to lithium bromide (ca. 500 mg) in dry toluene (3 mL). This mixture was kept at 70 °C for 48 h. ^{13}C NMR analysis of the filtered mixture revealed no reaction.

3,7-Dimethyl-1,6,7-octanetriol (54) was prepared (60% yield) from the reaction of citronellol (16.25 g, 0.104 mol) with formic acid (63 mL, 88%, 1.43 mol) and hydrogen peroxide (30%, 14.5 mL) followed with base hydrolysis: bp 145–150 °C (1.0 torr) [lit.[79] bp 160–161 °C (2 torr)]; ^1H NMR ($CDCl_3$) δ 0.92 (d, 3 H, J = 4.5 Hz, $CHCH_3$), 1.16 (s, 3 H, CH_3), 1.20 (s, 3 H, CH_3), 0.99–1.88 (m, 1 H, CH_2, $CHCH_3$), 2.66–3.44 (brs, 4 H, OH, COH), 3.68 (t, 2 H, J = 6 Hz, CH_2OH).

3,7-Dimethyl-6,7-epoxyoctan-1-ol (55) was prepared (30% yield) by oxidation of citronellol (5.0 g, 0.032 mol) with *m*-CPBA (6.88 g, 0.032 mol): bp 75 °C (0.05 torr) [lit.[80] bp 104–105 °C (2.5 torr)]; ^1H NMR ($CDCl_3$) δ 0.92 (d, 3 H, J = 5 Hz, $CHCH_3$), 1.25 (s, 3 H, CH_3), 1.30 (s, 3 H, CH_3), 1.40–1.90 (m, 7 H, CH_2, CH), 2.30–2.85 (m, 2 H, OH, CHO), 3.65 (t, 2 H, J = 6 Hz, CH_2OH).

1-Methylcyclohexane-*trans*-1,2-diol (58) was prepared (40% yield) from the oxidation of 1-methylcyclohexane (10.0 g, 0.104 mol) with formic acid (63 mL, 88%, 1.43 mol) and 30% H_2O_2 (10.0 g, 0.104 mol) followed with base hydrolysis: mp 83–85 °C [lit.[81] mp 83–84 °C]; ^1H NMR ($CDCl_3$) δ 1.20 (s, 3 H, CH_3), 1.22–2.00 (m, 8 H, CH_2), 2.80 (brs, 1 H, CH_3CO*H*), 3.50 (brs, 1 H, C*H*OH).

1-Methylcyclohexene 1,2-oxide (58) was prepared (16% yield) by oxidation of 1-methylcyclohexene (5.0 g, 0.052 mol) with *m*-CPBA (11.18 g, 0.052 mol): bp 52 °C (35 torr) [lit.[82] bp 60–61 °C (40 torr)]; ^{13}C NMR ($CDCl_3$) δ 59.51 (C_1), 57.44 (C_2), 23.96 (C_3)*, 24.83 (CH_3)*, 20.10 (C_4), 19.68 (C_5), 29.93 (C_3). For procedures for assigning the ^{13}C NMR resonances, see ref 83. The asterisk (*) indicates that these assignments may be interchangeable.

9,10-Dihydrophenanthrene-9,10-diol (66) was prepared (19% yield) by reduction of phenanthrenequinone (12 g, 0.058 mol) with $LiAlH_4$ (6 g in 1 L of ether: mp 193–194 °C (lit.[58b] mp 185–190 °C); ^1H NMR ($CDCl_3$) δ 4.47 (brs, 2 H, OH), 5.64 (m, 2 H, C*H*OH), 7.27–7.58 (m, 4 H, Ar CH), 7.76 (dd, 2 H, J = 2.8 Hz, Ar CH), 7.79 (dd, 2 H, J = 2, 8 Hz, Ar CH); ^{13}C NMR ($CDCl_3$) δ 72.37 (CHOH), 123.39, 126.45, 127.95, 132.36, 138.19.

9,10-Epoxy-9,10-dihydrophenanthrene (65): ^1H NMR (Me_2SO-d_6) δ 4.66 (s, 2 H, CHO), 7.42 (t, 2 H, J = 8 Hz, Ar CH), 7.52 (t, 2 H, J = 2.8 Hz, Ar CH), 7.76 (d, 2 H, J = 2.8 Hz, Ar CH), 8.24 (d, 2 H, J = 8 Hz, Ar CH); ^{13}C NMR (Me_2SO-d_6) δ 55.69 (CHO), 123.96, 128.24, 129.50, 131.13, 131.79.

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Registry No. (+)-**4**, 4254-15-3; (+)-**5**, 25779-13-9; (−)-**6**, 56718-04-8; (+)-**7**, 16088-62-3; **5** (tosylate), 40435-14-1; (−)-**8**, 63798-13-0; *dl*-**9**, 6982-25-8; **10**, 579-43-1; *dl*-**11**, 655-48-1; *dl*-**12**, 38628-70-5; **13**, 1689-71-0; *dl*-**14**, 96455-82-2; *dl*-**15**, 96455-83-3; **16**, 504-63-2; **17**, 24765-56-8; **18**, 13912-01-1; **19**, 110-63-4; **20**, 111-29-5; **21**, 629-11-8; **22**, 15753-50-1; **23**, 13149-01-4; **24**, 96553-66-1; **25**, 96455-84-4; **27**, 6117-80-2; **28**, 1708-29-8; **29**, 821-11-4; *dl*-**30**, 22910-58-3; *dl*-**33**, 81096-87-9; *dl*-**34**, 91049-45-5; *dl*-**35**, 96553-67-2; *dl*-**36**, 19881-97-1; *dl*-**37**, 96553-68-3; *dl*-**38**, 89968-90-1; *dl*-**39**, 96481-54-8; **40**, 32162-29-1; **41**, 94480-84-9; **42**, 76-09-5; **43**, 49595-63-3; **44**, 5076-20-0; **45**, 75-97-8; **46**, 10473-13-9; **47**, 96455-85-5; **48**, 96553-69-4; **49**, 565-69-5; **50**, 96611-53-9; **51**, 96481-55-9; **54**, 31558-25-5; **55**, 1564-98-3; *dl*-**57**, 54383-22-1; *dl*-**58**, 96455-86-6; **59**, 286-20-4; *dl*-**60**, 60363-27-1; **61**, 1792-81-0; **62**, 96553-70-7; **63**, 108-94-1; **65**, 585-08-0; **66**, 25061-61-4; DEP, 628-37-5; DTPP, 86852-11-1; $(HexO)_2$, 3903-89-7; $Ph_3P(OHex)_2$, 96481-56-0; $HexOSO_2Me$, 16156-50-6; HexOH, 111-27-3; $MeSO_2Cl$, 124-63-0; $HO(H_2)_3OEt$, 111-35-3; $HO(CH_2)_6OEt$, 40868-73-3; *p*-$Me(C_6H_4SO_2Cl$, 98-59-9; *trans*-PhCH=CHPh, 103-30-0; *dl*-PhCOCHOHPh, 579-44-2; *m*-CPBA, 937-14-4; *cis*-PhCH=CHPh, 645-49-8; $PhCH_2CH=CH_2$, 300-57-2; HCO_2H, 64-18-6; HCO_3H, 107-32-4; $CH_2=C(CH_3)(CH_2)_2CH_3$, 763-29-1; $Me_3SO^+I^-$, 1774-47-6; $CH_3CO(CH_2)_2CH_3$, 107-87-9; $(CH_3)_2C=C(CH_3)_2$, 563-79-1; $(CH_3)_2C=CHCH_2CH_3$, 625-27-4; (*S*)-(−)-ethyl lactate, 687-47-8; (*S*)-(+)-mandelic acid, 17199-29-0; L-glutamic acid, 56-86-0; (*S*)-(+)-γ-[(tosyloxy)methyl]-γ-butyrolactone, 58879-34-8; (*S*)-(+)-γ-(hydroxymethyl)-γ-butyrolactone, 32780-06-6; (*S*)-(+)-γ-butyrolactone-γ-carbonyl chloride, 54848-33-8; β-pinene, 127-91-3; citronellol, 106-22-9; 1-methylcyclohexene, 591-49-1; phenanthrenequinone, 84-11-7; (*S*)-styrene oxide, 20780-54-5; *dl*-styrene oxide, 67253-49-0; *cis*-2,3-epoxybutane, 1758-33-4; oxetane, 503-30-0; tetrahydrofuran, 109-99-9; tetrahydropyran, 142-68-7; oxepane, 592-90-5; *dl*-1,2-epoxydecane, 67210-45-1.

Total Synthesis of (±)-Tirandamycin A

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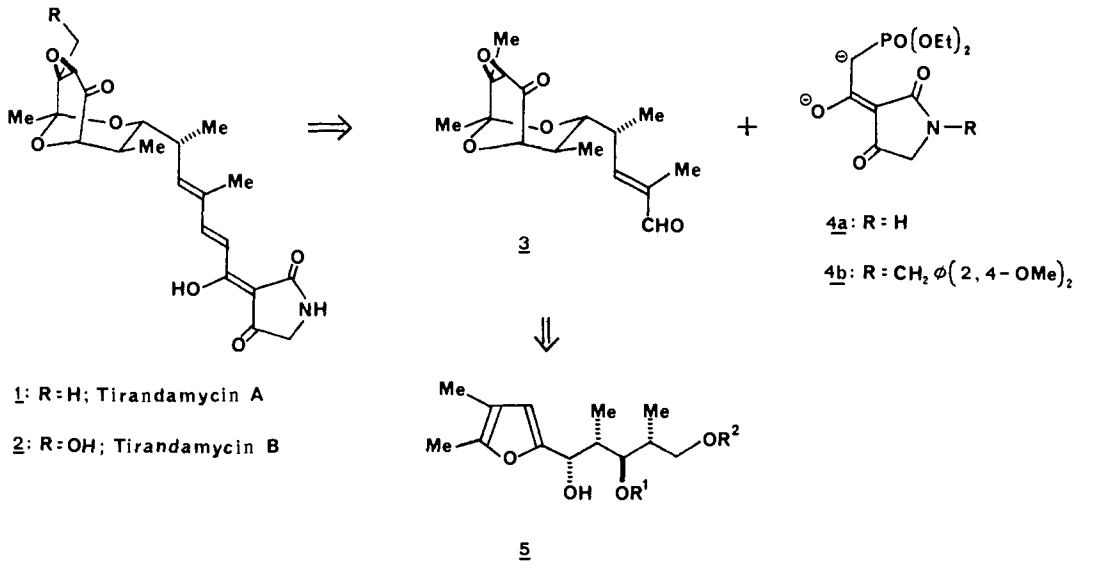
Abstract: A convergent, 12-step synthesis of racemic tirandamycin A is described. The key features of the synthesis are preparation of the 2,9-dioxabicyclo[3.3.1]nonane system of the natural product by oxidation of furfuryl alcohol **8a** and attachment of the 3-acyl tetramic acid moiety via the dianion of phosphonate **4b**.

Tirandamycin A (**1**)[1] is a member of the 3-dienoyl tetramic acid family of antibiotics. This family of antibiotics includes several structurally similar substances such as tirandamycin B[2] (**2**), streptolydigin,[1a,3] nocamycin,[4] and Bu-2313 A and B.[5] These substances display a diversity of biological activities. For instance,

(1) (a) Duchamp, D. J.; Branfman, A. R.; Button, A. C.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 4077, and references cited therein. (b) MacKeller, F. A.; Grostic, M. F.; Olson, E. C.; Wuuk, R. J.; Branfman, A. R.; Rinehart, K. L., Jr. *Ibid.* **1971**, *93*, 4943.
(2) Hagenmaier, H.; Jaschke, K. H.; Santo, L.; Scheer, M.; Zahner, H. *Arch. Microbiol.* **1976**, *109*, 65.
(3) (a) Gross structure: Rinehart, K. L., Jr.; Borders, D. B. *J. Am. Chem. Soc.* **1963**, *85*, 4035, 4037. Rinehart, K. L., Jr.; Beck, J. R.; Borders, D. B.; Kinstle, T. W.; Kraus, D. *Ibid.* **1963**, *85*, 4038. (b) Absolute stereochemistry: Duchamp, D. J.; Branfman, A. R.; Button, A. C.; Rinehart, K. L., Jr. *Ibid.* **1973**, *95*, 4077.
(4) Horvath, G.; Brazhnikova, M. G.; Konstantinova, N. V.; Tolstykh, I. V.; Potapova, N. P. *J. Antibiot.* **1979**, *32*, 555.

0002-7863/85/1507-5219$01.50/0

Scheme I



tirandamycin A has been shown to possess antimicrobial activity[6] and inhibitory activity against bacterial DNA-directed RNA polymerase.[7]

We have recently embarked upon the development of a general strategy for the synthesis of the diverse members of the 3-dienoyl tetramic acid family of antibiotics and chose to initially demonstrate the viability of the strategy by preparing tirandamycin A. The plan required that the penultimate step in the total synthesis be the coupling of α,β-unsaturated aldehyde **3** with the dianion of phosphonate tetramic acid **4a**. We previously reported a method for the preparation of phosphonate **4a**,[8,9] and have demonstrated that furfuryl alcohol derivatives such as **5** could be elaborated into 2,9-dioxabicyclo[3.3.1]nonane systems similar to those found in tirandamycin A and related natural products.[10,11] In this paper we report the successful application of the convergent strategy outlined in Scheme I to the total synthesis of tirandamycin A.

Lithiation of 2,3-dimethylfuran[12] (**6**) and condensation with aldehyde **7**[13] gave a 1:1 mixture of α- and β-alcohols **8** and **8b** in 75% yield. Attempts to improve the stereoselectivity of the condensation by either (1) using furyl copper, zirconium, magnesium, or zinc reagents or (2) the use of additives in conjunction with the aldehyde were unsuccessful. Aldehyde **7** was prone to both α-epimerization and β-elimination of the siloxy substituent. Therefore, the condensation reaction had to be carefully monitored to avoid these side reactions. The β-alcohol **8b** could be recycled by a two-step process involving barium manganate oxidation[14] to give ketone **9** (80%) followed by reduction with $Zr(BH_4)_4$[15] (80%) to produce a 1:1.7 mixture of **8a** and **8b**[16] (Scheme II).

Oxidation of the furan ring of alcohol **8a** with *m*-CPBA[17] gave pyranone **10** in 90% yield. Removal of the silyl ether protecting group from **10** and concomitant acid-catalyzed ketalization to produce bicyclic ketal **11** could be accomplished in two ways. Treatment of pyranone **10** with BF_3–Et_2O gave bicyclic enone **11** in 65% yield. Alternatively, pyranone **10** could be converted into enone **11** in 70% yield when treated with 5% HF in acetonitrile for 1 h. The latter method, however, had to be carefully monitored since prolonged treatment of **11** with HF resulted in the rearrangement of **11** to lactone **12** (vide infra).

Oxidation of furan β-alcohol **8b** with *m*-CPBA followed by treatment of the resulting pyranone with aqueous HF in acetonitrile led to rapid (<1 h) formation of lactone **12**. The relative stereochemistry at the three contiguous asymmetric centers of the tetrahydrofuran ring cannot be unambiguously assigned from analysis of the 360-MHz ^{1}H NMR spectrum. However, we speculate that **12** possesses the indicated relative stereochemistry on mechanistic grounds. Lactone **12** was produced by acid treatment of both pyranone **10** and **13**, which differ only in configuration at C-5 of the pyranone ring. Pyranone **10** required 15 h for complete conversion to lactone **12**, while pyranone **13** rearranged in less than an hour under the same conditions, suggesting that pyranone **13** already possessed the C-5 configuration required in the rearrangement. Pyranone **10**, on the other hand, had to first undergo slow, acid-catalyzed epimerization at C-5 before it was able to rearrange to the lactone.

Treatment of pyranone **13** with BF_3·Et_2O did not result in formation of lactone **12**; instead, bicyclic enone **14** was produced in 61% yield. Unlike bicyclic enone **11** which has the C-3 and C-4 substituents equatorially disposed on the chair dioxolane ring, enone **14** would have these substituents in axial orientations if the dioxolane ring was in the chair conformation (conformation A, Scheme III). Conformation A would experience severe 1,3-diaxial interactions with the enone bridge. These unfavorable interactions are absent in boat conformation B. The ^{1}H NMR coupling pattern

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(7) Reusser, F. *Infect. Immun.* **1970**, *2*, 77, and references cited therein.

(8) DeShong, P.; Lowmaster, N. E.; Baralt, O. *J. Org. Chem.* **1983**, *48*, 1149.

(9) Phosphonate tetramic acid **4a** has been independently synthesized by Professor Boeckmann's group: Boeckmann, R. K., Jr.; Thomas, A. J. *J. Org. Chem.* **1982**, *47*, 2823. See also: Schlessinger, R. H.; Beberwitz, G. R. *Ibid.*, in press.

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(11) Several approaches to the total synthesis of tirandamycin A have appeared. See: Ireland, R. E.; Wuts, P. G. M.; Ernst, B. *J. Am. Chem. Soc.* **1981**, *103*, 3205. Ziegler, F. E.; Thottathil, J. K. *Tetrahedron Lett.* **1981**, *22*, 4883. Ziegler, F. E.; Wester, R. T. *Ibid.* **1984**, *25*, 617. Martin, S. F.; Gluchowski, C.; Campbell, C. L.; Chapman, R. C. *J. Org. Chem.* **1984**, *49*, 2512. Schlessinger, R. H.; Beberwitz, G. R.; Lin, P. *J. Am. Chem. Soc.* **1985**, *107*, 1777.

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(13) Aldehyde **7** occupies a critical niche in our generalized strategy for the synthesis of the 3-dienoyl tetramic acid family of antibiotics because it allows introduction of three of the four contiguous asymmetric centers found in all members of this family as a single entity. The preparation of aldehyde **7** is described in ref 10b.

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(15) Reid, W. E., Jr.; Bish, J. M.; Brenner, A. *J. Electrochem. Soc.* **1951**, *104*, 21.

(16) We inadvertently reported that $Zn(BH_4)_2$ reduced ketone **9** with high selectivity to give the α-alcohol **8a**. A correction has been published; see: *J. Org. Chem.* **1984**, *49*, 3874.

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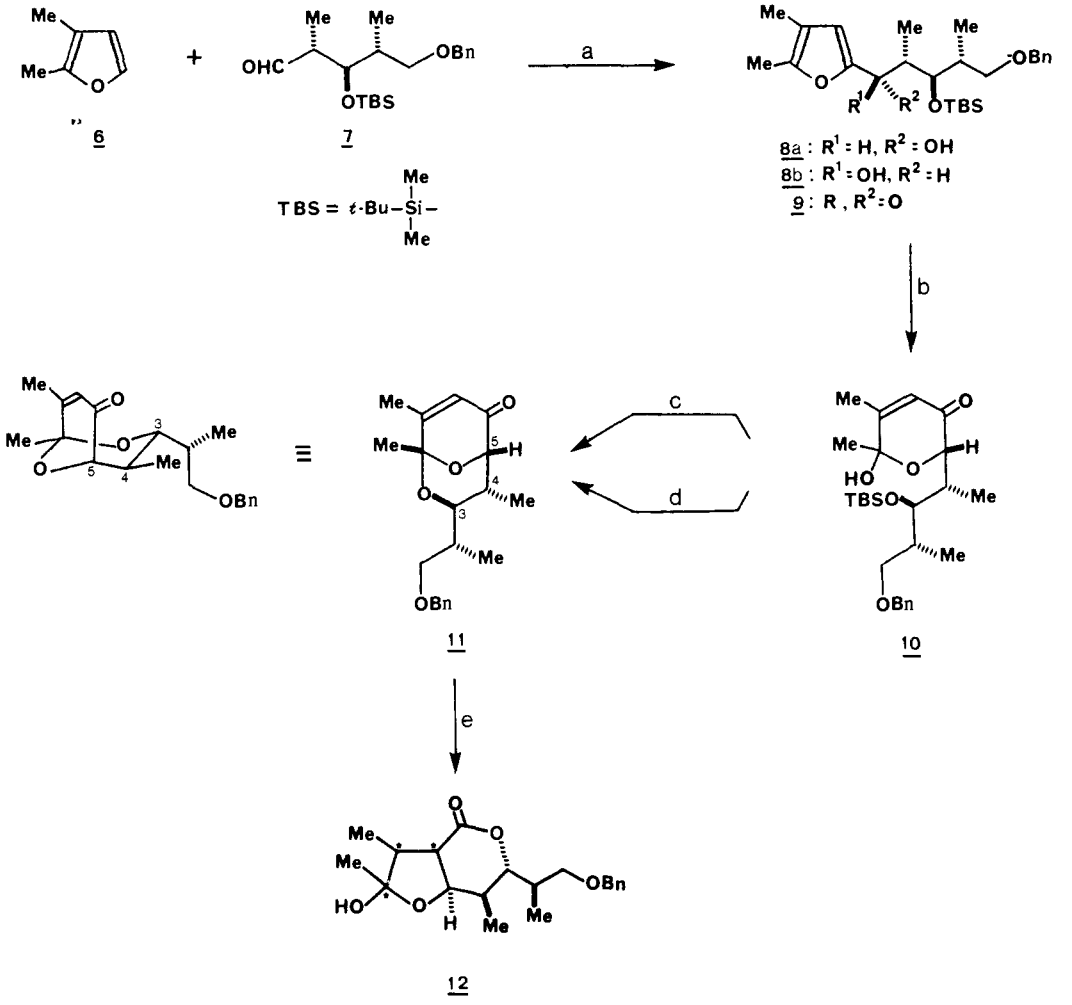
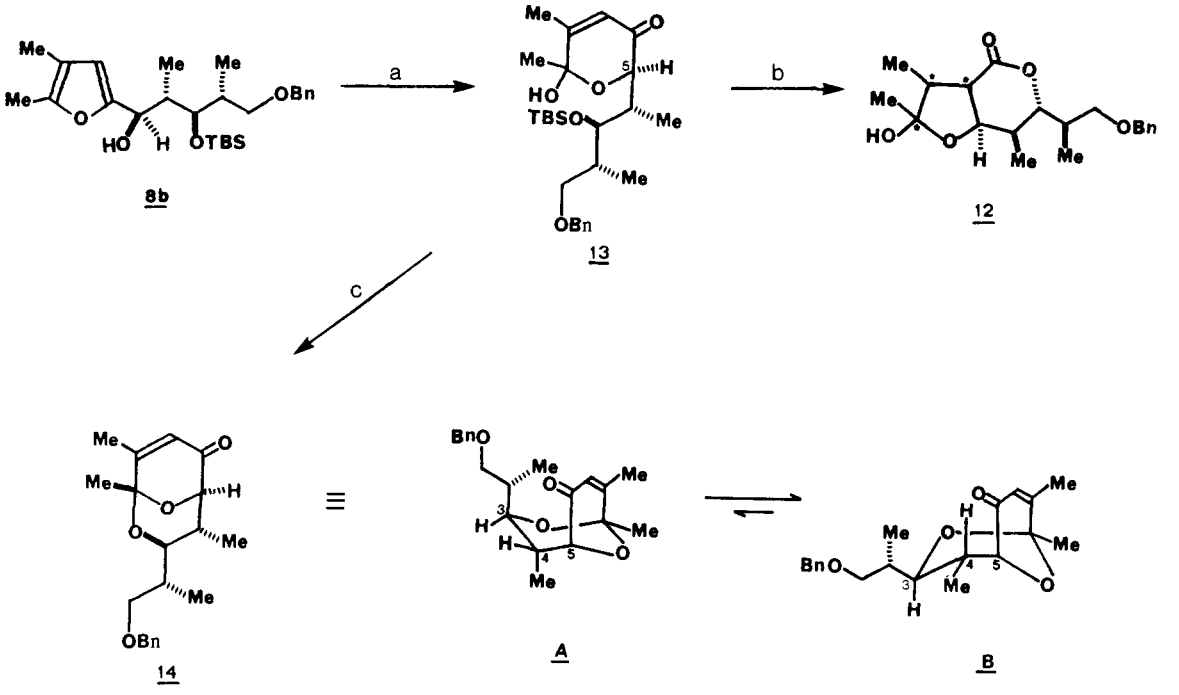
Scheme II



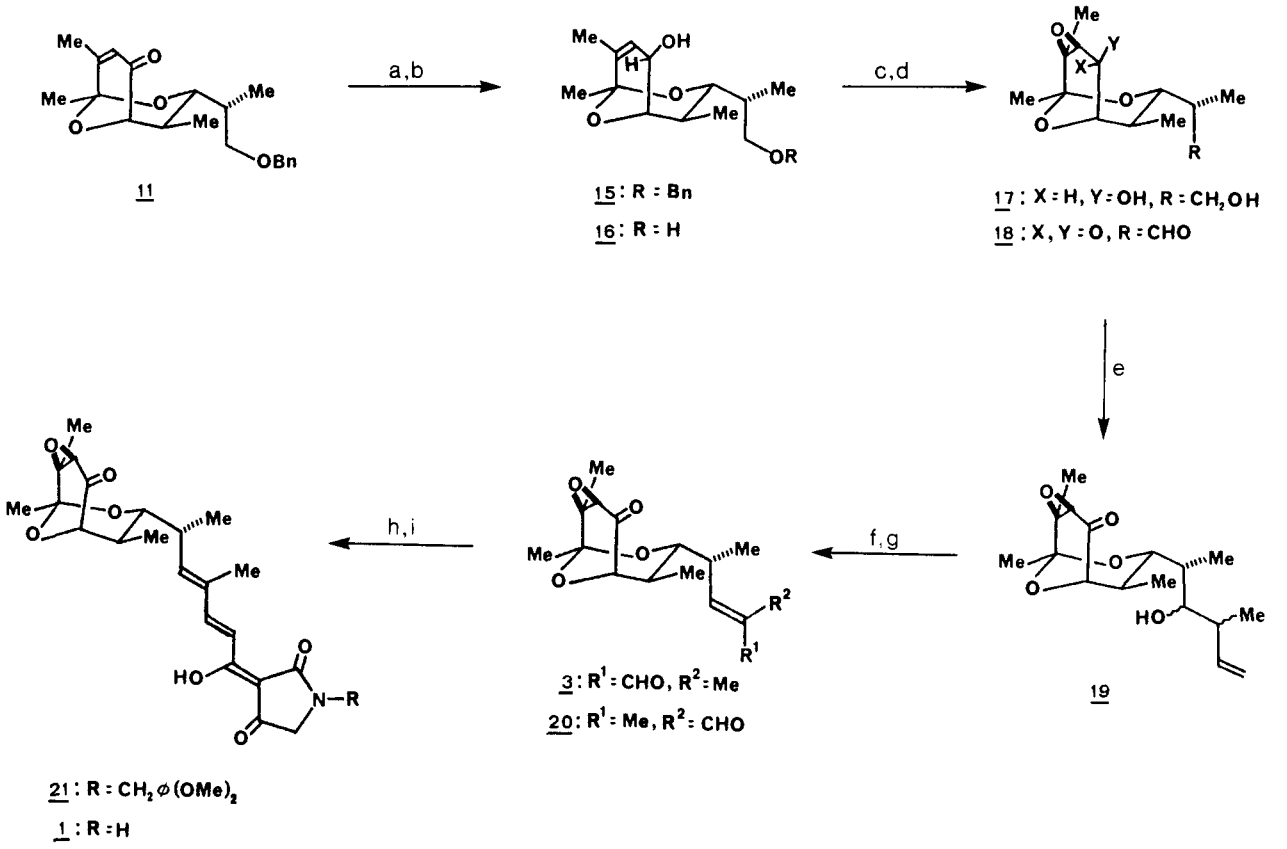
[a] *t*-BuLi, TMEDA, ether, −78 °C. [b] *m*-CPBA, CH_2Cl_2, 0 °C. [c] $BF_3 \cdot Et_2O$, CH_2Cl_2, −50 °C. [d] 5% aqueous HF/CH_3CN, 0 °C, 1 h. [e] 5% aqueous HF/CH_3CN, 0 °C, 15 h.

Scheme III



[a] *m*-CPBA, CH_2Cl_2, 0 °C. [b] 5% aqueous HF/CH_3CN, 0 °C, 1 h. [c] $BF_3 \cdot Et_2O$, CH_2Cl_2, −50 °C.

Scheme IV



[a] $NaBH_4$, $CeCl_3$, MeOH, room temp. [b] Na, NH_3, −78 °C. [c] *m*-CPBA, CH_2Cl_2, room temp. [d] PDC, CH_2Cl_2, room temp. [e] Crotyl bromide, $CrCl_2$, THF, room temp. [f] O_3, CH_2Cl_2, −78 °C; Me_2S, −78 °C. [g] *p*-TsOH, PhH, reflux. [h] Phosphonate 4b, KO^{t}Bu (2 equiv), THF, 0 °C. [i] CF_3COOH, room temp.

of the C-3, C-4, C-5 protons of enone **14** clearly confirmed that conformation B had been adopted.[18]

Direct introduction of the epoxide moiety into enone **11** could not be accomplished in good yield, so an indirect method was developed (Scheme IV). Enone **11** was reduced with $NaBH_4$/$CeCl_3$[19] (82%) to give allylic alcohol **15** in which the hydride was introduced exclusively onto the exo face of the carbonyl group.[18,20] Removal of the benzyl ether of **15** with Na/NH_3 (85%) gave diol **16** which underwent facile epoxidation with *m*-CPBA to give epoxy diol **17** in 81% yield. As expected, the reagent had approached selectively from the exo face of the bicyclo[3.3.1] system.[20] The assignment of epoxide stereochemistry was confirmed by oxidation of diol **17** with 7 equiv of PDC to give ketoaldehyde **18**, which was identical spectroscopically with the aldehyde obtained from ozonolysis of tirandamycin A.[21]

Homologation of **18** was accomplished by treatment of the aldehyde with 1.2 equiv of crotylchromium[22] to produce a mixture of diastereomeric homoallylic alcohols **19** in 79% yield. Ozonolysis of the alcohol mixture followed by dehydration of the resulting epimeric β-hydroxy aldehydes gave α,β-unsaturated aldehydes **3** and **20** in a 1.6:1 ratio in 82% overall yield from **19**. The major enal produced in the elimination reaction was identical with the compound obtained from the ozonolysis of natural tirandamycin A.[21]

Once the enal **3** had been synthesized, the stage was set for the completion of the total synthesis of tirandamycin A as outlined in Scheme I. However, all attempts to induce the dianion of **4a** to undergo condensation with enal **3** were unsuccessful, even though a diversity of conditions was studied. Model studies in this laboratory demonstrated that the failure of the condensation reaction could be attributed to the lack of a substituent on the tetramic acid nitrogen. We observed that tetramic acid phosphonates similar to **4a** which carry an alkyl group on the tetramic acid nitrogen underwent condensation reactions in excellent yields.[23] Thus, the dianion of **4b**[9] reacted with enal **3** to produce tetramic acid **21** in 77% yield. The trans stereochemistry of the newly formed olefinic bond was indicated by the large coupling constant (J = 15.8 Hz) observed in the ^{1}H NMR spectrum of **21**. (±)-Tirandamycin A was obtained in 90% yield by brief treatment of **21** with neat trifluoroacetic acid at room temperature. The synthetic material was identical spectroscopically and chromatographically with a sample of natural tirandamycin A.

The convergent, 12-step synthesis of tirandamycin A outlined in this report proves the viability of our strategy for the synthesis of the 3-dienoyl tetramic acid family of antibiotics. The application of this methodology to the synthesis of related natural products is underway and will be reported in due course.

Experimental Section

Formation of Pyranone 10. *m*-Chloroperbenzoic acid (22 mg, 0.10 mmol) was added to a solution of hydroxyfuran **8a**[10b] (45 mg, 0.10 mmol) in CH_2Cl_2 (15 mL) at 0 °C. After stirring at 0 °C for 30 min, the reaction mixture was washed with $NaHCO_3$ (3 × 15 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude pyranone was purified by PLC (0.5 mm, 4:1 hexane/EtOAc) to give 42 mg (90%) of pyranone **10**: IR (CCl_4) 3590 (w), 3350 (bd, w), 3090–3030 (w), 2960–2860 (vs), 1685 (vs), 1040 (w), 1120–1000 (vs), 895 (s); ^{1}H NMR

(18) DeShong, P.; Perez, J. J., unpublished results. See also: Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergammon: New York, 1969; pp 280–304.

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(20) Ireland[11] has observed high exo-face selectivity in the epoxidation of related 2,6-dioxabicyclo[3.3.1]nonane systems.

(21) Ozonolysis of tirandamycin A gave a mixture of keto-aldehyde **18** and enal **3**. See Experimental Section for details.

(22) Hiyama, T.; Okude, Y.; Kimura, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 561.

(23) Cipollina, J.; DeShong, P.; Elango, V., unpublished results.

($CDCl_3$) 0.09 (s, 3), 0.11 (s, 3), 0.76 (d, 3, J = 7 Hz), 0.88 (s, 9), 1.06 (d, 3, J = 7 Hz), 1.62 (s, 3), 1.79 (bd, s, 1), 2.02 (d, 3, J = 1 Hz), 2.07–2.19 (m, 1), 2.49–2.65 (m, 1), 3.32 (t, 1, J = 9 Hz), 3.66 (dd, 1, J = 9, 5 Hz), 3.73 (dd, 1, J = 8, 2 Hz), 4.46 (A of ABq, 1, J = 12, 4 Hz), 4.53 (B of ABq, 1, J = 12, 4 Hz), 4.64 (d, 1, J = 2 Hz), 5.91 (d, 1, J = 1 Hz), 7.34 (m, 5); mass spectrum, m/z (relative intensity) 387 (M^+ – 75, 8), 91 (100), 57 (24), 49 (40), 28 (66); mass spectrum, m/z 462.2784 (calcd for $C_{26}H_{42}O_5Si$, 462.2801).

Formation of Enone 11 Using HF. The pyranone **10** (42 mg, 0.091 mmol) from the previous reaction was dissolved in acetonitrile (9 mL) and transferred to a polyethylene tube. Aqueous HF (53% solution, 1 mL) was added and the resulting yellow solution was stirred at room temperature for 1 h. The solution was heated with satd K_2CO_3 and the organic layer was separated. The aqueous layer was extracted with Et_2O (2 × 20 mL) and the organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo. Purification by PLC (0.5 mm, 7:3 hexane/EtOAc) provided 21 mg (70%) of bicyclic enone **11**: mp 92–94 °C; IR (CCl_4) 3090–3040 (w), 2970–2860 (m), 1690 (vs), 1635 (w), 1455 (m), 1090–1015 (s), 870 (w), 675 (m); ^1H NMR ($CDCl_3$) 0.79 (d, 3, J = 7 Hz), 0.99 (d, 3, J = 7 Hz), 1.50 (s, 3), 1.90 (d, 3, J = 2 Hz), 2.05 (m, 1), 2.42 (m, 1), 3.32 (dd, 1, J = 9, 6 Hz), 3.42 (dd, 1, J = 12, 2 Hz), 3.78 (dd, 1, J = 9, 6 Hz), 4.05 (d, 1, J = 6 Hz), 4.51 (s, 2), 6.12 (s, 1), 7.34 (s, 5); mass spectrum, m/z (relative intensity) 330 (M^+, 1), 312 (1), 239 (4), 224 (7), 215 (9), 206 (3), 181 (9), 153 (8), 137 (6), 125 (21), 111 (28), 91 (100); mass spectrum, m/z 330.1827 (calcd for $C_{20}H_{26}O_4$, 330.1831); ^{13}C NMR ($CDCl_3$) 195.5, 155.7, 138.6, 128.3, 127.4, 127.3, 96.0, 79.4, 73.0, 71.2, 34.0, 32.9, 24.4, 19.2, 15.6, 11.8. Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.42; H, 8.00.

Formation of Enone 11 Using BF_3·Et_2O. BF_3·Et_2O (37 mg, 0.26 mmol) was added to a solution of pyranone **10** (120 mg, 0.26 mmol) in CH_2Cl_2 (15 mL) at −50 °C. The reaction mixture was stirred at −50 °C for 10 h, then quenched by the addition of 10% $NaHCO_3$ (20 mL), and allowed to warm to room temperature. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification by radial chromatography (1 mm silica gel, 9:1 hexane/EtOAc) afforded 56 mg (65%) of bicyclic enone **11** whose spectroscopic features (360 MHz ^1H NMR, IR) were identical with that of bicyclic enone **11** obtained in the HF reaction.

Conversion of Enone 11 to Lactone 12. A mixture of bicyclic enone **11** (10 mg, 0.030 mmol) and 5% HF in CH_3CN (5 mL) was stirred at room temperature for 17 h. TLC indicated the appearance of a major low R_f compound and a trace of starting enone. The low R_f compound was isolated by PLC (0.25 mm, 1:1 hexane/EtOAc) and found to be identical (360-MHz ^1H NMR, IR) with the lactone **12** produced in the reaction of pyranone **13** with HF.

Formation of Pyranone 13. Treatment of hydroxyfuran **8b**[10b] (44 mg, 0.10 mmol) with *m*-chloroperbenzoic acid (21 mg, 0.10 mmol) in CH_2Cl_2 (15 mL) at 0 °C and workup as described above gave 40 mg (88%) of pyranone **13**: IR (CCl_4) 3600 (w), 3350 (bd, w), 1690 (vs).

Formation of Lactone 12 from Pyranone 13. Treatment of pyranone **13** (44 mg, 0.095 mmol) with 5% HF/CH_3CN as described above afforded 27 mg (81%) of lactone **12** as an oil: IR (CCl_4) 3580 (m), 2900 (s), 2870 (s), 1725 (vs), 1185 (m), 1100–1060 (s), 995 (m), 890–870 (m); ^1H NMR ($CDCl_3$) 1.09 (d, 3, J = 7 Hz), 1.13 (d, 3, J = 7 Hz), 1.27 (d, 3, J = 7 Hz), 1.45 (s, 3), 1.63–1.82 (m, 1), 2.02–2.28 (m, 4), 2.90 (t, 1, J = 10 Hz), 3.35 (dd, 1, J = 9, 7 Hz), 3.63 (dd, 1, J = 10, 6 Hz), 3.86 (dd, 1, J = 10, 2 Hz), 4.03 (t, 1, J = 10 Hz), 4.49 (s, 2), 7.31 (s, 5); mass spectrum, m/z (relative intensity) (M^+ – 18, 6), 287 (3), 259 (5), 239 (10), 229 (2), 209 (1), 197 (2), 181 (6), 160 (9), 141 (8), 123 (14), 107 (11), 96 (56), 91 (100); mass spectrum, CI, m/z 348 (M^+).

Formation of Enone 14 from Pyranone 13 Using BF_3·Et_2O. To a cold solution (−50 °C) of pyranone **13** (20 mg, 0.04 mmol) in CH_2Cl_2 (10 mL), BF_3·Et_2O (6 mg, 0.04 mmol) was added and stirred at −50 °C for 8 h. The reaction mixture was worked up using the procedure previously described to give 8 mg (61%) of the oily bicyclic enone **14**: IR (CCl_4) 3040 (w), 2980 (m), 2880 (m), 1680 (vs), 1450 (m), 1380 (m), 1080 (s), 670 (w); ^1H NMR ($CDCl_3$) 0.98 (d, 3, J = 7 Hz), 1.16 (d, 3, J = 7 Hz), 1.48 (s, 3), 1.92 (d, 3, J = 2 Hz), 2.00–2.21 (m, 2), 3.21 (dd, 1, J = 9 Hz), 3.52 (dd, 1, J = 9, 5 Hz), 3.70 (dd, 1, J = 8, 4 Hz), 3.90 (d, 1, J = 3 Hz), 4.44 (s, 2), 5.68 (d, 1, J = 1 Hz), 7.31 (m, 5); mass spectrum, m/z (relative intensity) 330 (M^+, 2), 273 (1), 239 (1), 224 (6), 181 (7), 152 (5), 137 (5), 125 (11), 111 (31), 91 (100); mass spectrum, m/z 330.1837 (calcd for $C_{20}H_{26}O_4$, 330.1831).

Formation of Allylic Alcohol 15. Sodium borohydride (16 mg, 0.42 mmol) was added to a solution containing enone **11** (136 mg, 0.412 mmol) and $CeCl_3$ (164 mg, 0.421) in MeOH (5 mL). Evolution of gas occurred and after 5 min the pH of the solution was adjusted to neutrality with dilute aqueous HCl. The mixture was extracted with Et_2O (2 × 20 mL); the organic layers were removed, dried ($MgSO_4$), and concentrated in vacuo. Purification by radial chromatography (1 mm silica gel, 7:3 hexane/EtOAc) gave 111 mg (82%) of allylic alcohol **15** as an oil: IR (CCl_4) 3620 (m), 3480 (bd, w), 3080–3030 (w), 2960–2860 (s), 1550 (s), 1370 (s), 1090 (vs), 1020 (vs), 910 (m), 720 (w); ^1H NMR ($CDCl_3$) 0.95 (d, 3, J = 7 Hz), 0.97 (d, 3, J = 7 Hz), 1.29 (s, 3), 1.53 (dd, 3, J = 2, 1 Hz), 1.99–2.09 (m, 1), 2.23–2.35 (m, 1), 3.24 (dd, 1, J = 9, 8 Hz), 3.66 (m, 3), 3.89 (t, 1, J = 5 Hz), 4.43 (s, 2), 4.68 (bds, 1), 5.64 (d, 1, J = 1 Hz), 7.23 (m, 5); mass spectrum, m/z (relative intensity) 332 (M^+, 10), 125 (9), 109 (71), 91 (100); mass spectrum, m/z 332.1985 (calcd for $C_{20}H_{28}O_4$, 332.1988).

Debenzylation of 15 with Na/NH_3 To Give Diol 16. Sodium (2 mg, 0.08 g equiv) was added to a solution of allylic alcohol **16** (27 mg, 0.081 mmol) in ammonia (10 mL) at −78 °C under an argon atmosphere, and the mixture was stirred for 30 min. The reaction was quenched with NH_4Cl. Ammonia was allowed to evaporate at room temperature and the residue was taken up in water (10 mL) and extracted with Et_2O (2 × 20 mL). The organic extract was dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (10 mm diameter, 150 mm silica gel, 3:2 hexane/EtOAc) gave 16 mg (85%) of diol **16** as an oil: IR (CCl_4) 3630 (m), 3540 (m), 2970–2920 (s), 1380 (m), 1090–1020 (s), 910 (w); ^1H NMR ($CDCl_3$) 1.03 (d, 3, J = 8 Hz), 1.12 (d, 3, J = 7 Hz), 1.41 (s, 3), 1.63 (dd, 3, J = 2, 1 Hz), 1.82–1.92 (m, 1), 2.36–2.49 (m, 1), 2.79 (d, 1, J = 8 Hz), 3.52–3.58 (m, 1), 3.87 (dd, 2, J = 11, 2 Hz), 3.95–4.08 (m, 2), 4.79–4.85 (m, 1), 5.76 (d, 1, J = 1 Hz); mass spectrum, m/z (relative intensity) 242 (M^+, 16), 129 (18), 109 (88), 95 (13), 85 (60), 71 (33), 57 (19), 43 (71), 28 (100); mass spectrum, m/z 242.1513 (calcd for $C_{13}H_{22}O_4$, 242.1518).

Formation of Epoxy Alcohol 17. A CH_2Cl_2 solution (5 mL) of allylic alcohol **16** (22 mg, 0.091 mmol) and mCPBA (30 mg, 0.17 mmol) was stirred at room temperature for 23 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with 5% $NaHSO_3$ (10 mL) and 5% $NaHCO_3$ (2 × 10 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by PLC (0.5 mm, 20 × 20 cm silica gel; 1:1 hexane/EtOAc) gave 19 mg (81%) of epoxy alcohol **17**: IR (CCl_4) 3620 (sh, m), 3530 (bd, m), 2940 (s), 2920 (s), 2860 (s) 1450 (s), 1370 (s), 1190 (s), 1110 (s), 1060 (vs), 1020 (s), 940 (s), 880 (m), 870 (m); ^1H NMR ($CDCl_3$) 1.04 (d, 3, J = 8 Hz), 1.21 (d, 3, J = 7 Hz), 1.38 (s, 3), 1.39 (s, 3), 1.88–2.08 (m, 1), 2.38–2.50 (m, 1), 2.77 (bd, s, 2), 3.20 (s, 1), 3.56 (dd, 1, J = 11, 4 Hz), 3.95 (dd, 1, J = 11, 3 Hz), 4.01–4.09 (m, 2), 4.42 (d, 1, J = 7 Hz); mass spectrum, m/z (relative intensity), 130 (M^+ – 128, 5), 112 (12), 98 (38), 87 (40), 71 (26), 55 (14), 43 (100), 29 (6); mass spectrum, m/z 258.1461 (calcd for $C_{13}H_{22}O_5$, 258.1467).

Formation of Aldehyde 18. Pyridinium dichromate (PDC, 51 mg, 0.14 mmol) was added to a solution containing epoxy diol **17** (5 mg, 0.02 mmol) in CH_2Cl_2 (3 mL) and the suspension was stirred for 4 h at room temperature. The reaction mixture was filtered through a bed of Celite and the residue was washed with CH_2Cl_2 (3 × 10 mL). The solvent was removed in vacuo to give 3 mg (60%) of keto epoxy aldehyde **18** as an oil: IR (CCl_4) 2980–2860 (m), 2720 (w), 1730 (vs), 1460 (m), 1385 (m), 1110 (s), 1065 (m), 930 (w); ^1H NMR ($CDCl_3$) 0.84 (d, 3, J = 7 Hz), 1.28 (d, 3, J = 7 Hz), 1.48 (s, 3), 1.54 (s, 3), 2.27–2.39 (m, 1), 2.52–2.58 (m, 1), 3.31 (s, 1), 3.79 (dd, 1, J = 12, 2 Hz), 4.09 (d, 1, J = 6 Hz), 9.77 (d, 1, J = 2 Hz); mass spectrum, m/z (relative intensity 165 (M^+ – 89, 6), 125 (9), 109 (9), 98 (17), 84 (27), 69 (31), 55 (7), 43 (100), 28 (8); mass spectrum, m/z 254.1147. (calcd for $C_{13}H_{18}O_5$, 254.1154). Aldehyde **18** was identical in all spectroscopic features (360-MHz ^1H NMR, IR) with the aldehyde produced by ozonolysis of tirandamycin A.[21]

Formation of Homoallylic Alcohol 19. To a suspension of anhydrous $CrCl_3$ (38 mg, 0.24 mmol) in THF (3 mL) at 0 °C, $LiAlH_4$ (4.5 mg, 0.12 mmol) was added. Once the addition was complete, the reaction mixture was warmed to room temperature and a solution of aldehyde **18** (25 mg, 0.098 mmol) and crotyl bromide (16 mg, 0.12 mmol) in THF (1 mL) was added over a period of 5 min. The reaction mixture was stirred for 3 h at room temperature. The reaction was quenched with H_2O (10 mL) and extracted with Et_2O (4 × 10 mL). The combined organic extracts were washed with brine (20 mL) and H_2O (2 × 20 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by PLC (0.5 mm, 20 × 20 cm silica gel, 7:3 hexane/EtOAc) gave 24 mg (80%) of a mixture of homoallylic alcohols **19**, which were used in the next reaction without further characterization: IR (neat) 3540 (s), 3080 (m), 2980–2780 (vs), 1730 (vs), 1450 (s), 1380 (s), 1130–1100 (vs), 895 (s).

Formation of Enals 3 and 20. A CH_2Cl_2 (20 mL) solution of homoallylic alcohols **19** (9 mg, 0.03 mmol) was cooled to −78 °C, and ozone (0.06 mmol) was passed through the solution via a gas dispersion tube. The ozonide was reduced by the addition of Me_2S (2 drops) at −78 °C and the mixture was allowed to warm to room temperature. Concentration of the solution in vacuo gave a residue of oily β-hydroxy aldehyde.

A solution containing β-hydroxy aldehyde and *p*-toluenesulfonic acid (one crystal) in benzene (5 mL) was refluxed for 30 min. The reaction

mixture was concentrated in vacuo and the residue was purified by PLC (0.25 mm, 20 × 20 cm silica gel, 7:3 hexane/EtOAc) to give 7 mg (78%) of a 1.6:1 ratio of enals **3** and **20**. The ratio was determined by ^{1}H NMR by comparing the intensities of epoxy protons. Enal **3** and **20** could be separated by HPLC on silica (hexane–EtOAc). Enal **3**: IR (CCl_4) 2980 (m), 2930 (m), 1740 (vs), 1690 (s), 1450 (m), 1370 (m), 1230 (s), 1030 (s), 930 (w), 895 (w); ^{1}H NMR ($CDCl_3$): 0.73 (d, 3, J = 7 Hz), 1.19 (d, 3, J = 7 Hz), 1.49 (s, 3), 1.59 (s, 3), 1.77 (d, 3, J = 1 Hz), 1.90–2.02 (m, 1), 2.92–3.01 (m, 1), 3.31 (s, 1), 3.63 (dd, 1, J = 12, 2 Hz), 4.05 (d, 1, J = 6 Hz), 6.66 (dd, 1, J = 10, 1 Hz), 9.46 (s, 1); mass spectrum, m/z (relative intensity) 255 (M^+ – 29, 7), 237 (1), 226 (1), 213 (2), 195 (5), 158 (10), 149 (6), 137 (6), 127 (12), 111 (18), 99 (10), 85 (44), 69 (53), 55 (29), 43 (100), 29 (12); mass spectrum, m/z 294.1468 (calcd for $C_{16}H_{22}O_5$, 294.1467). Enal **3** was identical in all spectroscpic features with the enal produced by ozonolysis of tirandamycin A.[21]

A sample of enal **20** contaminated with ~10% of enal **3** gave the following spectral data: ^{1}H NMR ($CDCl_3$) 0.83 (d, 3, J = 7.0 Hz), 1.11 (d, 3, J = 7.0 Hz), 2.22–2.35 (m, 1), 2.81–2.92 (m, 1), 3.26 (s, 1), 3.58 (dd, 1, J = 11.0, 2.6 Hz), 4.10 (d, 1, J = 6.0 Hz), 6.59 (dd, 1, J = 9.7, 1.4 Hz), 9.43 (s, 1).

Formation of Tetramic Acid 21 from Enal 3. Phosphonate **4b** was prepared according to the procedure of Schlessinger et al.[9] Potassium *tert*-butoxide (77 mg, 0.68 mmol) was added to a THF (5 mL) solution of phosphonate **4b** (130 mg, 0.317 mmol) at 0 °C and the mixture was stirred for 45 min. Enal **3** (51 mg, 0.18 mmol) in THF (1 mL) was added dropwise over a period of 10 min and the mixture was stirred for 14 h at 0 °C. The reaction mixture was diluted with CH_2Cl_2 (30 mL), quenched with 2% HCl (0.5 mL), and washed with water (15 mL). The organic layer was removed, dried (Na_2SO_4), and concentrated in vacuo. Purification by radial chromatography (1 mm silica gel, $CHCl_3$) gave 58 mg (85% based on recovered starting enal **3**) of tetramic acid **21**: IR (CCl_4) 3160 (m), 2980–2950 (m), 2860 (w), 1725 (vs), 1700 (vs), 1650–1610 (bd, vs) 1460 (s), 1420 (s), 1370 (s), 1285 (s), 1250 (s), 1220 (s), 1190 (s), 1120 (s), 980 (m), 960 (m), 890 (m); ^{1}H NMR ($CDCl_3$) 0.71 (d, 3, J = 7 Hz) 1.12 (d, 3, J = 7 Hz), 1.47 (s, 3), 1.56 (s, 3), 1.89 (d, 3, J = 1 Hz), 1.96 (m, 1), 2.83 (ddd, 1, J = 10, 7, 2 Hz), 3.28 (s, 1), 3.56 (dd, 1, J = 12, 2 Hz), 3.66 (s, 2), 3.80 (s, 3), 3.81 (s, 3), 4.01 (d, 1, J = 6 Hz), 4.57 (s, 2), 6.17 (d, 1, J = 10 Hz), 6.45 (m, 2), 7.12 (d, 1, J = 16 Hz), 7.18 (dd, 1, J = 6, 3 Hz), 7.52 (d, 1, J = 16 Hz); mass spectrum, m/z (relative intensity) 567 (M^+, 7), 445 (3), 371 (5), 333 (10), 289 (5), 233 (26), 204 (4), 197 (5), 170 (5), 152 (12), 151 (100); mass spectrum, m/z 567.2473 (calcd for $C_{31}H_{37}NO_9$, 567.2468).

Conversion of Tetramic Acid 21 to Tirandamycin A (1). Tetramic acid **21** (23 mg, 0.041 mmol) was dissolved in CF_3COOH (1 mL), and the resulting purple solution was stirred at room temperature for 5 min. The reaction mixture was quenched with ice, extracted with CH_2Cl_2 (30 mL), washed with $NaHCO_3$, dried (Na_2SO_4), and concentrated in vacuo. Purification by PLC (0.5 mm, 20 × 20 cm silica gel, 10:1 CH_2Cl_2/MeOH) afforded the sodium salt of tirandamycin A. The salt was taken up in CH_2Cl_2 (30 mL), quenched with MeOH/HCl (0.5 mL), washed with H_2O (10 mL), dried (Na_2SO_4), and concentrated in vacuo to give 15 mg (90%) of tirandamycin A: IR ($CHCl_3$) 3440 (sh, m), 2910 (m), 1720 (s), 1655 (vs), 1610 (vs), 1560 (vs), 1440 (m), 980 (m), 880 (s); ^{1}H NMR ($CDCl_3$) 0.72 (d, 3, J = 7 Hz), 1.14 (d, 3, J = 7 Hz), 1.48 (s, 3), 1.58 (s, 3), 1.92 (d, 3, J = 1 Hz), 1.95–2.10 (m, 1), 2.80–2.90 (m, 1), 3.29 (s, 1), 3.58 (dd, 1, J = 12, 2 Hz), 3.83 (s, 2), 3.94 (bd, s, 1), 4.03 (d, 1, J = 6 Hz), 5.81 (bd, s, 1), 6.22 (d, 1, J = 10 Hz), 7.17 (d, 1, J = 16 Hz), 7.59 (dd, 1, J = 16, 1 Hz); mass spectrum, m/z (relative intensity) 417 (M^+ – 30), 368 (1), 221 (61), 197 (26), 181 (9), 126 (40), 109 (8), 95 (18), 85 (15), 69 (100). Compound **1** was identical in all spectroscopic features (360 MHz ^{1}H NMR, IR) with an authentic sample of tirandamycin A.

Ozonolysis of Tirandamycin A. A solution of tirandamycin A (34 mg, 0.10 mmol) in 75 mL of CH_2Cl_2 was cooled to −78 °C; then a stream of ozone (~0.5 mmol) was passed through the solution to produce a dark blue color. After the mixture was stirred at −78 °C for 50 min, Me_2S (0.5 mL) was added and the resulting solution was allowed to slowly warm to room temperature over 3.5 h. Evaporation of the volatiles in vacuo gave a yellow oil which was purified by rapid column chromatography on silica (CH_2Cl_2) to give a mixture of aldehyde **18** (68%) and the unstable enal **3** (13%). Aldehyde **18**: mp 123–5 °C (hexane–CH_2Cl_2); IR (CCl_4): 1730 (s), 1110 (s), 1070 (s); ^{1}H NMR ($CDCl_3$) 0.84 (d, 3, J = 7 Hz), 1.28 (d, 3, J = 7 Hz), 1.48 (s, 3), 1.54 (s, 3), 2.27–2.39 (m, 1), 2.52–2.58 (m, 1), 3.31 (s, 1), 3.79 (dd, 1, J = 12, 2 Hz), 4.09 (d, 1, J = 6 Hz), 9.77 (d, 1, J = 2 Hz); mass spectrum, m/z (relative intensity) 239 (0.5), 197 (2), 165 (5), 43 (100). Enal **3**: amorphous solid, IR (CCl_4) 1740 (vs), 1690 (vs); ^{1}H NMR ($CDCl_3$) 0.73 (d, 3, J = 7 Hz), 1.19 (d, 3, J = 7 Hz), 1.49 (s, 3), 1.59 (s, 3), 1.77 (d, 3, J = 1 Hz), 1.90–2.02 (m, 1), 2.92–3.01 (m, 1), 3.31 (s, 1), 3.63 (dd, 1, J = 12, 2 Hz), 4.05 (d, 1, J = 6 Hz), 6.66 (dd, 1, J = 10, 1 Hz), 9.46 (s, 1); mass spectrum, m/z (relative intensity) 255 (M^+ – 29, 7), 237 (1), 226 (1), 213 (2), 195 (5), 158 (10), 149 (6), 137 (6), 127 (12), 111 (18), 99 (10), 85 (44), 69 (53), 55 (29), 43 (100), 29 (13).

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