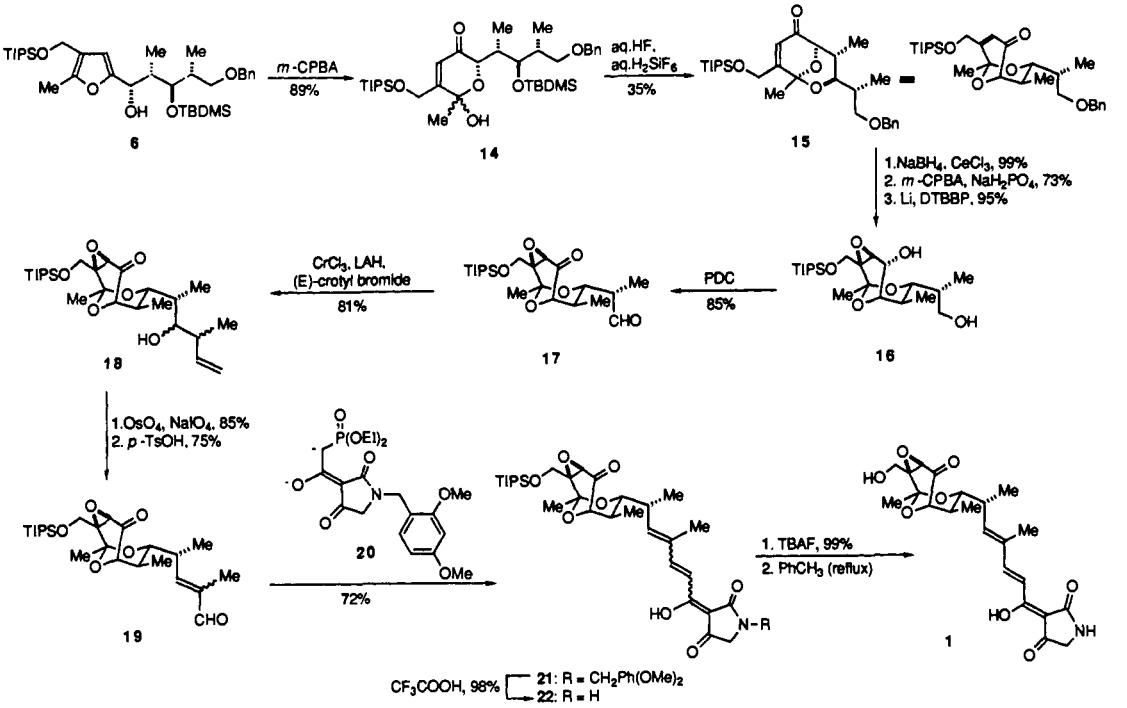
Scheme III



addition, several laboratories have reported synthetic studies relating to degradation products of members of this family.[13]

The strategy that was originally adopted for the total synthesis of tirandamycin B was analogous to that which was implemented for the synthesis of tirandamycin A. In this approach, oxidative cyclization of furfuryl alcohol **6** provides the "northern" portion (**4**) of the natural product. Following the manipulation of protecting groups and adjustment of oxidation states, coupling of phosphonate **5** with enal **4** should afford the intact skeleton of tirandamycin B (see Scheme I). Having completed a synthesis of tirandamycin A that employed this strategy, we anticipated that the total synthesis of tirandamycin B would be accomplished with minimal modification of the original synthetic protocols. As is outlined below, however, several major modifications in the strategy were required to complete the synthesis of tirandamycin B (**1**) as outlined in Scheme I.

Initial concern centered on the choice of a protecting group for the primary alcohol function of tirandamycin B. The protecting group had to be robust enough to survive an assortment of reaction conditions required and yet be removed readily from a sensitive molecule at the final stages of the synthesis. After numerous false leads, it was determined that the triisopropylsilyl (TIPS) group was the protecting group of choice for the primary hydroxyl group. Noteworthy in this regard was the development of modified protocols for transformations such that the various alcohol functions could be selectively protected/deprotected as needed. For example, selective removal of the *tert*-butyldimethylsilyl group on pyranone **14** in the presence of the TIPS-protected primary alcohol was particularly problematic. Similarly, reductive debenzylation of the primary alcohol to give diol **16** in the presence of the TIPS ether (see Scheme III) could not be effected by employing the assigned conditions that saved the tirandamycin A system (vide infra).

Racemic aldehyde **7**[14] was converted by chromium-mediated crotyl coupling[17] to a 1:1 mixture of anti alcohols **8** in 77% yield. The extremely sensitive aldehyde **10** was prepared by ozonolysis of homoallylic ether **9** (95%). Metalation of furan **11**[18,19,20] and addition of the resulting furyllithium **12** to aldehyde **10** provided furfuryl alcohols **6** and **13** in a ca. 1:1 ratio.[21] The lack of stereoselectivity in the condensation of **12** and aldehyde **10** is a common feature in β-silyloxy aldehyde systems.[22] We have investigated a series of additions in this and related aldehydes and observed analogous results (Scheme II).

Oxidative cyclization of furfuryl alcohol **6** employing the original protocol[8] failed to yield the anticipated enone **15**. Peracid oxidation of the furfuryl alcohol to yield a pyranone proceeded as in the previous examples;[7c,d,i,8,23] however, HF-catalyzed ketalization

(12) Neukom, C.; Richardson, D. P.; Myerson, J. H.; Bartlett, P. A. *J. Am. Chem. Soc.* **1986**, *108*, 5559.

(13) (a) Lacey, R. N. *J. Chem. Soc.* **1954**, 850. (b) Harris, S. A.; Fisher, L. V.; Folkers, K. *J. Med. Chem.* **1965**, *8*, 478. (c) Lee, V. J.; Branfman, A. R.; Herrin, T. R.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 4225. (d) Cartwright, D.; Lee, V. J.; Rinehart, K. L., Jr. *Ibid.* **1978**, *100*, 4237. (e) Jones, R. C. F.; Sumaria, S. *Tetrahedron Lett.* **1978**, *34*, 3173. (f) Stachel, H.-D.; Harigel, K. K.; Poschenrieder, H.; Burghard, H. *J. Heterocycl. Chem.* **1980**, *17*, 1195. (g) Igglessi-Markpoulou, O.; Sandris, C. *Ibid.* **1982**, *19*, 883. (h) Boeckman, R. K., Jr.; Thomas, A. J. *J. Org. Chem.* **1982**, *47*, 2823. (i) DeShong, P.; Lowmaster, N. E.; Baralt, O. *Ibid.* **1983**, *48*, 1149. (j) Jones, R. C. F.; Peterson, G. E. *Tetrahedron Lett.* **1983**, *24*, 4751, 4755, 4757. (k) Kochhar, K. S.; Carson, H. J.; Clouser, K. A.; Elling, J. W.; Gramens, L. A.; Parry, J. L.; Sharman, H. L.; Braat, K.; Pinnick, H. W. *Ibid.* **1984**, *25*, 1871. (l) Schlessinger, R. H.; Graves, D. D. *Ibid.* **1987**, *28*, 4381, 4385. (m) Boeckman, R. K., Jr.; Potenza, J. C.; Enholm, E. J. *J. Org. Chem.* **1987**, *52*, 472. (n) Hort, K.; Arai, M.; Nomura, K.; Yoshii, E. *Chem. Pharm. Bull.* **1987**, *35*, 4368. (o) Jones, R. C. F.; Bates, A. D. *Tetrahedron Lett.* **1987**, *28*, 1565. (p) DeShong, P.; Cipollina, J. A.; Lowmaster, N. K. *J. Org. Chem.* **1988**, *53*, 1356.

(14) Racemic **7** was used in these experiments, prepared by using standard methods. However, both enantiomers of ester **7** can be prepared beginning with "Roche acid".[15,16]

(15) *Aldrichemica Acta* **1984**, *17*, 42.

(16) Cohen, N.; Eichel, W. F.; Lopresti, R. J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3505. Nagaoka, H.; Rutsch, W.; Schmid, G.; Iio, H.; Johnson, M. R.; Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7962. Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. Kishi, Y. *Pure Appl. Chem.* **1981**, *53*, 1163. Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737. Evans, D. A.; Sjogren, E. B.; Bartroli, J.; Dow, R. L. *Tetrahedron Lett.* **1986**, *27*, 4957. Trost, B. M.; Kondo, Y. *Ibid.* **1991**, *32*, 1613.

(17) Buse, C. T.; Heathcock, C. H. *Tetrahedron Lett.* **1978**, *19*, 1685. Hiyama, T.; Okude, Y.; Kimura, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 561. Hoffman, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555. Lewis, M. D.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2343.

(18) Rice, K. C.; Dyer, J. R., Jr. *J. Heterocycl. Chem.* **1975**, *12*, 1325.

(19) TIPS furan **11** was prepared in three steps, starting from methyl acetoacetate and chloroacetaldehyde.[20]

(20) Winberg, H. E.; Fawcett, F. S.; Mochel, W. E.; Theobold, C. W. *J. Am. Chem. Soc.* **1960**, *82*, 1428.

(21) Changing a variety of reaction parameters and additives did not result in a significant alteration in the ratio of diastereomers produced.[7d,8]

(22) Kahn, S. D.; Keck, G. E.; Hehre, W. J. *Tetrahedron Lett.* **1987**, *28*, 279. Keck, G. E.; Castellino, S. *Ibid.* **1987**, *28*, 281.

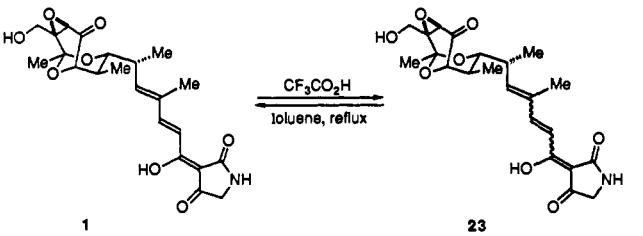
under a host of experimental conditions led to complete destruction of the sample. In the tirandamycin A series, concomitant removal of the TBDMS ether and acid-catalyzed closure of the bicyclic system was accomplished in high yield with excess aqueous HF/acetonitrile. Unfortunately, in this system these conditions resulted in the simultaneous removal of the TBDMS and TIPS silyl ether protecting groups (vide supra). Other protocols for the removal of TBDMS silyl ethers also failed to display selectivity. This dilemma was circumvented when it was discovered that the treatment of pyranone **14** with aqueous HF in the presence of a catalytic amount of fluorosilicic acid in acetonitrile resulted in the selective removal of the TBDMS ether and intramolecular ketalization to provide enone **15** (Scheme III). Subsequently, this reagent has been demonstrated to be highly selective for the removal of TBDMS ethers in the presence of the TIPS protecting group.[24]

Having successfully constructed the heterocyclic framework of the bicyclic "northern" region, the next phase of the synthesis required stereoselective epoxidation of enone **15** from the exo face of the bicyclic system. Previous studies of this process in related compounds had shown that direct epoxidation was not viable due to base lability of the enone.[8] In addition, the benzyl ether protecting group on the side chain could not be removed once the epoxy ketone was present. Both problems were avoided by Luche reduction[25] of enone **15** to afford exclusively the endo alcohol (99%). Epoxidation of the alkene with *m*-CPBA occurred with complete exo face selectivity to give alcohol **16** in 73% yield. Reductive removal of the benzyl ether at this point could not be accomplished with standard reagents without concomitant removal of the TIPS ether. After extensive experimentation, it was determined that the radical anion of di-*tert*-butylbiphenyl[26] in THF at −78 °C removed the benzyl ether (95%) without affecting the silyl ether. PDC oxidation of diol **16** provided aldehyde **17**, which was the key substrate for diene homologation and tetramic acid attachment.

Homologation of aldehyde **17** was accomplished by employing the strategy developed for tirandamycin A, which avoids strongly basic reaction conditions to minimize the possibility of aldehyde epimerization. Chromium-mediated coupling of crotyl bromide[17] with aldehyde **17** produced a ca. 3.4:1 mixture of homoallylic alcohols **18** in 81% yield. The stereoselectivity of the condensation was not critical since both of these stereogenic centers were removed in the subsequent transformation to the enal. Oxidative cleavage of the alkene with OsO_4–$NaIO_4$ and acid-catalyzed dehydration of the resulting β-hydroxy aldehyde afforded a 3.5:1 mixture of enal diastereomers **19** in which the *E* diastereomer predominated. The major diastereomer, (*E*)-**19**, was spectroscopically identical with the enal obtained by degradation of an authentic sample of (+)-tirandamycin B and confirmed the stereochemical assignments of the synthetic material.[27] The diastereomers of enal **19** were not separated since degradation studies had demonstrated that both geometric isomers would afford tirandamycin B in the final stages of the synthesis (vide infra).

Coupling of the potassium dianion of Schlessinger's phosphonate (**20**) with the mixture of enals **19** under carefully defined conditions provided dienoyl tetramic acid derivative **21** as a mixture of diastereomers in 72% yield. Brief treatment of **21** with neat trifluoroacetic acid solvolyzed the 2,4-dimethoxybenzyl protecting group on nitrogen to yield tetramic acid **22**. Prolonged treatment with trifluoroacetic acid also resulted in partial removal of the TIPS group, yielding tirandamycin B (**1**) and its geometric isomers. However, the longer exposure times to trifluoroacetic acid resulted in significant decomposition of tirandamycin B. An improved procedure for deprotection included brief treatment of tetramic acid **21** with neat trifluoroacetic acid to remove the protecting group on the tetramic acid nitrogen followed by silyl ether removal with TBAF. With use of this protocol, tirandamycin B (**1**) and its geometric isomers **23** were obtained in excellent yield by chromatography on Bio-Sil A.[28,29,30]

Studies with the natural material had demonstrated that the geometric isomers of tirandamycin B could be equilibrated to the most stable *E,E* configuration. For example, brief treatment of tirandamycin B with trifluoroacetic acid under the conditions described above resulted in isomerization of the diene system of the natural product to yield diene isomers **1** and **23**. Heating the mixture of isomers at reflux in toluene isomerized the dienes and provided exclusively tirandamycin B (**1**).



1 **23**

The synthesis of tirandamycin B (**1**) described above demonstrates the generality of the furfuryl alcohol based strategy for the preparation of 2,6-dioxabicyclo[3.3.1]nonane derivatives. Application of this protocol to the synthesis of other members of the dienoyl tetramic acid family of antibiotics will be reported in due course.

Experimental Section

General Experimental Procedures. Melting points were taken in Kimex soft-glass capillary tubes on a Thomas-Hoover Uni-Melt capillary melting point apparatus (Model 6406 K) equipped with a calibrated thermometer.

Nuclear magnetic resonance (^1H and ^{13}C NMR) spectra were recorded on a Bruker WP-200 or AF-200 spectrometer or a Bruker AM-400. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane. Coupling constants (*J* values) are given in hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Deuterated NMR solvents contained 99.0–99.8% deuterium in the indicated position. Infrared spectra were recorded on a Nicolet Model 5DXC FT-IR spectrometer. Band positions are given in reciprocal centimeters (cm^{-1}) and relative intensities are listed as: bd (broad), vs (very strong), s (strong), m (medium), or w (weak).

Mass spectral data were obtained on a Hewlett-Packard 5988A or a Finnigan 3200 twin EI and CI quadrupole mass spectrometer equipped with a Finnigan 6000 computer. The chemical ionization gas was methane unless specified otherwise. Elemental analyses were performed by Midwest Microlab, Indianapolis, IN. Thin-layer chromatography (TLC) was performed on 0.25-mm Merck silica-coated glass plates, with the compounds being identified in one or more of the following manners: UV (254 nm, unless otherwise specified), iodine, sulfuric acid, *p*-anisaldehyde/sulfuric acid, or vanillin/sulfuric acid charring. Flash chromatography was performed with thick-walled glass columns and "medium-pressure" silica (Merck, 32–63 mm). Flash chromatography

(23) Achmatowicz, O., Jr.; Buckowski, P.; Szechner, B.; Zwierzchowska, Z.; Zamojski, A. *Tetrahedron* **1971**, *27*, 1973 and references cited therein. Lefebvre, Y. *Tetrahedron Lett.* **1972**, *2*, 133. Achmatowicz, O., Jr.; Grynkiewicz, G.; Szechner, B. *Tetrahedron* **1976**, *32*, 1051. Weeks, P. D.; Kuhla, D. E.; Allingham, R. P.; Watson, H. A.; Wlodecki, B. *Carbohydr. Res.* **1977**, *56*, 195. Piancatelli, G.; Scettri, A.; D'Auria, M. *Tetrahedron Lett.* **1977**, *25*, 2199. Piancatelli, G.; Scettri, A.; D'Auria, M. *Tetrahedron* **1980**, *36*, 661. Weeks, P. D.; Brennan, T. M.; Brannegan, D. P.; Kuhla, D. E.; Elliot, M. L.; Watson, H. A.; Wlodecki, B.; Breitenbach, R. *J. Org. Chem.* **1980**, *45*, 1109. Hendrickson, J. B.; Farina, J. S. *Ibid.* **1980**, *45*, 3359.

(24) It has been demonstrated that fluorosilicic acid and fluorosilicic acid HF mixtures can be employed to effect highly selective desilylations in the presence of "acid-labile" protecting groups such as THP, MEM, and acetonide: DeShong, P.; Pilcher, A.; Waltermire, R. E.; Shimshock, S. J. Manuscript in preparation.

(25) Luche, J. L.; Gemal, A. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

(26) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924. Ireland, R. E.; Smith, M. G. *J. Am. Chem. Soc.* **1988**, *110*, 854.

(27) Oxidation (OsO_4/$NaIO_4$) and silylation (TIPSOTf) of (+)-tirandamycin B gave *E* enal **19**. See the Experimental Section for details.

(28) Tetramic acids **1**, **21**, and **22** possessed a strong affinity for chelation of sodium ion. Washing solutions of these materials with brine or chromatographing them on silica gel resulted in complexes that were impossible to purify or characterize. Similar behavior was reported by Bartlett[12] and Paquette.[29] Bio-Sil A proved to be a practical alternative to silica gel.[13c,l,m,30]

(29) Paquett, L. A.; Macdonald, D.; Anderson, L. G. *J. Am. Chem. Soc.* **1990**, *112*, 9292.

(30) Graves, D. D. Ph.D. Dissertation, University of Rochester, Rochester, NY, 1987.

data is reported as column diameter, column height, solvent. Radial chromatography was performed on a chromatotron (Harrison Research Inc., Palo Alto, CA). Radial chromatography data is reported as plate thickness, solvent. All solvents were distilled from calcium chloride before use unless noted otherwise. Tetrahydrofuran (THF), diethyl ether (Et_2O), and benzene were distilled from sodium benzophenone ketyl, while acetonitrile and methylene chloride (CH_2Cl_2) were distilled from calcium hydride. All reagents were distilled, recrystallized, or chromatographed prior to use unless otherwise noted.

Glassware used in the reactions described below was dried in an oven at 120 °C and assembled under an inert atmosphere of nitrogen or argon.

Gas chromatography was performed on a Hewlett-Packard Model 5890 gas chromatograph equipped with a flame ionization detector and a 25-m capillary column coated with cross-linked methyl silicone. Gas chromatography data is reported as temperature (°C), retention time (minutes).

Homoallylic Alcohols 8a,b. LAH (2.72 g, 71.7 mmol) was added portionwise to $CrCl_3$ (22.8 g, 144 mmol) suspended in 300 mL of THF at 0 °C. After the addition was completed, the black suspension was allowed to warm to room temperature, and a solution of aldehyde **7** (5.80 g, 32.6 mmol) and (*E*)-crotyl bromide (9.62 g, 71.2 mmol) in 30 mL of THF was added dropwise. After an additional 5 h, saturated NH_4Cl (150 mL) was added to the purple mixture and the phases were separated. The aqueous phase was extracted with Et_2O (4 × 100 mL), and the organic phases were washed with brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification of the green oil by flash chromatography (60-mm o.d., 25-cm silica gel, 0–10% EtOAc/hexane) gave 5.84 g (77%) of a 1:1.6 mixture of diastereomeric homoallylic alcohols **8** (ratio determined by GC). The less polar, minor diastereomer, **8a**: IR (neat) 3650–3150 (s), 3080 (w), 3040 (w), 2970 (s), 2940 (s), 2880 (s), 1640 (w), 1610 (w), 1500 (w), 1455 (s), 1420 (m), 1370 (m); ^1H NMR ($CDCl_3$) 0.86 (d, 3, J = 6.9), 1.08 (d, 3, J = 6.9), 1.93–2.03 (m, 1), 2.21–2.33 (m, 1), 3.34 (dd, 1, J = 8.0, 3.7), 3.48–3.59 (m, 2), 4.48 (s, 2), 4.98–5.09 (m, 2), 5.71–5.85 (m, 1), 7.22–7.33 (m, 5); ^{13}C NMR ($CDCl_3$) 13.8, 17.6, 36.1, 41.0, 73.3, 75.0, 79.3, 115.0, 127.5, 127.6, 128.3, 137.7, 139.7; mass spectrum, m/z (relative intensity) 234 (M^+, 0.1), 179 (3), 108 (11), 107 (21), 92 (14), 91 (100); mass spectrum, m/z 234.1622 (M^+, calcd for $C_{15}H_{22}O_2$ 234.1620). The more polar, major diastereomer, **8b**: IR (neat) 3650–3150 (s), 3070 (s), 3040 (s), 2980 (s), 2940 (s), 1640 (s), 1610 (s), 1500 (s), 1455 (s), 1420 (m), 1370 (m); ^1H NMR ($CDCl_3$) 0.90 (d, 3, J = 6.9), 1.11 (d, 3, J = 6.9), 1.90–2.00 (m, 1), 2.15–2.31 (m, 1), 3.41–3.57 (m, 4), 4.48 (s, 2), 5.04–5.13 (m, 2), 5.69–5.87 (m, 1), 7.21–7.32 (m, 5); ^{13}C NMR ($CDCl_3$) 9.9, 16.5, 35.0, 41.6, 73.1, 74.4, 75.3, 115.3, 127.4, 128.2, 138.2, 141.6; mass spectrum, m/z (relative intensity) 179 (M^+ − 55, 1), 108 (12), 107 (23), 92 (15), 91 (100).

Homoallylic Silyl Ether 9. To a solution of homoallylic alcohol **8a** (1.01 g, 4.30 mmol) in 20 mL of DMF were added imidazole (0.324 g, 4.78 mmol) and *tert*-butyldimethylchlorosilane (0.716 g, 4.74 mmol). After 5 days, the solution was poured into 10% HCl (150 mL) and extracted with Et_2O (4 × 100 mL). The organic phases were washed with brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by flash chromatography (45-mm o.d., 15-cm silica gel, 0–10% EtOAc/hexane) gave 1.23 g (82%) of ether **9** as a colorless oil: IR (neat) 3070 (w), 3030 (w), 2960 (s), 2935 (s), 2890 (s), 2860 (s), 1635 (w), 1570 (s), 1380 (m), 1255 (m), 1095 (s), 1075 (s), 1040 (s), 1000 (m), 915 (m), 860 (m); ^1H NMR ($CDCl_3$) −0.06 (s, 3), −0.04 (s, 3), 0.79 (m, 9), 0.86 (d, 3, J = 7.0), 0.93 (d, 3, J = 7.0), 1.87–2.10 (m, 1), 2.28–2.35 (m, 1), 3.21 (dd, 1, J = 9.1, 7.4), 3.37–3.49 (m, 2), 4.33 (d, A of AB q, 1, J = 12.0), 4.44 (d, B of AB q, 1, J = 12.0), 4.82 (d, 1, J = 0.8), 4.88–4.91 (dd, 1, J = 4.1, 0.8), 5.71–5.89 (m, 1), 7.20–7.26 (m, 5); ^{13}C NMR ($CDCl_3$) −4.1, −3.7, 12.4, 17.2, 18.5, 26.2, 37.2, 42.9, 72.9, 73.7, 76.0, 114.1, 127.4, 128.3, 138.8, 141.9; mass spectrum m/z (relative intensity) 293 (M^+ − 55, 12), 199 (22), 187 (50), 145 (13), 131 (7), 115 (14), 91 (100); mass spectrum, m/z 293.1934 (M^+, calcd for $C_{17}H_{29}O_2Si$ 293.1937).

Aldehyde 10. Ozone (9 min at 2.2 mmol/min, 19.8 mmol) was bubbled through a solution of homoallylic silyl ether **9** (3.49 g, 10.0 mmol) in 100 mL of CH_2Cl_2 at −78 °C. The solution was then purged of excess ozone by bubbling nitrogen through the reaction mixture for 20 min. Once the solution was determined to be free of ozone with use of a soluble starch indicator solution (10% soluble starch, 10% KI, 10% HOAc), it was dried ($MgSO_4$) and concentrated in vacuo to give a clear oil. Acetic acid (100 mL of a 50% aqueous solution) was added to a suspension of freshly activated zinc dust (10.1 g, 156 mmol) and intermediate ozonide in Et_2O (100 mL). After 2 h of vigorous stirring, the layers were separated, and the organic layer was carefully washed with saturated $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo to give 3.34 g (95%) of aldehyde **10** as a colorless oil: IR (CCl_4) 3075 (w), 3063 (w), 3030 (w), 2960 (s), 2935 (s), 2885 (s), 2860 (s), 2730 (w), 2710 (w), 1715 (s), 1475 (s), 1455 (s), 1390 (m), 1310 (m), 1258 (s), 1075 (vs), 840 (s); ^1H NMR ($CDCl_3$) −0.01 (d, 6, J = 1.0), 0.79 (s, 9), 0.84 (d, 3, J = 7.0), 1.02 (d, 3, J = 7.0), 2.01 (m, 1), 2.47 (m, 1), 3.33 (m, 2), 3.91 (dd, 1, J = 5.5, 3.7), 4.33 (d, A of AB q, 1, J = 12.0), 4.45 (d, B of AB q, 1, J = 12.0), 7.24 (s, 5), 9.7 (s, 1).

Furfuryl Alcohols 6 and 13. A solution of *tert*-butyllithium (1.02 mL of a 1.70 M solution in THF, 1.73 mmol) was slowly added to a 0 °C solution of TIPS-furan **11**[18,19] (0.463 g, 1.73 mmol) and TMEDA (0.200 g, 1.73 mmol) in ether (25 mL). The reaction mixture was stirred at 0 °C for 1 h and then cooled to −78 °C. A solution of β-silyloxy aldehyde **10** (0.403 g, 1.15 mmol) in Et_2O was then added dropwise (~10 min). When the addition was complete, the reaction mixture was stirred for an additional 3 h at −78 °C. Saturated, aqueous NH_4Cl (25 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 25 mL), and the combined ethereal layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the 1:1 mixture of diastereomers by radial chromatography (2 mm, 500 mL of 10% EtOAc/hexane) afforded 0.255 g of *anti*-furfuryl alcohol 6 as an oil, 0.260 g of *syn*-furfuryl alcohol **13** as an oil, and 0.080 g of a mixture of alcohols 6 and **13**. Total yield 0.595 g (84%). ***anti*-Furfuryl alcohol 6**: IR (neat) 3480 (bd, w), 2940 (s), 2860 (s), 1460 (s), 1250 (s), 1080 (s), 1060 (s); ^1H NMR ($CDCl_3$) 0.08 (s, 3), 0.13 (s, 3), 0.91 (s, 9), 1.08–1.24 (m, 27), 2.09–2.20 (m, 2), 2.23 (s, 3), 3.25 (d, 1, J = 2.0), 3.37 (dd, A of ABX, 1, J = 9.0, 6.7), 3.54 (dd, B of ABX, 1, J = 9.0, 5.0), 3.78 (dd, 1, J = 6.0, 3.1), 4.47 (d, A of AB, 1, J = 13.0), 4.53 (d, B of AB, 1, J = 13.0), 4.54 (s, 2), 5.08 (bd s, 1), 6.15 (s, 1), 7.22–7.32 (m, 5); ^{13}C NMR ($CDCl_3$) −4.3, −4.0, 11.8, 12.1, 12.2, 14.7, 18.0, 18.3, 26.1, 38.4, 39.2, 57.7, 68.6, 72.6, 73.1, 78.6, 107.1, 119.9, 127.5, 128.3, 138.6, 146.5, 153.5; mass spectrum, m/z (relative intensity) 601 (M^+ − 17, 2), 453 (54), 337 (8), 293 (9), 187 (40), 145 (20), 131 (9), 115 (9), 91 (100); mass spectrum, m/z 601.4111 (M^+ − 17, calcd for $C_{35}H_{61}O_4Si_2$ 601.4108). ***syn*-Furfuryl alcohol 13**: IR (neat) 3440 (bd, w), 2940 (s), 2860 (s), 1460 (s), 1250 (s), 1080 (s), 1060 (s); ^1H NMR ($CDCl_3$) 0.12 (s, 3), 0.16 (s, 3), 0.69 (d, 3, J = 7.0), 0.92 (s, 9), 1.07 (m, 24), 2.18 (m, 2), 2.24 (s, 3), 3.32 (dd, A of ABX, 1, J = 9.3, 7.0), 3.55 (dd, B of ABX, 1, J = 9.3, 6.2), 3.70 (d, 1, J = 2.3), 3.85 (dd, 1, J = 5.2, 4.6), 4.48 (m, 2), 4.54 (s, 2), 6.19 (s, 1), 7.32 (m, 5); ^{13}C NMR ($CDCl_3$) −4.5, −4.2, 11.9, 12.1, 14.1, 15.4, 18.0, 18.2, 26.0, 39.2, 40.7, 57.6, 71.0, 72.5, 73.0, 78.5, 108.6, 119.8, 127.4, 127.5, 128.3, 138.6, 147.1, 152.9; mass spectrum, m/z (relative intensity) 601 (M^+ − 17, 2), 600 (5), 451 (100), 293 (4), 187 (12), 145 (7), 131 (6), 115 (5), 91 (40); mass spectrum, m/z 601.4099 (M^+ − 17, calcd for $C_{35}H_{61}O_4Si_2$ 601.4108).

***anti*-Pyranone 14.** *m*-Chloroperbenzoic acid (80–85%, 0.215 g, 0.992 mmol) was added to a solution of *anti*-furfuryl alcohol **6** (0.486 g, 0.786 mmol) in CH_2Cl_2 (10 mL) at room temperature. After the mixture was stirred for 3 h, excess *m*-CPBA was reduced by the additon of saturated $NaHCO_3$ (10 mL), and the reaction mixture was concentrated in vacuo. Et_2O (10 mL) was added and the organic layer separated. The organic layer was washed with saturated $NaHSO_3$ (10 mL) and saturated $NaHCO_3$ (10 mL), dried ($MgSO_4$), and concentrated in vacuo to give a pale yellow solid. Crude pyranone **14** was purified by flash chromatography (30-mm o.d., 15-cm silica gel, 5% EtOAc/hexane) to afford 0.445 g (89%) of **14** as a white solid: mp 94–95 °C; IR (neat) 3390 (bd, s), 2953 (s), 1683 (s), 1463 (s), 1052 (vs); ^1H NMR ($CDCl_3$) 0.06 (s, 3), 0.08 (s, 3), 0.85 (s, 9), 1.02–1.24 (m, 27), 1.53 (s, 3), 2.05–2.14 (m, 1), 2.52–2.58 (m, 1), 3.29 (t, 1, J = 9.4), 3.62 (dd, 1, J = 9.4, 5.1), 3.70 (dd, 1, J = 8.3, 2.3), 4.44–4.47 (m, 4), 4.63 (d, 1, J = 1.6), 6.23 (t, 1, J = 1.7), 7.31 (m, 5); ^{13}C NMR ($CDCl_3$) −4.1, −3.7, 11.2, 12.0, 15.3, 17.9, 18.4, 26.2, 26.7, 37.5, 38.3, 61.7, 72.3, 73.0, 75.2, 75.8, 93.5, 121.7, 127.3, 127.5, 128.3, 160.5, 197.0; mass spectrum, m/z (relative intensity) 634 (M^+, 0.02), 617 (M^+ − 17, 0.13), 591 (3.5), 385 (9), 293 (7), 187 (26), 145 (27), 91 (100); mass spectrum, m/z 617.4068 (M^+ − 17, calcd for $C_{35}H_{61}O_5Si_2$ 617.4058).

Bicyclic Enone 15. Pyranone **14** (51.4 mg, 0.081 mmol) was added to a polyethylene tube and dissolved in CH_3CN (16 mL). Aqueous HF (48% solution, 5.0 μL, 0.12 mmol) and H_2SiF_6 (30% solution, 5.0 μL, 0.01 mmol) was added and the resulting yellow solution was stirred at room temperature for 20 min. Excess H_2SiF_6 was quenched by addition of 1 mL of saturated K_2CO_3. Et_2O (50 mL) and brine (50 mL) were added and the organic layer was separated. The aqueous layer was extracted with Et_2O (2 × 50 mL), and the organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo to give a clear oil. Flash chromatography (15-mm o.d., 15-cm silica gel, 5% Et_2O/hexane) afforded 14.2 mg (35%) of bicyclic enone **15** as a fine white solid: mp 87–88 °C; IR (CCl_4) 2964 (s), 2945 (s), 1688 (vs), 1462 (m), 1261 (m), 1117 (s), 1063 (s), 884 (m); ^1H NMR ($CDCl_3$) 0.78 (d, 3, J = 7.0), 0.94 (d, 3, J = 7.0), 1.04–1.17 (m, 21), 1.40 (s, 3), 2.08–2.13 (m, 1), 2.35–2.45 (m, 1), 3.27 (dd, A of ABX, 1, J = 9.3, 6.8), 3.42 (dd, 1, J = 11.4, 1.8), 3.71 (dd, B of ABX, 1, J = 9.4, 6.2), 4.03 (d, 1, J = 6.0), 4.18 (dd, A of ABX, 1, J = 18.1, 2.1), 4.45 (dd, B of ABX, 1, J = 18.1, 2.1), 4.48

(s, 2), 6.50 (bd s, 1), 7.29–7.33 (m, 5); ^{13}C NMR ($CDCl_3$) 11.7, 11.9, 15.5, 17.8, 17.9, 24.0, 32.9, 34.0, 60.8, 71.1, 73.0, 79.3, 94.6, 123.5, 127.2, 127.3, 128.3, 138.6, 157.9, 195.4; mass spectrum, *m/z* (relative intensity) 503 (M^+, 100), 459 (21), 353 (30), 331 (93), 281 (24), 148 (67), 131 (27); mass spectrum, *m/z* 503.3195 (M^+, calcd for $C_{29}H_{47}O_5Si$ 503.3192). Single-crystal X-ray determination confirmed the structural assignments.

Epoxy Diol 16. Sodium borohydride (46.7 mg, 1.23 mmol) was added to a solution containing bicyclic enone **15** (75.8 mg, 0.151 mmol) and $CeCl_3$ (59.2 mg, 0.151 mmol) in MeOH (12 mL). Evolution of gas occurred, and after ~5 min the reaction mixture was diluted with water (50 mL) and the pH of the solution adjusted to neutrality with 5% aqueous HCl. The mixture was extracted with Et_2O (3 × 50 mL); the organic layers were removed, dried ($MgSO_4$), filtered through a pad of silica gel (3 cm), and concentrated in vacuo to give 75.7 mg (99%) of the allylic alcohol as a colorless solid: mp 65–66 °C; IR (CCl_4) 3627 (m), 2963 (s), 2944 (s), 2867 (s), 1463 (s), 1377 (m), 1137 (s), 1112 (s), 1100 (m), 883 (s); ^{1}H NMR ($CDCl_3$) 0.90 (d, 3, *J* = 7.0), 0.95 (d, 3, *J* = 7.5), 0.98–1.07 (m, 21), 1.24 (s, 3), 1.62 (bd s, 1), 1.99–2.06 (m, 1), 2.23–2.31 (m, 1), 3.20 (dd, A of ABX, 1, *J* = 9.3, 8.9), 3.63 (dd, B of ABX, 1, *J* = 9.3, 5.2), 3.66 (dd, 1, *J* = 10.3, <1), 3.83 (dd, 1, *J* = 14.5, <1), 3.89–3.92 (m, 1), 4.15 (ddd, 1, *J* = 14.5, 2.5, 2.2), 4.34 (d, A of AB, 1, *J* = 12.0), 4.47 (d, B of AB, 1, *J* = 12.0), 4.74–4.80 (bd s, 1), 6.02 (bd s, 1), 7.16–7.25 (m, 5); ^{13}C NMR ($CDCl_3$) 12.0, 13.1, 15.7, 18.0, 24.4, 30.3, 33.9, 35.3, 61.0, 68.9, 71.2, 73.0, 73.5, 94.7, 126.3, 127.4, 128.3, 136.2, 138.8; mass spectrum, *m/z* (relative intensity) 504 (M^+, 29), 503 (59), 487 (15), 353 (12), 331 (100), 313 (28), 281 (17), 225 (16), 207 (15), 183 (30), 177 (26), 148 (61), 111 (17).

m-Chloroperbenzoic acid (80–85%, 72.7 mg, 0.336 mmol) was added to a CH_2Cl_2 solution (15 mL) of benzyl allylic alcohol (133 mg, 0.264 mmol), sodium phosphate (47.0 mg, 0.329 mmol), and H_2O (2 drops, ca. 0.15 mL) and stirred at room temperature for 24 h. The reaction mixture was diluted with Et_2O (50 mL) and extracted with saturated $NaHCO_3$ (50 mL), saturated $NaHSO_3$ (50 mL), and saturated $NaHCO_3$ (50 mL), sequentially. The organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo to give a yellow oil. Purification by flash chromatography (15-mm o.d. column, 15-cm silica gel, 20% EtOAC/hexane) afforded 0.100 g (73%) of benzyl epoxy alcohol as a colorless oil: IR (CCl_4) 3630 (m), 3615 (w), 3025 (m), 3015 (s), 3005 (s), 2835 (s), 1430 (m), 1290 (w), 1280 (w), 1230 (m), 1220 (m), 1205 (m), 1180 (m), 1090 (m), 1080 (m), 1030 (m), 1020 (m), 840 (m), 830 (m); ^{1}H NMR (C_6D_6) 1.03–1.11 (m, 27), 1.34 (s, 3), 2.11–2.18 (m, 2), 2.37–2.40 (m, 1), 3.29 (dd, 1, *J* = 9.3, 7.7), 3.54 (bd s, 1), 3.70 (d, 1, *J* = 9.3), 3.71 (d, 1, *J* = 8.3), 3.90–4.04 (m, 3), 4.40 (d, 1, *J* = 7.0), 4.47 (d, A of AB, 1, *J* = 12.0), 4.51 (d, B of AB, 1, *J* = 12.0), 7.31–7.36 (m, 5); ^{13}C NMR ($CDCl_3$) 11.9, 13.2, 15.6, 17.8, 17.9, 23.0, 34.2, 35.5, 59.0, 59.3, 59.5, 67.1, 70.6, 71.7, 73.1, 76.0, 95.3, 127.4, 128.3, 138.8.

Freshly activated lithium wire (~3 cm) was added to a solution of di-*tert*-butylbiphenyl (DTBBP, 1.51 g, 5.67 mmol) in THF (20 mL) at 0 °C under argon. The resulting green solution was cannulated (via 18-gauge polyethylene tubing) dropwise over a period of 3 h into a −78 °C solution of benzyl epoxy alcohol (0.138 g, 0.265 mmol) in THF (20 mL) under argon. Cannulation was performed at such a rate as to maintain a persistent green color of the reaction mixture.

Upon reaction completion, excess reducing reagent was quenched by the addition of saturated NH_4Cl (50 mL). Ether (50 mL) was added and the organic layer was separated. The aqueous layer was washed with Et_2O (3 × 50 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated to give a white powder. Flash chromatography (30-mm o.d. column, 24-cm silica gel, 30% EtOAc/hexane) afforded 0.109 g (95%) of epoxy diol **16** as a colorless oil: IR (CCl_4) 3648 (m), 3628 (m), 3548 (bd, m), 2962 (vs), 2892 (s), 2868 (vs), 1462 (s), 1379 (m), 1205 (m), 1135 (s), 1067 (s), 1040 (m), 997 (m), 883 (s); ^{1}H NMR ($CDCl_3$) 1.02–1.15 (m. 24), 1.19 (d, 3, *J* = 7.1), 1.38 (s, 3), 1.87–1.97 (m, 1), 2.40–2.46 (m, 1), 2.71 (bd s, 2), 3.55 (dd, A of ABX, 1, *J* = 11.3, 3.8), 3.56 (s, 1), 3.93 (dd, B of ABX, 1, *J* = 11.3, 2.9), 3.95 (d, A of AB, 1, *J* = 11.8), 4.04 (d, B of AB, 1, *J* = 11.8), 3.92–4.08 (m, 2), 4.42 (d, 1, *J* = 7.2); ^{13}C NMR ($CDCl_3$) 11.9, 13.2, 15.0, 17.9, 23.2, 34.5, 36.0, 58.7, 59.2, 59.4, 62.9, 66.9, 71.5, 78.3, 95.8; mass spectrum, *m/z* (relative intensity) 430 (M^+, 0.6), 387 (8), 309 (10), 241 (26), 215 (55), 185 (80), 157 (29), 131 (61), 103 (69), 75 (100); mass spectrum, *m/z* 430.2740 (M^+, calcd for $C_{22}H_{42}O_6Si$ 430.2750).

Epoxy Keto Aldehyde 17. Pyridinium dichromate (PDC, 0.103 g, 0.273 mmol) was added to a solution of epoxy diol **16** (14.5 mg, 0.034 mmol) in CH_2Cl_2 (5 mL), and the resulting brown suspension was stirred for 7 h at room temperature under N_2. The reaction mixture was filtered through a bed of Celite (~1 cm), diluted with Et_2O (50 mL), and washed with saturated cupric sulfate (2 × 50 mL) and water (2 × 50 mL). The organic layer was dried ($MgSO_4$), filtered through a pad of silica gel (3 cm), and concentrated in vacuo to give 12.1 mg (85%) of epoxy keto aldehyde **17** as a yellow oil: IR (CCl_4) 2963 (m), 2948 (vs), 2945 (vs), 2892 (s), 2868 (vs), 2727 (w), 2720 (w), 1733 (vs), 1690 (m), 1462 (vs), 1392 (m), 1378 (m), 1256 (m), 1230 (m), 1209 (s), 1142 (vs), 1123 (vs), 1089 (s), 1066 (s), 1048 (s), 1014 (m), 996 (m), 953 (m), 884 (vs); ^{1}H NMR ($CDCl_3$) 0.94 (d, 3, *J* = 7.1), 1.02–1.06 (m, 24), 1.48 (s, 3), 1.87–2.01 (m, 2), 3.54 (dd, 1, *J* = 11.7, 2.2), 3.77 (d, 1, *J* = 6.0), 3.79 (s, 1), 3.93 (d, A of AB, 1, *J* = 12.0), 4.07 (d, B of AB, 1, *J* = 12.0), 9.48 (d, 1, *J* = 2.2).

Homoallylic Alcohol 18. LAH (0.92 mL of a 1.0 M solution *in* Et_2O, 0.92 mmol) was added to a suspension of anhydrous $CrCl_3$ (18.1 mg, 1.15 mmol) in THF (5 mL) at 0 °C under argon. After 1 h, ~1 mL of the resulting black suspension was cannulated dropwise over a period of 1 min into a THF (2 mL) solution of epoxy keto aldehyde **17** (12.1 mg, 0.028 mmol) and crotyl bromide (4.0 μL, 0.039 mmol) at room temperature under argon. The reaction mixture was stirred for 2 h at room temperature and then quenched with H_2O (50 mL) and extracted with two 50-mL portions of Et_2O. The organic extracts were washed with brine (50 mL) and H_2O (50 mL), dried ($MgSO_4$), and concentrated in vacuo to give a colorless oil. Purification by filtration through a short column of silica gel (3 cm, 10% EtOAc/hexane) afforded 11.1 mg (81%) of a (3.4:1) diastereomeric mixture of homoallylic alcohols **18** as a colorless oil. The ratio of diastereomers was determined by ^{1}H NMR by comparing the intensities of epoxy protons: IR (CCl_4) 3548 (bd, m), 2966 (vs), 2963 (vs), 2945 (s), 2868 (vs), 1729 (s), 1690 (s), 1462 (s), 1391 (m), 1379 (s), 1295 (m), 1260 (m), 1229 (m), 1143 (s), 1118 (s), 1066 (vs), 1049 (m), 996 (s), 890 (s), 883 (s); ^{1}H NMR ($CDCl_3$, reported for major diastereomer) 0.72 (d, 3, *J* = 7.1), 0.93 (d, 3, *J* = 7.1), 1.44 (d, 3, *J* = 7.0), 1.51 (s, 3), 1.86 (m, 1), 2.24 (m, 1), 2.37 (m, 1), 3.31 (s, 1), 3.97–4.08 (m, 3), 4.02 (m, 2), 4.13 (dd, A of ABX, 1, *J* = 18.3, 2.0), 4.46 (dd, A of ABX, 1, *J* = 18.3, 2.0), 5.03 (m, 2), 5.83 (m, 1).

Enal 19. Osmium tetroxide (15 μl of a 2.5 wt% solution in *t*-BuOH, 1.20 μmol) was added to a room temperature solution of homoallylic alcohol **18** (22.1mg, 0.046 mmol) in 75% 1,4-dioxane (3.75 mL)/water (1.25 mL). Ground sodium periodate (23.5 mg, 0.110 mmol) was added to the black solution, and the reaction mixture was stirred for 7 h at room temperature. Brine (10 mL) and Et_2O (10 mL) were added and the layers were partitioned. The aqueous layer was washed with Et_2O (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo. The oily residue was purified by filtration through a short column of silica gel (3 cm, Et_2O) and concentrated in vacuo to give 18.7 mg (85%) of a 4:1 diastereomeric mixture of β-hydroxy aldehydes. The ratio of aldehydes was determined by ^{1}H NMR by comparing the intensities of the aldehydic protons: IR (CCl_4) 3550 (m), 2940 (vs), 2875 (vs), 2720 (w), 1730 (vs), 1460 (m), 1385 (m), 1150–1100 (vs), 885 (m).

A solution of the crude β-hydroxy aldehydes and *p*-toluenesulfonic acid (one crystal) in 5 mL of benzene was refluxed for 2 h. The reaction mixture was diluted with Et_2O (10 mL) and washed with 1% NaOH (10 mL). The aqueous layer was washed with Et_2O (3 × 10 mL), and the organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo. Purification of the oily residue by filtration through a short column of silica gel (3 cm, $CHCl_3$) gave 13.5 mg (75%) of a 3.5:1 ratio of enals **19**. The ratio was determined by comparing the intensities of the aldehydic protons. The major enal was identical with the enal produced by oxidation and silylation of tirandamycin B:[27] IR (CCl_4) 2960 (vs), 2925 (vs), 2860 (s), 2700 (w), 1725 (vs), 1690 (s), 1460 (m), 1365 (m), 1260 (vs), 1090–1000 (vs), 940 (m), 880 (m); ^{1}H NMR ($CDCl_3$) 0.72 (d, 3, *J* = 7.1), 0.92–1.10 (m, 21), 1.14 (d, 3, *J* = 7.0), 1.53 (s, 3), 1.74 (s, 3), 1.92 (m, 1), 2.94 (m, 1), 3.67 (m, 2), 4.03 (m, 3), 6.60 (d, 1, *J* = 10.1), 9.43 (s, 1).

Tetramic Acid 21. Potassium *tert*-butoxide (73.0 μL of a 1.0 M solution in THF, 0.073 mmol) was added to a 0 °C solution of phosphonate **5** (15.1 mg, 0.635 mmol) in THF (1.50 mL), and the mixture was stirred for 2 h. The resulting dianion **20** was cannulated dropwise over a period of 1 min into a solution of enal **19** (5.9 mg, 0.013 mmol) in THF (0.75 mL), and the mixture was stirred for 16 h at 0 °C. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with 5 mL of 1% HCl. The aqueous layer was extracted with Et_2O (3 × 5 mL). The organic layers were combined and concentrated in vacuo. Toluene (10 mL) was added and the solution was reconcentrated in vacuo. Purification by filtration through a short column of Bio-Sil A (3 cm, $CHCl_3$) gave 6.7 mg (72%) of **21** as a bright yellow oil: IR (CCl_4) 2946 (s), 2868 (s), 1726 (s), 1703 (s), 1644 (vs), 1617 (vs), 1589 (vs), 1571 (m), 1466 (vs), 1379 (s), 1296 (s), 1272 (s), 1158 (vs), 1137 (vs), 1006 (s), 883 (m); ^{1}H NMR ($CDCl_3$) 0.70 (d, 3, *J* = 7.0), 0.92–1.10 (m, 24), 1.51 (s, 3), 1.87 (s, 3), 1.89–2.01 (m, 1), 2.77–2.85 (m, 1), 3.55–3.68 (m, 4), 3.78 (s, 3), 3.79 (s, 3), 3.99–4.14 (m, 3), 4.5 (s, 2), 6.12 (d, 1, *J* = 10.1), 6.45 (m, 2), 7.05–7.23 (m, 2), 7.49 (d, 1, *J* = 15.8); ^{13}C NMR ($CDCl_3$) 11.4, 11.9, 12.3, 16.9, 17.6, 17.9, 23.4, 34.5, 34.6, 40.1, 55.4,

55.6, 55.7, 56.5, 58.3, 60.2, 77.1, 78.7, 95.9, 98.6, 101.1, 104.5, 116.1, 117.0, 131.3, 134.9, 142.6, 148.6, 158.7, 161.0, 173.3, 173.6, 192.0, 202.4.

Conversion of Tetramic Acid 21 to Tirandamycin B. Tetramic acid **21** (6.7 mg, 9.1 μmol) was dissolved in trifluoroacetic acid (2.0 mL), and the resulting red solution was stirred at room temperature for 5 min. The reaction mixture was concentrated in vacuo, redissolved in toluene (10 mL), and reconcentrated in vacuo. The residue was purified by filtration through a short column of Bio-Sil A (3 cm, 5% EtOH/CH_2Cl_2) to give 5.0 mg (98%) TIPS-tirandamycin B **22**: IR ($CHCl_3$) 3447 (m), 2928 (s), 2872 (s), 1792 (m), 1726 (s), 1660 (s), 1616 (vs), 1569 (vs), 1454 (vs), 1390 (m), 1294 (s), 1143 (vs), 1085 (s), 1006 (s), 883 (m); ^1H NMR ($CDCl_3$) 0.71 (d, 3, J = 7.0), 0.92-1.14 (m, 24), 1.52 (s, 3), 1.89 (s, 3), 1.93-2.01 (m), 2.76-2.87 (m, 1), 3.57-4.15 (m, 7), 5.84 (bd s, 1), 6.18 (d, 1, J = 9.8), 7.13 (d, 1, J = 15.8), 7.55 (d, 1, J = 15.8); ^{13}C NMR ($CDCl_3$) 11.4, 11.9, 12.3, 16.9, 17.6, 17.8, 17.9, 23.4, 34.6, 51.5, 56.6, 58.3, 60.1, 77.1, 78.7, 96.0, 100.0, 116.8, 134.9, 143.5, 149.7, 175.1, 176.4, 192.3, 202.4.

Tetrabutylammonium fluoride (5.8 μL of a 1.0 M solution in THF, 5.8 μmol) was added to a solution of TIPS-tirandamycin B **22** (0.3 mg, 5.3 μmol) in 2.0 mL of THF. The reaction mixture was stirred at room temperature for 21 h. Deionized water (10 mL) and CH_2Cl_2 (10 mL) were added and the phases partitioned. The aqueous layer was washed with CH_2Cl_2 (3 × 10 mL). The organic layers were combined and concentrated in vacuo. The residue was dissolved in toluene (10 mL) and reconcentrated in vacuo. The resulting yellow oil was purified by filtration through a short column of Bio-Sil A (3 cm, 50% EtOAc/$CHCl_3$) to give 0.2 mg of tirandamycin B (**1**). This material was identical by TLC, IR, and ^1H NMR with an authentic sample of (+)-tirandamycin B provided by Upjohn Co.: IR ($CHCl_3$) 3450 (m), 2943 (m), 2930 (m), 2856 (m), 1728 (m), 1662 (s), 1616 (vs), 1568 (s), 1455 (s), 1118 (m), 1099 (s), 1005 (s); ^1H NMR ($CDCl_3$) 0.70 (d, 3, J = 7.0), 1.10 (d, 3, J = 7.0), 1.56 (s, 3), 1.90 (s, 3), 1.94-2.07 (m, 1), 2.80-2.87 (m, 1), 3.62-4.05 (m, 7), 5.67 (bd s, 1), 6.17 (d, 1, J = 9.9), 7.14 (d, 1, J = 15.8), 7.59 (d, 1, J = 15.8).

Oxidation/Silylation of Tirandamycin B. Osmium tetroxide (15.0 μL of a 2.5 wt % solution in t-BuOH, 1.2 μmol) was added to a solution of (+)-tirandamycin B (23.2 mg, 0.054 mmol) in 75% 1,4-dioxane (3.75 mL)/water (1.25 mL). Ground sodium periodate (24.2 mg, 0.113 mmol) was subsequently added and the reaction mixture stirred for 3 days at room temperature. Brine (10 mL) was added and the solution was extracted with Et_2O (3 × 10 mL). The ethereal layers were combined, dried ($MgSO_4$), and concentrated in vacuo. Purification by filtration through a short column of silica gel (3 cm, 25% EtOAc/hexane) gave 12.2 mg (73%) of the corresponding enal: IR (CCl_4) 3610 (w), 2981 (s), 2960 (s), 2929 (s), 2870 (m), 2850 (m), 2710 (w), 1742 (vs), 1695 (s), 1572 (vs), 1373 (s), 1240 (vs), 1048 (s), 1007 (m); ^1H NMR ($CDCl_3$) 0.72 (d, 3, J = 7.0), 1.15 (d, 3, J = 7.0), 1.58 (s, 3), 1.74 (d, 3, J = 1.3), 1.81-2.01 (m, 1), 2.86-2.99 (m, 1), 3.68 (dd, 1, J = 11.5, 2.0), 3.69 (s, 1), 3.99 (bd s, 2), 6.60 (dd, 1, J = 10.1, 1.3).

Triisopropylsilyl triflate (10.0 μL, 0.037 mmol) was added to a 0 °C solution of enal (4.2 mg, 0.014 mmol) and imidazole (4.5 mg, 0.071 mmol) in DMF (3.0 mL). The reaction mixture was stirred at 0 °C for 3 h. The solution was diluted with Et_2O (10 mL) and washed with 1% HCl (10 mL). The ethereal layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by filtration through a short column of silica gel (3 cm, Et_2O) to give 6.3 mg (99%) of TIPS enal **19**: IR (CCl_4) 2960 (vs), 2925 (vs), 2860 (s), 1725 (s), 1690 (vs), 1460 (m), 1365 (m), 1260 (vs), 1090 (vs), 1000 (vs); ^1H NMR ($CDCl_3$) 0.72 (d, 3, J = 7.1), 0.92-1.10 (m, 21), 1.14 (d, 3, J = 7.0), 1.53 (s, 3), 1.74 (d, 3, J = 1.2), 1.86-1.99 (m, 1), 2.89-2.99 (m, 1), 3.61-3.69 (m, 2), 3.99-4.10 (m, 3), 6.60 (dd, 1, J = 10.1, 1.3), 9.43 (s, 1); ^{13}C NMR ($CDCl_3$) 11.4, 12.0, 12.6, 16.4, 17.6, 17.9, 23.4, 34.5, 34.8, 56.7, 58.7, 60.2, 77.5, 78.7, 96.2, 140.2, 151.6, 194.7, 201.9.

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Asymmetric Syntheses of 1-Aminocyclopropane-1-carboxylic Acid Derivatives

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Abstract: Optically active D-*erythro*-4-(*tert*-butoxycarbonyl)-3-(dimethoxyphosphoryl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (**13**) can be efficiently condensed with various aldehydes via the Emmons-Horner-Wadsworth procedure to provide α,β-dehydrolactone adducts (**14**). It was found that the adducts (**14**) were smoothly cyclopropanated with the ylide of racemic [[(diethylamino)methyl]phenyl]oxosulfonium tetrafluoroborate to furnish in high chemical and optical yields the desired cyclopropanes (**15**). Final deblocking to the requisite amino acids was accomplished with dissolving-metal reduction. The syntheses of [$^2H_2$]ACC, MeACC (norcoronamic acid), EtACC (coronamic acid), and BuACC are described.

Introduction

During the past decade, much effort has been directed toward the syntheses of 1-aminocyclopropane-1-carboxylic acid (**1**, ACC) derivatives; this work has recently been reviewed.[1,2] Several members of this unique class of amino acids are naturally occurring; the first example being the isolation of the parent compound (ACC) from cider apples and perry pears by Burroughs[3a] and from cowberries by Virtanen.[3b] Subsequently, coronamic acid (**2**) was isolated from the hydrolysis of coronatine (**4**), a plant toxin produced by *Pseudomonas coronafacience* var. *atropupurea*,[4] and norcoronamic acid (**3**) was similarly isolated from norcoronatine (**5**), a minor component of the phytotoxic fraction of *Pseudomonas syringae* pv. *glycinea*.[5] In addition, N-methylated norcoronamic acid has been found to be a constituent of the cyclic peptide portion of the newly discovered DNA-intercalating antibiotics of the quinomycin family (**8-10**), isolated from *Streptomyces braegensis*

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