3-Acyltetramic Acid Antibiotics. 2. Synthesis of (+)-Streptolic Acid

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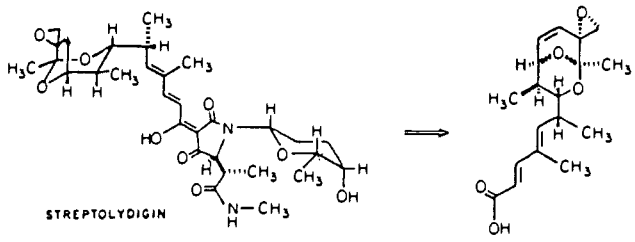
Abstract: An efficient synthesis of streptolic acid, a product obtained from cleavage of the antibiotic streptolydigin, is described. The approach is based on the use of D-(+)-glucose for the source of absolute stereochemistry, and the transfer of asymmetry is accomplished by the application of the ester enolate Claisen rearrangement and the Sharpless asymmetric epoxidation.

Extension of the synthetic strategy developed in these laboratories for construction of the 2,9-dioxabicyclononane skeleton[2] has recently culminated in the synthesis of streptolic acid (**2**),[3] a degradation product from streptolydigin,[4] the most potent[5] member of the small family of 3-acyltetramic acid antibiotics.[4,6] Much



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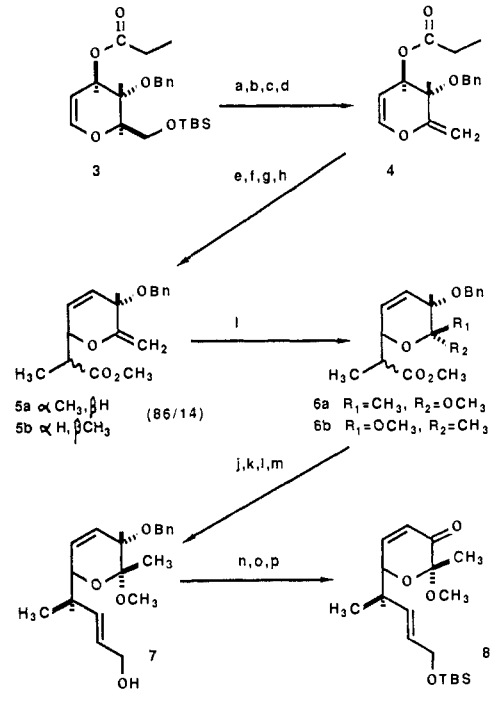
recent synthetic work has centered on the construction of tirandamycin A,[2,7] Bu2313,[8] and the tetramic acid[7d,9] components of these antibiotics. The work by the Bartlett[7g] and Boeckman[7f] groups suggests that this acid **2** can serve as a key intermediate for the synthesis of the natural product itself. The current strategy allows divergence from an advanced intermediate and provides access to the substitution pattern necessary for the synthesis of other members of the family as well as streptolydigin and synthetic analogues.

Scheme I. Construction of Versatile Enone **8**[a]



[a] Reagents and conditions: (a) Bu_4NF, THF, 98%; (b) TsCl, pyridine CH_2Cl_2, 89%; (c) NaI, MEK, reflux, 4 **h**, 87%; (d) DBU, C_6H_5, reflux, 1 h, 99%; (e) $(TMS)_2NLi$, (TBS)Cl, HMPA, THF, -78 °C; (f) C_6H_6, reflux, 1 h; (g) KF-$2H_2O$, $KHCO_3$, HMPA; (h) CH_3I, HMPA, 85% from **4**; (i) CH_3OH, catalytic TsOH, 99%; (j) DIBAL, Et_2O, -78 °C; (k) $(COCl)_2$, DMSO, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, -78 °C; (l) $C_2H_5O_2C\text{-}C(CH_3)=P(C_6H_5)_3$, CH_2Cl_2, 87% from **6a,b**; (m) DIBAL, Et_2O, Et_2O, -78 °C; (n) (TBS)Cl, imidazole, DMF; (o) $Li^+[pip'(t\text{-}Bu)_2\text{-}(C_6H_5)_2]^{\bullet-}$, THF, -78 °C, 97%; (p) $(COCl)_2$, DMSO, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, -78 °C, 93%.

As in the tirandamycic acid synthesis,[2] development of the bicyclic portion of streptolic acid began with an ester enolate Claisen rearrangement[10] of a glycal derived from D-glucose (Scheme I). Preparation of the glycal intermediate **3** followed the earlier procedure.[2] To avoid the troublesome elimination sequence[2] required to deoxygenate C-6 of the Claisen product, however, this process was explored at an early stage. Thus, the glycal **3** was transformed into the iodide through the corresponding tosylate and then dehydroiodinated to the surprisingly stable bis(enol ether) **4**. This proved to be an excellent substrate for the ester enolate Claisen, and the enol ether **5** was readily obtained as a mixture of methyl epimers **5a** and **5b**. The epimeric ratio was determined after ketalization gave the mixed ketals **6a** and **6b** (4:1 anomeric mixture). The anomers proved to be readily separable by flash chromatography, but resolution of the side chain

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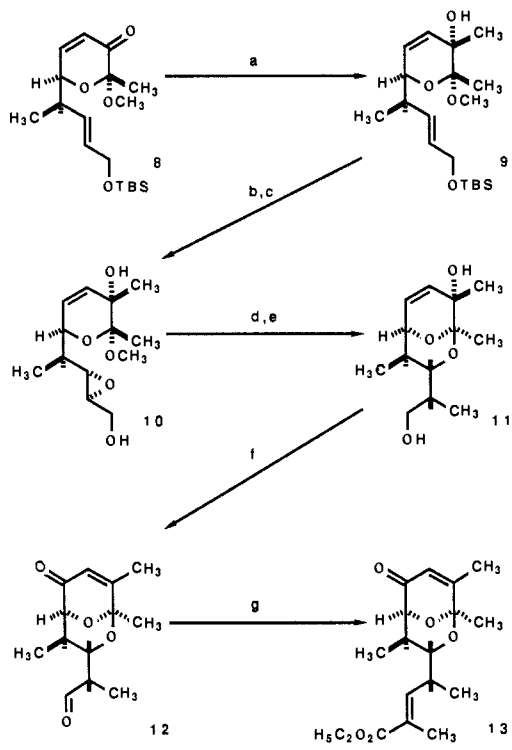
Scheme II. Tirandamycic Acid Synthesis[a]



[a] Reagents and conditions: (a) CH_3Li, THF, −78 °C, 96%; (b) Bu_4NF, THF, 99%; (c) (+)-DIPT, $Ti(O\text{-}i\text{-}Pr)_4$, t-BuOOH, CH_2Cl_2, −20 °C, 90%; (d) $(CH_3)_2CuLi$, Et_2O, 0 °C; (e) catalytic TsOH, $CHCl_3$, 81% from **10**; (f) PCC, Celite, CH_2Cl_2 (g) $C_2H_5O_2CC(CH_3)$-$=P(C_6H_5)_3$, C_6H_6, 38% from **11**.

methyl epimers was not possible even by TLC. Analysis of the major anomer (capillary GC) showed the 86:14 mixture of diastereomers that usually corresponds to the geometric selectivity observed under the enolization conditions used.[10] (The anomeric center of the minor anomer was readily equilibrated to the same 4:1 anomeric mixture. Separation of these methyl epimers, however, was not possible until much later in the sequence.)

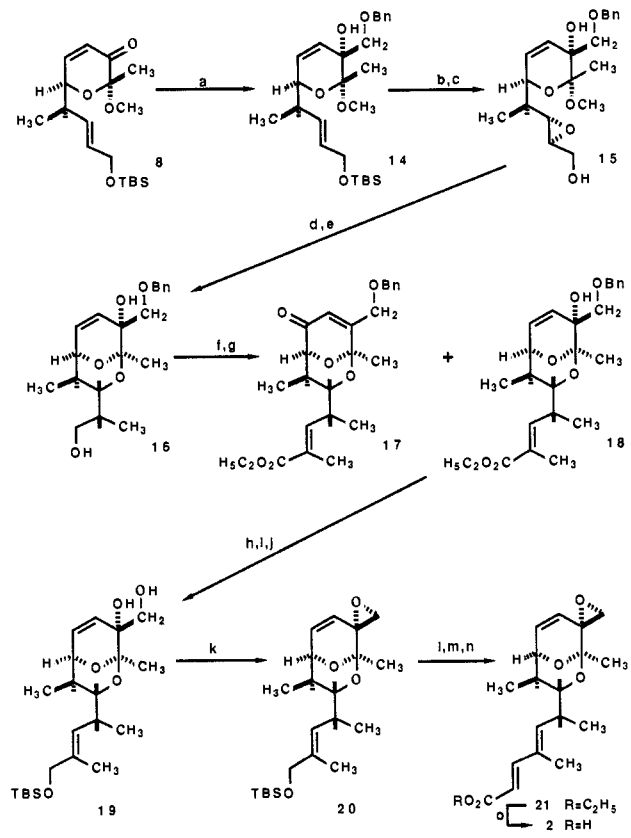
Standard reactions converted the ester to allylic alcohol **7** in excellent yield. Protection of this hydroxyl as a TBS ether then allowed deprotection of benzyl ether, which was accomplished with lithium di-*tert*-butylbiphenyl radical anion.[11] This novel application of the familiar reagent allowed almost quantitative removal of the benzyl group with no observable byproducts.[12]

Swern oxidation of the resulting alcohol provided the versatile enone **8** from which access to either the tirandamycic acid or the streptolic acid series was possible.

For synthesis in the former series (Scheme II) addition of either methyllithium or methylmagnesium iodide to this enone **8** or vice versa led exclusively to β-face (axial) attack and the formation of the tertiary alcohol **9** in excellent yield. This insensitivity toward reaction conditions suggests that addition to the carbonyl of the enone **8** is sterically controlled rather than chelation controlled.

Further transformations of this intermediate alcohol **9** require modification of the unsaturated side chain in the presence of the tertiary allylic alcohol in the pyran ring. In an effort to avoid a lengthy blocking–deblocking process, this operation was explored de novo. After removal of the TBS group, Sharpless oxidation[13]

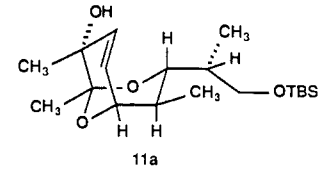
Scheme III. Streptolic Acid Synthesis[a]



[a] Reagents and conditions: (a) $BnOCH_2Li$, THF, −78 °C, 89%; (b) Bu_4NF, THF, 93%; (c) (+)-DIPT, $Ti(O\text{-}i\text{-}Pr)_4$, t-BuOOH, CH_2Cl_2, −20 °C, 90%; (d) $(CH_3)_2$ CuLi, Et_2O, 0 °C; (e) catalytic TsOH, $CHCl_3$, 68% from **15**; (f) PCC, CH_2Cl_2 (g) $C_2H_5O_2CC(CH_3)$=$P(C_6H_5)_3$, C_6H_6, 80 °C, 12 h, 61% from **16** (5% yield of **17**); (h) DIBAL, Et_2O, −78 °C, 95%; (i) (TBS)Cl, imidazole, DMF, 93%; (j) $Li^+[pip'\text{-}(t\text{-}Bu)_2(C_6H_5)_2]^{\bullet-}$, THF, −78 °C, 94%; (k) (tolylsulfonyl)imidazolide, NaH, THF, 0 °C, 96%; (l) Bu_4NF, THF, 97%; (m) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (n) $C_2H_5O_2CC(CH_3)$=$P(C_6H_5)_3$, CH_2C_2, 74% for two steps; (o) CH_3OH, 10% NaOH, 10% HCl quench, 86%.

led cleanly to the desired epoxide **10**. At this point it was possible to separate by chromatography the isomers that arose during the Claisen rearrangement.

Cleavage of the epoxide **10** with lithium dimethylcuprate and cyclization of the resulting crude triol led in an 81% yield to the desired bicyclic diol **11**, with which NMR spectral analysis, including NOE, proved that the methyl lithium addition to the unsaturated ketone **8** had indeed taken place from the β- (axial) face. Just as significant was the fact that PCC oxidation of this diol **11** proceeded smoothly to aldehyde-β-methylenone **12** in which process the tertiary allylic alcohol was oxidized with rearrangement. When a similar oxidative process was attempted earlier[14] with the epimeric tertiary alcohol **11a**, no oxidation was observed due to the steric congestion about this epimeric tertiary alcohol.



11a

Treatment of the crude aldehyde-β-methylenone **12** with (carbethoxyethylidene)triphenylphosphorane then led in good yield to the unsaturated ester **13**, which was identical with the intermediate prepared in the earlier[2] tirandamycic acid synthesis. This new approach, therefore, greatly facilitates this carbohydrate-based

(11) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924–1930. Ireland, R. E.; Norbeck, D. W.; Mandell, G. S.; Mandel, N. S. *J. Am. Chem. Soc.* **1985**, *107*, 3285–3294.

(12) Several other applications of this reagent for cleavage of benzyl ethers (cf. compound **18** on "conversion to" **19**) suggest that this is an excellent alternative to the Birch conditions generally used when an olefin precludes hydrogenolysis.

(13) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976. (b) Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 464–465.

(14) Wuts, P. G. M., unpublished observation in early synthesis work in these laboratories.

synthesis of tirandamycic acid and hence tirandamycic A as a result of the work of Bartlett.[7g]

For the streptolic acid **2** synthesis the enone **8** was also used as the starting point (Scheme III). The reaction of this enone[11] in the THF at −78 °C with [(benzyloxy)methyl]lithium[13] afforded essentially one product, the ether **14**, along with traces of a mixture of conjugate addition products. As expected, the major product was derived from axial attack of the nucleophile at the carbonyl. Thus, the requisite structural features for the sensitive allylic epoxide unit were efficiently and stereoselectively introduced.

Cleavage of the silyl ether with fluoride revealed the allylic alcohol unit for the application of the Sharpless asymmetric epoxidation.[13] As expected, epoxidation of the side chain led in a fast and selective manner to the epoxide **15**, and no epoxidation of the cyclic allylic alcohol was observed.[13] Opening of the epoxide with lithium dimethylcuprate in ether (0 °C) required 4–5 h due to the low solubility of the diol **15** substrate but provided the expected triol in good yield. This set up the cyclization, which occurred very readily with a trace of toluenesulfonic acid in $CHCl_3$ and gave a mixture of bicyclic ketals that corresponded to the methyl epimers obtained from the Claisen rearrangement. Careful chromatography at this point allowed separation of the diastereomers and provided the desired ketal **16** in a 68% yield from the epoxide **15**.

Development of the conjugated side chain began with oxidation of the primary alcohol (PCC) and addition of (carboxyethylidene)triphenylphosphorane. This provided the desired ester **18** in 60% yield (from the alcohol) along with ester **17**[15] derived from rearrangement of the tertiary allylic hydroxyl moiety caused by the chromium reagent.[16] Reduction of the ester **18** and silylation of the resulting hydroxyl allowed the unveiling of the vicinal diol system by removal of the benzyl protecting group with lithium di-*tert*-butylbiphenyl radical anion[11] treatment of this diol **19** with tosylimidazole and sodium hydride in the cold (0 °C),[17] which then gave the desired exocyclic epoxide **20**. Deprotection of the silyl ether, Swern oxidation, and addition of the stabilized Wittig reagent then provided the ethyl ester **21**, which on saponification afforded streptolic acid **2** (86% yield after chromatography on silica gel). This material was identical with the natural material.[18] Work is currently in progress to complete the synthesis of streptolydigin as well as analogues of the natural antibiotics.

Experimental Section

1,5-Anhydro-2-deoxy-3-*O*-propanoyl-4-*O*-benzyl-6-*O*-(*tert*-butyldimethylsilyl)-D-*gluco*-hex-1-enitol (3). This compound was prepared from tri-*O*-acetyl-D-glucal (Aldrich) by following the procedure of Ireland, Wuts, and Ernst.[2]

1,5-Anhydro-2-deoxy-3-*O*-propanoyl-4-*O*-benzyl-D-*gluco*-hex-1-enitol. Silyl ether **3** (692.7 mg, 1.71 mmol) was dissolved in 3.0 mL of THF and the resultant mixture cooled to 0 °C in an ice bath. Tetra-*n*-butylammonium fluoride trihydrate (642 mg, 2.03 mmol) dissolved in 5.0 mL of THF was added, and the mixture was stirred at 0 °C for 1 h. The reaction mixture was then diluted with 100 mL of ether and extracted twice with 25-mL portions of water. The product was purified by flash chromatography (20% ethyl acetate/petroleum ether eluant) providing 490 mg (98% yield) of colorless oil, which crystallized slowly (mp 43–45 °C). Analysis and spectral data: R_f 0.32 (4:1 petroleum ether/ethyl acetate); IR ($CHCl_3$) 3560, 1715, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (t, 3 H, J = 8 Hz), 2.23 (q, 2 H, J = 8 Hz), 2.3 (br s, 1 H), 3.8 (m, 4 H), 4.70 (s, 3 H), 5.50 (m, 1 H), 5.74 (m, 1 H), 6.36 (dd, $J_{1,2}$ = 6 Hz, $J_{1,3}$ = 1.5 Hz), 7.32 (s, 5 H); $[\alpha]^{23}_D$ −50.9° (*c* 1.52, $CHCl_3$). Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.80; H, 7.00.

1,5-Anhydro-2-deoxy-3-*O*-propanoyl-4-*O*-benzyl-6-*O*-[(4-methylphenyl)sulfonyl]-D-*gluco*-hex-1-enitol. The (hydroxymethyl)dihydropyran (5.44 g, 18.6 mmol) was added to 25 mL of pyridine cooled to 0 °C. Crystalline *p*-toluenesulfonyl chloride (11.0 g, 57.6 mmol) was added, and the suspension was stirred to dissolve it. The reaction was then allowed to warm to ambient temperature and stirred overnight. Judged complete by TLC, the reaction was then poured into 300 mL of dichloromethane and extracted with three 150-mL portions of saturated copper sulfate solution, 150 mL of ammonium chloride, 150 mL of sodium bicarbonate, and 100 mL of brine. The organic layer was then dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was chromatographed (15% ethyl acetate/petroleum ether) to provide 7.45 g (90% yield) of the tosylate. Analysis and spectral data: R_f 0.46 (4:1 petroleum ether/ethyl acetate); IR ($CHCl_3$) 1720, 1638, 1168 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11 (t, 3 H, J = 8 Hz), 2.25 (q, 2 H), J = 8 Hz), 2.42 (s, 3 H), 3.78 (dd, 1 H, $J_{3,4}$ = 6 Hz, $J_{4,5}$ = 8 Hz), 4.1 (m, 1 H), 4.27 (m, 2 H), 4.62 (s, 2 H), 4.71 (m, 1 H), 5.3 (m, 1 H), 6.23 (d, 1 H, J = 6 Hz), 7.3 (m, 7 H), 7.78 (m, 2 H); $[\alpha]^{23}_D$ −9.1° (*c* 1.20, $CHCl_3$). Anal. Calcd for $C_{23}H_{26}O_7S$: C, 61.87; H, 5.87. Found: C 61.79; H, 5.86.

4(*R*)-(Propanoyloxy)-5(*S*)-(benzyloxy)-6-methylenedihydro-4*H*-pyran (4). Freshly prepared tosylate above (7.44 g, 16.6 mmol) was dissolved in 35 mL of methyl ethyl ketone, and the flask was wrapped with foil to exclude light. Sodium iodide (17.0 g, 113 mmol) was added, and the suspension was immersed in a heating oil bath equilibrated at 80 °C. The red suspension was stirred at this temperature for 4 h, allowed to cool to room temperature, and diluted with 400 mL of dichloromethane. Water (100 mL) was added to give two phases with no precipitates. The layers were separated, and the organic solution was shaken with 50 mL of sodium sulfite. This reductive process was repeated giving an almost colorless solution, which was washed with brine and dried with $MgSO_4$. The resultant slightly yellow crude iodide (6.07 g, clean by TLC and NMR) was used in the next reaction without further purification.

Benzene (50 mL) was added to the crude iodide. Diazabicycloundecene (DBU; 4.5 mL, 30.1 mmol) was also added, and the reaction flask was wrapped with foil. This solution was then heated in an 84 °C oil bath for 4 h. (The reaction could not be monitored by TLC because the starting iodide had the same R_f as the product. Subsequent experiments indicated that the reaction was complete in less than 1 h.) The solvent was then removed under reduced pressure, and the residue was flash chromatographed, eluting with 5% ethyl acetate/petroleum ether, to give 3.92 g (86% yield from the tosylate) of the divinyl ether **4**. Analysis and spectral data: R_f 0.26 (10:1 petroleum ether/ethyl ether); IR ($CHCl_3$) 1715, 1638 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (t, 3 H, J = 8 Hz), 2.21 (q, 2 H, J = 8 Hz), 3.89 (m, 1 H), 4.49 (s, 1 H), 4.54 (q, 2 H, J = 11 Hz), 4.89 (d, 1 H, J = 1 Hz), 5.0 (m, 2 H), 6.45 (d, 1 H, J = 5 Hz), 7.30 (s, 5 H); $[\alpha]^{23}_D$ −122° (*c* 4.62, $CHCl_3$). Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 69.91; H, 6.59.

Methyl 2(*S*)-[(1*R*)-3-Methylene-4(*S*)-(benzyloxy)-1,4-dihydro-3*H*-pyranyl]propanoate (5a,b). Hexamethyldisilazane (3.40 mL, 16.3 mmol) in 30 mL of THF was cooled to −78 °C and *n*-BuLi (5.9 mL of a 2.55 M solution in hexanes, 15.0 mmol) was added dropwise with stirring. After the mixture was stirred for 10 min more, *tert*-butyldimethylsilyl chloride [(TBS)Cl; 2.45 g, 16.2 mmol] dissolved in 10 mL of hexamethylphosphoramide (HMPA) was added, and the reaction solution was stirred for 3 min. Divinyl ether **4** (2.05 g, 7.48 mmol) dissolved in 4.0 mL of THF was then added dropwise over 2 min, and after 5 min more the reaction was allowed to warm slowly. When the reaction was at about 0 °C (as judged by the melting of the frost condensed on the flask), the mixture was poured into 300 mL of petroleum ether layered on 200 mL of ice–water in a separatory funnel. This mixture was shaken until both layers had cleared, and then it was quickly separated. The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure.

The residue was briefly dried under high vacuum, and 20 mL of benzene was added. After this solution was refluxed for 1 h to allow the silyl ketene acetal to rearrange, the solvent was again removed, and 10 mL of HMPA was added. Potassium fluoride dihydrate (2.2 g, 23 mmol) and potassium bicarbonate (2.2 g, 22 mmol) were added to hydrolyze the silyl ester resulting from Claisen rearrangement. After 5 min of stirring this suspension at room temperature, methyl iodide (2.5 mL, 40 mmol) was added, and the reaction was stirred overnight at ambient temperature to methylate the potassium carboxylate. The reaction was then diluted with 100 mL of ether and extracted with two 100-mL portions of water and then with 100 mL of brine. The clear solution was dried over $MgSO_4$, the solvent was removed on a rotary evaporator, and the residue was flash chromatographed, eluting with 15% ethyl acetate/petroleum ether. This provided 1.832 g (85% yield) of the desired ethers **5a** and **5b** as an inseparable mixture of methyl epimers.

Methyl 2(*S*)-[(1*R*)-3(*R*)-Methoxy-3-methyl-4(*S*)-(benzyloxy)-1,4-dihydro-3*H*-pyranyl]propanoate (6a,b). The enol ether products from several Claisen rearrangements were combined to give 9.50 g of crude

(15) Prolonged exposure to PCC provides **17** as the major product. This provides the top half functionality for a synthesis of tirandamycin B.[7b]

(16) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682–685.

(17) Ireland, R. E.; Courtney, L.; Fitzsimmons, B. F. *J. Org. Chem.* **1983**, *48*, 5186–5198.

(18) Spectral data match those published. The synthetic sample exhibited mp 168–169 °C (lit.[2] 168–170 °C) and $[\alpha]^{22}_D$ +138° (*c* 0.55, 95% ethanol) [lit.[2] $[\alpha]^{26}_D$ +147° (*c* 1.22, 95% ethanol)]. A satisfactory combustion analysis was also obtained.

material, which was dissolved in 120 mL of methanol. A few small crystals of anhydrous *p*-toluenesulfonic acid were added, and the reaction was stirred overnight at ambient temperature. Ether (500 mL) was then added, and the solution was extracted with four 200-mL portions of saturated sodium bicarbonate solution and 50 mL of brine. The yellow organic solution was then dried with $MgSO_4$, and the solvent was removed under reduced pressure. Flash chromatography of the residue resulted in isolation of 3.08 g (29% yield) of the minor anomeric ketals **6b** and 7.40 g (70% yield) of the mixed major anomers **6a**. This represented Claisen rearrangements starting with a total of 38.6 mmol and therefore constituted an 85% yield from the divinyl ether. The minor anomer was readily recycled by treatment with catalytic *p*-toluenesulfonic acid in methanol. (It is noteworthy that an anomeric ratio of 4.0:1 was usually observed for this ketalization. This particular reaction provided the anomers in a 2.4:1 ratio, which was probably due to stopping the reaction before equilibrium had been established.) Analysis and spectral data: R_f 0.18 (9:1 petroleum ether/ethyl acetate); IR ($CHCl_3$) 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (d, 3 H, J = 8 Hz), 1.34 (s, 3 H), 2.5 (m, 1 H), 3.30 (s, 3 H), 3.65 (s, 3 H), 3.81 (m, 1 H), 4.38 (m, 1 H), 4.55 (AB, 1 H, J = 10 Hz), 4.70 (AB, 1 H, J = 10 Hz), 5.69 (m, 2 H), 7.30 (s, 5 H). Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.52; H, 7.59.

2(*S*)-[(1*R*)-3(*R*)-Methoxy-3-methyl-4(*S*)-(benzyloxy)-1,4-dihydro-3*H*-pyranyl]propan-1-ol. The major anomer from ketalization (**6a** mixed; 19.7 g, 61.6 mmol) was dissolved in 400 mL of ether and cooled to −78 °C with stirring. A hexane solution of DIBAL-H (160 mL of a 1 M solution) was added in 20-mL portions via syringe. After being stirred for 1 h in a dry ice bath, the bath was removed and the reaction was allowed to warm to ambient temperature. Methanol (15 mL) was carefully added, resulting in a milky suspension. More ether (300 mL) was added followed by 500 mL of 0.5 M aqueous sodium potassium tartrate solution. This biphasic mixture was stirred overnight at room temperature and then separated. The aqueous layer was extracted with 50 mL of ether, and the combined organic layers were dried over anhydrous sodium sulfate. The solvent was removed with a rotary evaporator to give the crude alcohol, which was normally used for the next reaction without further purification. Analysis and spectral data: R_f 0.16 (7:3 petroleum ether/ethyl acetate); IR ($CHCl_3$) 3500 cm^{-1} (br); ^1H NMR ($CDCl_3$) δ 0.90 (d, 3 H, J = 8 Hz), 1.48 (s, 3 H), 2.1 (br s, 1 H), 3.32 (s, 3 H), 3.60 (d, 2 H, J = 5 Hz), 3.87 (m, 1 H), 4.22 (m, 1 H), 4.57 (AB, 1 H, J = 12 Hz), 4.73 (AB, 1 H, J = 12 Hz), 5.74 (m, 2 H), 7.35 (s, 5 H). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.97; H, 8.36.

Ethyl 4(*R*)-[(1*S*)-3(*R*)-Methoxy-3-methyl-4(*S*)-(benzyloxy)-1,4-dihydro-3*H*-pyranyl]pent-2(*Z*)-enoate. Dichloromethane (300 mL) was cooled to −78 °C and 7.0 mL of oxalyl chloride (80 mmol) was added with stirring. Dimethyl sulfoxide (DMSO; 7.0 mL, 99 mmol) was then added dropwise over 7 min. After the resultant mixture was stirred for 20 min, the alcohol from the preceding experimental procedure dissolved in 20 mL of dichloromethane was added over 5 min. This was stirred for 30 min, giving a milky suspension to which Hunig's base (28 mL, 160 mmol) was added. The dry ice bath was removed, and the reaction was allowed to warm slowly. When it had reached approximately 0 °C, (carbethoxymethylene)triphenylphosphorane (30.3 g, 87 mmol) was added as a crystalline solid. The reaction was stirred overnight at ambient temperature. Workup of the reaction consisted of dilution with 500 mL of ether and extraction with 200 mL of water and then 200 mL of brine. The solvent was removed under reduced pressure, and the residue was flash chromatographed (eluting with 20% ethyl acetate/petroleum ether) to give a trace of material that appeared to be the *E*-olefin and 19.4 g (87% yield based on the methyl esters **6a**) of the desired product, which was homogeneous by TLC and NMR. Analysis and spectral data: R_f 0.27 (4:1 petroleum ether/ethyl acetate); IR ($CHCl_3$) 1700 (br), 1647 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (d, 3 H, J = 7 Hz), 1.17 (t, 3 H, J = 7 Hz), 1.40 (s, 3 H), 2.5 (m, 1 H), 3.30 (s, 3 H), 3.8 (m, 1 H), 3.95 (m, 1 H), 4.15 (q, 2 H, J = 7 Hz), 4.56 (AB, 1 H, J = 12 Hz), 4.70 (AB, 1 H, J = 12 Hz), 5.73 (m, 2 H), 5.80 (d, 1 H, J 16 Hz), 6.96 (dd, 1 H, $J_{3,4}$ = 8 Hz, $J_{2,3}$ = 16 Hz), 7.35 (s, 5 H). Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.98; H, 7.83. Found: C, 69.82; H, 7.74.

4(*R*)-[(1*S*)-3(*R*)-Methoxy-3-methyl-4(*S*)-(benzyloxy)-1,4-dihydro-3*H*-pyranyl]pent-2(*E*)-en-1-ol (7). The unsaturated ester (19.4 g, 53.9 mmol) above was dissolved in 300 mL of ether and cooled to −78 °C. DIBAL-H was added (130 mL of a 1 M solution in hexanes, 130 mmol) via syringe in portions, and the reaction was stirred for 1 h. It was then allowed to warm to about 0 °C and was quenched slowly with methanol. Ether (200 mL) was then added followed by addition of 300 mL of 0.5 M sodium potassium tartrate solution. The biphasic mixture was stirred overnight at room temperature and was then separated. The aqueous layer was washed with 50 mL of ether, and the combined organic solutions were dried over anhydrous magnesium sulfate. Removal of the solvent and flash chromatography of the residue gave 16.4 g (96% yield) of the alcohol **7** as a colorless, viscous oil. Analysis and spectral data: R_f 0.19 (3:2 petroleum ether/ethyl acetate); IR ($CHCl_3$) 3590, 3440 (br), 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (d, 3 H, J = 7 Hz), 1.36 (s, 3 H), 2.2 (m, 1 H), 3.29 (s, 3 H), 3.8 (m, 2 H), 4.1 (br s, 3 H), 4.56 (AB, 1 H, J = 13 Hz), 4.68 (AB, 1 H, J = 13 Hz), 5.70 (m, 4 H), 7.32 (s, 5 H). Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.73; H, 8.19.

1-[(*tert*-Butyldimethylsilyl)oxy]-4(*R*)-[(1*S*)-3(*R*)-methoxy-3-methyl-4(*S*)-(benzyloxy)-1,4-dihydro-3*H*-pyranyl]pent-2(*E*)-ene. The allylic alcohol **7** (16.4 g, 51.6 mmol) was dissolved in 50 mL of dichloromethane and 50 mL of dimethylformamide. Imidazole (4.3 g, 63.2 mmol) was added followed by the *tert*-butyldimethylsilyl chloride (9.4 g, 62.5 mmol). The reaction was complete by TLC in 30 min at room temperature. It was then diluted with 300 mL of ether and washed twice with 100-mL portions of water and then with 100 mL of sodium bicarbonate solution. The solution was dried ($MgSO_4$), and the solvent was removed with a rotary evaporatory. Flash chromatography of the residue, eluting with 10% ethyl acetate/petroleum ether, provided 21.6 g (97% yield) of the silyl ether as a colorless oil. Analysis and spectral data: R_f 0.29 (9:1 petroleum ether/ethyl acetate); IR ($CHCl_3$) 1060–1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (s, 6 H), 0.88 (s, 9 H), 0.98 (d, 2 H, J = 7 Hz), 1.32 (s, 3 H), 2.2 (m, 1 H), 3.25 (s, 3 H), 3.8 (m, 2 H), 4.06 (d, 2 H, J = 3 Hz), 4.49 (AB, 1 H, J = 12 Hz), 4.65 (AB, 1 H, J = 12 Hz), 5.5 (m, 2 H), 5.70 (s, 2 H), 7.30 (s, 5 H). Anal. Calcd for $C_{25}H_{40}O_4Si$: C, 69.40; H, 9.32. Found: 69.45; H, 9.22.

1-[(*tert*-Butyldimethylsilyl)oxy]-4(*R*)-[(1*S*)-3(*R*)-methoxy-3-methyl-4(*S*)-hydroxy-1,4-dihydro-3*H*-pyranyl]pent-2(*E*)-ene. The lithium di-*tert*-butylbiphenyl radical anion reagent solution[9] was prepared as follows: 32 g (0.12 mol) of *p,p'*-di-*tert*-butylbiphenyl was dissolved in 700 mL of THF with careful exclusion of oxygen and moisture. Lithium wire (1.0 g, 0.14 mol) in 0.5-cm pieces (which had been washed with petroleum ether to remove oil, immersed in methanol to clean the surface, rinsed in ether, and then submerged in anhydrous THF while being mashed with pliers) was added. This mixture was stirred vigorously at room temperature until dark green radical anion developed, at which time the reaction was cooled in an ice bath. Stirring was continued at 0 °C for 6 h more before the reagent was used.

The silyl ether substrate (21.40 g, 49.5 mmol) was dissolved in 400 mL of THF and cooled to −78 °C in a dry ice/acetone bath with stirring. The dark green reagent solution was added in portions via syringe, allowing 4–5 min between additions for cooling, until the dark green color persisted in the reaction. At this time the reaction was judged complete by TLC and was quenched with aqueous ammonium chloride. It was allowed to warm to room temperature, diluted with 400 mL of 1:1 ether/petroleum ether, and separated. Drying over magnesium sulfate was followed by filtration and removal of the solvent in vacuo. The residue was purified by flash chromatography, eluting with 15% ethyl acetate/petroleum ether. This resulted in recovery of most of the di-*tert*-butylbiphenyl, which could be reused after a single recrystallization from ethanol, and isolation of 16.4 g (97% yield) of the desired debenzylated material as a colorless oil. Analysis and spectral data: R_f 0.17 (9:1 petroleum ether/ethyl acetate); IR ($CHCl_3$) 3540, 1050, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.07 (s, 6 H), 0.90 (s, 9 H), 0.99 (d, 3 H, J = 7 Hz), 1.40 (s, 3 H), 2.2 (m, 2 H), 3.27 (s, 3 H), 3.7–4.0 (m, 2 H), 4.10 (d, 2 H, J = 4 Hz), 5.6 (m, 5 H). Anal. Calcd for $C_{18}H_{34}O_4Si$: C, 63.11; H, 10.00. Found: C, 63.19; H, 9.82.

1-[(*tert*-Butyldimethylsilyl)oxy]-4(*R*)-4(*R*)-)(1*S*)-3(*R*)-methoxy-3-methyl-4-oxo-1,4-dihydro-3*H*-pyran-1-yl]pent-2(*E*)-ene (8). A 100-mL two-necked flask equipped with a magnetic stirring bar was charged with 60 mL of dichloromethane and cooled in a dry ice/acetone bath. Oxalyl chloride (1.20 mL, 13.7 mmol) was added via syringe followed by dimethyl sulfoxide (1.10 mL, 15.5 mmol), which was added dropwise. After this mixture was stirred for 20 min, the alcohol **7** (3.95 g, 11.5), dissolved in 5 mL of dichloromethane, was added, and stirring was continued for 30 min more. Hunig's base (5.0 mL, 28.8 mmol) was added, and the reaction mixture was allowed to warm to room temperature. This mixture was then diluted with ether (150 mL) and extracted with water (50 mL) and then with two 50-mL portions of brine. The organic layer was then dried ($MgSO_4$). The solvent was removed with a rotary evaporator, and the residue was flash chromatographed. The column was eluted first with 10% ethyl acetate/petroleum ether and then with 15% ethyl acetate/petroleum ether to give the enone **8** as a colorless oil (3.65 g, 93% yield). Analysis and spectral data: R_f 0.63 (6:1 petroleum ether/ethyl acetate); IR ($CHCl_3$) 1680, 1120, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (s, 6 H), 0.90 (s, 9 H), 1.08 (d, 3 H, J = 7 Hz), 1.43 (s, 3 H), 2.5 (m, 1 H), 3.30 (s, 3 H), 4.2 (m, 3 H), 5.6 (m, 2 H), 5.96 (dd, 1 H, $J_{2',3'}$ = 3 Hz, $J_{3',4'}$ = 11 Hz), 6.91 (dd, 1 H, $J_{3',4'}$ = 11 Hz, $J_{2',4'}$ = 1.5 Hz). Anal. Calcd for $C_{18}H_{32}O_4Si$: C, 63.49; H, 9.47. Found: C, 63.56; H, 9.47.

1-[(*tert*-Butyldimethylsilyl)oxy]-4(*R*)-[(1*S*)-3(*R*)-methoxy-3,4(*S*)-dimethyl-4-hydroxy-1,4-dihydro-3*H*-pyran-1-yl]pent-2(*E*)-ene (9). THF (2.5 mL) was cooled to −78 °C, and 0.25 mL of a 1 M solution of methyllithium (MeLi) in ether was added. The enone **8** (107 mg, 0.31 mmol) dissolved in 2.0 mL of THF was added by syringe. After this solution was stirred for 15 min, the starting material had been consumed (judging by TLC). The reaction was quenched with methanol and diluted with 100 mL of ether. It was then washed with 25 mL of NH_4Cl and 25 mL of water and dried over $MgSO_4$. Flash chromatography, eluting with 10% ethyl acetate/petroleum ether, provided 107 mg (96%) of analytically pure alcohol **9**. Analysis and spectral data: R_f 0.50 (15% ethyl acetate/petroleum ether); IR ($CHCl_3$) 3520, 1090, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (s, 6 H), 0.88 (s, 9 H), 0.99 (d, 3 H, J = 6 Hz), 1.19 (s, 3 H), 1.31 (s, 3 H), 2.3 (m, 1 H), 2.73 (s, 1 H), 3.29 (s, 3 H), 3.78 (m, 1 H), 4.09 (d, 2 H, J = 3 Hz), 5.56 (m, 4 H). Anal. Calcd for $C_{19}H_{36}O_4Si$: C, 64.00; H, 10.18. Found: C, 64.05; H, 10.18.

4(*R*)-[(1*R*)-3(*R*)-Methoxy-3,4(*S*)-dimethyl-4-hydroxy-1,4-dihydro-3*H*-pyran-1-yl]pent-2(*E*)-en-1-ol (10). A sample of the alcohol **9** (3.465 g, 9.73 mmol) was dissolved in 15 mL of THF, and 12 mL of a 1 M solution of Bu_4NF in THF was added. The reaction solution turned orange in 1–2 min, and no starting material could be detected by TLC after 20 min. The reaction was then diluted with 400 mL of ether and extracted with two 100-mL portions of brine. The clear solution thus obtained was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. Flash chromatography, eluting with 50% ethyl acetate/petroleum ether, provided 2.320 g (99%) of the deprotected alcohol. Analysis and spectral data: R_f 0.19 (3:2 petroleum ether/ethyl acetate); IR ($CHCl_3$) 3519, 3430, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (d, 3 H, J = 7 Hz), 1.20 (s, 3 H), 1.33 (s, 3 H), 2.3 (m, 1 H), 2.5 (br s, 1 H), 2.9 (br s, 1 H), 3.30 (s, 3 H), 2.9 (br s, 1 H), 3.30 (s, 3 H), 3.81 (d, 1 H, J = 5 Hz), 4.06 (m, 2 H), 5.56 (m, 4 H). Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.24; H, 9.05.

4(*R*)-[(1*S*)-3(*R*)-Methoxy-3,4(*S*)-dimethyl-4-hydroxy-1,4-dihydro-3*H*-pyran-1-yl]-2(*S*),3(*S*)-epoxypentan-1-ol (10). The allylic alcohol obtained from the preceding procedure (2.32 g, 9.59 mmol) was dissolved in 80 mL of CH_2Cl_2 and cooled to −40 C. (+)-DIPT (2.8 mL, 13.3 mmol) was added, followed by 3.30 mL of $Ti(OR)_4$ (11.1 mmol). This solution was then stirred for 10 min before 6.0 mL of 4 M *t*-BuOOH in CH_2Cl_2 was added (24 mmol). The solution was then transferred to a −20 °C freezer and left there overnight. Dimethyl sulfide (2 mL) was added to consume the excess oxidant, and the solution was kept at −20 °C for an additional 4 h. It was then stirred vigorously with 3.5 mL of saturated Na_2SO_4 for 1 h and filtered through a pad of Celite. The solvents were removed from the filtrate under reduced pressure, and the residue was flash chromatographed, eluting with 50% ethyl acetate/petroleum ether, to provide 1.65 g of the desired epoxide **10** and some material mixed with a byproduct. Rechromatographing the mixture provided 0.20 g more of the desired product and a pure sample of the byproduct, which was identified as the methyl epimer carried along from the Claisen rearrangement. The epimer was thus obtained in 7% yield and the desired epoxide **10** in 75% yield, and a small uantity of the starting material was also recovered. Analysis and spectral data: R_f 0.17 (1:1 petroleum ether/ethyl acetate); IR ($CHCl_3$) 3520, 1110, 1076 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (d, 3 H, J = 7 Hz), 1.25 (s, 3 H), 1.38 (s, 3 H), 1.9 (br m, 2 H), 2.79 (s, 1 H), 2.9–3.1 (m, 2 H), 3.35 (s, 3 H), 3.7 (m, 1 H), 4.15 (m, 2 H), 5.3–5.7 (m, 2 H). Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58. Found: C, 60.30; H, 8.41.

4(*R*)-[(1*S*)-3(*R*)-Methoxy-3,4(*S*)-dimethyl-4-hydroxy-1,4-dihydro-3*H*-pyran-1-yl]-2(*R*)-methylpentane-1,3(*R*)-diol. Copper bromide–dimethyl sulfide complex (13.5 g, 65.7 mmol) was suspended in 20 mL of ether and cooled to 0 °C with stirring. A 1 M solution of MeLi in Et_2O was added slowly until the orange precipitate that formed had disappeared.

The epoxide **10** (1.65 g, 6.40 mmol) was dissolved in 10 mL of Et_2O and added slowly to the stirred lithium dimethylcuprate solution. After stirring the yellow-orange suspension for 4 h at 0 °C, it was diluted with ether (300 mL) and carefully quenched with aqueous NH_4Cl. The layers were separated. The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. Drying overnight under vacuum (0.1 mm) gave 1.68 g of an oily crystalline material, which was clean by TLC (ethyl acetate). Analysis and spectral data: R_f 0.35 (ethyl acetate); IR ($CHCl_3$) 3450, 1150, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (d, 3 H, J = 7 Hz), 0.99 (d, 3 H, J = 7 Hz), 1.25 (s, 3 H, 1.36 (s, 3 H), 1.8 (m, 3 H), 2.68 (s, 1 H), 3.35 (s, 3 H), 3.5 (m, 4 H), 4.31 (m, 1 H), 5.35 (dd, 1 H, J_1 = 1.5 Hz, J_2 = 10 Hz), 5.64 (dd, 1 H, J_1 = 2 Hz, J_2 = 10 Hz); mp 115–116 °C. Anal. Calcd for $C_{14}H_{26}O_5$: C, 61.29; H, 9.55. Found: C, 61.10; H, 9.58.

2(*R*)-[(1*R*)-4-Hydroxy-3(*R*),4(*S*),8(*S*)-trimethyl-2,9-dioxabicyclo-[3.3.1]non-5(*Z*)-en-1-yl]propan-1-ol (11). The above crude triol from the preceding procedure was dissolved in 70 mL of $CHCl_3$, and a few small crystals of *p*-TsOH were added. After being stirred for 2.5 h, solid anhydrous Na_2CO_3 was added and the suspension was stirred for an additional 2 h. The solids were removed by filtration, and the filtrate was concentrated under reduced pressure. Flash chromatography, eluting with 40% ethyl acetate/petroleum ether, provided 1.03 g of white crystalline material along with 410 mg of mixed material. Rechromatography of the mixed material provided an additional 0.23 g of the desired bicyclic diol **11** (total yield 81% from the epoxide **10**). Analysis and spectral data: R_f 0.25 (1:1 petroleum ether/ethyl acetate); IR ($CHCl_3$) 3520, 1100, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.71 (d, 3 H, J = 7 Hz), 1.11 (d, 3 H, J = 8 Hz), 1.20 (s, 3 H), 1.41 (s, 3 H), 1.8 (m, 1 H), 1.95 (s, 2 H), 2.2 (m, 1 H), 3.5 (m, 2 H), 3.89 (dd, 1 H, J_1 = 4 Hz, J_2 = 11 Hz), 4.2 (m, 1 H), 5.82 (dd, 1 H, J_1 = 4 Hz, J_2 = 10 Hz, 6.02 (d, 1 H, J = 10 Hz); mp 116–118 °C (lit.[19] 124 °C). Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.40; H, 9.22.

Ethyl 4(*R*)-[(1*R*)-3(*S*),4,8(*R*)-Trimethyl-6-oxo-2,9-dioxabicyclo-[3.3.1]non-4(*Z*)-en-1-yl]-2-methylpent-2(*E*)-enoate (13). The bicyclic diol **11** (39.8 mg, 0.16 mmol) was dissolved in 1.0 mL of CH_2Cl_2. Celite (210 mg) was added followed by PCC (198 mg, 0.92 mmol). The suspension was stirred at 20 °C for 4 h, at which time all of the starting material had been consumed (judging by TLC); one major spot, which was UV-active, was observed at R_f 0.62 (40% ethyl acetate/petroleum ether). The reaction solution was diluted with ether (100 mL) and washed with 20-mL portions of NH_4Cl, $NaHCO_3$, and brine. After drying over $MgSO_4$, the solvent was removed with a rotary evaporator, and the crude aldehydic ketone was used directly in the next experiment.

Benzene (1.0 mL) was added to this crude material. To this solution, 316 mg (0.87 mmol) of (carbethoxyethylidene)triphenylphosphorane was added, and the yellow solution was heated at 80 °C overnight. The reaction mixture was then poured directly onto a chromatography column and eluted with 12% ethyl acetate/petroleum ether. Along with unidentified byproducts, including some unreacted aldehyde, one major product was obtained (20.0 mg, 38% from **11**). Spectral comparisons of this product with the same intermediate in syntheses of tirandaymcic acid[2] and tirandamycin A confirmed its identity as the desired compound.

1-[(*tert*-Butyldimethylsilyl)oxy]-4(*R*)-[(1*S*)-3(*R*)-methoxy-3-methyl-4(*R*)-[(benzyloxy)methyl]-4-hydroxy-1,4-dihydro-3*H*-pyran-1-yl]pent-2(*E*)-ene (14). [(Benzyloxy)methyl]tri-*n*-butyltin was prepared by Still's procedure.[19] This material (5.4 g, 13 mmol) was dissolved in 120 mL of THF and the solution cooled to −78 °C. *n*-Butyllithium (5.0 mL of a 2.4 M hexane solution, 12 mmol) was then added dropwise, giving a pale yellow solution. This was stirred for 15 min.

The enone **8** (3.55 g, 10.4 mmol), dissolved in 15 mL of THF, was added to the above solution over 15 min. After 10 min more the reaction was complete as judged by TLC. It was then allowed to warm to room temperature, diluted with 200 mL of ether, and extracted twice with 100-mL aliquots of saturated ammonium chloride solution. The clear organic layer was then dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash chromatography of the residue, eluting with 20% ethyl acetate/petroleum ether, allowed isolation of 4.05 g of pure addition product **14** and some product contaminated with a slower moving material. Rechromatography of the mixed material gave 0.25 g more of the desired alcohol **14** for a total yield of 4.30 g (89%). The slower product proved to be an inseparable mixture of two conjugate addition products (identified by ^1H NMR and IR). Neither this mixture nor the major product (examined by 400-MHz ^1H NMR) contained a detectable quantity of the product corresponding to addition to [(benzyloxy)methyl]lithium to the opposite face of the enone. Analysis and spectral data: R_f 0.32 (6:1 petroleum ether/ethyl acetate); IR ($CHCl_3$) 3540, 1090, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (s, 6 H), 0.90 (s, 9 H), 0.96 (d, 3 H, J = 7 Hz), 1.30 (s, 3 H), 2.2 (m, 1 H), 2.87 (s, 1 H), 3.28 (s, 3 H), 3.43 (AB, 1 H, J = 10 Hz), 3.61 (AB, 1 H, J = 10 Hz), 3.82 (d, 1 H, J = 5 Hz), 4.08 (d, 2 H, J = 3 Hz), 4.57 (m, 2 H), 5.6 (m, 2 H), 5.70 (s, 2 H). Anal. Calcd for $C_{26}H_{42}O_5Si$: C, 67.49; H, 9.15. Found: C, 67.58; H, 9.13.

4(*R*)-[(1*R*)-3(*R*)-Methoxy-3-methyl-4(*R*)-[(benzyloxy)methyl]-4-hydroxy-1,4-dihydro-3*H*-pyran-1-yl]pent-2(*E*)-en-1-ol (15). A 4.00-g (8.66 mmol) sample of the silyl ether **14** was dissolved in 10 mL of THF and cooled to 0 °C. A 1 M solution of tetra-*n*-butylammonium fluoride (Aldrich; 10 mL, 10 mmol) was added slowly, and the reaction was stirred for 30 min. It was then allowed to warm to room temperature and stirred for 1 h more, at which time it was then diluted with 300 mL of ether and extracted twice with 100-mL portions of water and then with 50 mL of brine. The organic solution was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Elution from a flash chromatography column with 60% ethyl acetate/petroleum ether gave the desired primary alcohol (2.79 g) in 93% yield as a viscous oil. Analysis and spectral data: R_f 0.13 (3:2 petroleum ether/ethyl acetate);

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IR ($CHCl_3$) 3540, 1100, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (d, 3 H, J = 7 Hz), 1.32 (s, 3 H), 1.5 (br s, 1 H), 2.3 (m, 1 H), 2.9 (s, 1 H), 3.29 (s, 3 H), 3.46 (AB, 1 H, J = 10 Hz), 3.61 (AB, 1 H, J = 10 Hz), 3.85 (d, 1 H, J = 5 Hz), 4.03 (br s, 2 H , 4.48 (AB, 1 H, J = 12 Hz), 4.57 (AB, 1 H, J = 12 Hz), 5.6 (m, 4 H), 7.35 (s, 5 H). Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.82; H, 8.17.

4(*R*)-[(1*R*)-3(*R*)-Methoxy-3-methyl-4(*R*)-[(benzyloxy)methyl]-4-hydroxy-1,4-dihydro-3*H*-pyran-1-yl]-2(*S*),3(*S*)-epoxypentan-1-ol (15). The allylic alcohol (2.64 g, 7.59 mmol) was dissolved in 30 mL of dichloromethane, and the solution was cooled to −40 °C. (+)-Diisopropyl tartrate (2.40 mL, 11.4 mmol) was then added via syringe; this was followed by addition of titanium tetraisopropoxide (2.7 mL, 9.1 mmol) with stirring. The solution was stirred for 5 min more, 5.7 mL of 4 M *tert*-butyl hydroperoxide in dichloromethane (23 mmol) was added, and the reaction vessel was sealed and transferred to a freezer maintained at −20 °C. After 5 h the reaction was judged complete by TLC, and the excess oxidant was quenched by addition of 2 mL of dimethyl sulfide to the mixture in the freezer. The reaction mixture was removed from the freezer 1 h later and stirred at room temperature with 2 mL of saturated aqueous sodium sulfate until the slurry became nearly solid. It was then diluted with ether and filtered through a Celite pad. The solids and Celite were washed alternately with dichloromethane and ether and then with dichloromethane and THF until the washings contained no more product by TLC. The combined organic layers were dried ($MgSO_4$), and the solvent was evaporated. Flash chromatography of the crude product, eluting with 60% ethyl acetate/petroleum ether, allowed isolation of 2.482 g (90% yield) of the epoxy alcohol **15** as a very viscous oil. Analysis and spectral data: R_f 0.35 (2:3 petroleum ether/ethyl acetate). IR ($CHCl_3$) 3540, 1105, 1062 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (d, 3 H, J = 7 Hz), 1.30 (s, 3 H), 1.7 (br s, 1 H), 2.8–3.1 (m, 3 H), 3.30 (s, 3 H), 3.5–3.8 (m, 4 H), 4.13 (m, 1 H), 4.51 (AB, 1 H, J = 12 Hz), 4.59 (AB, 1 H, J = 12 Hz), 5.7 (m, 2 H), 7.30 (s, 5 H). Anal. Calcd for $C_{20}H_{28}O_6$: C, 65.92; H, 7.74. Found: C, 65.89, H, 7.69.

4(*R*)-[(1*S*)-3(*R*)-Methoxy-3-methyl-4(*R*)-[(benzyloxy)methyl]-4-hydroxy-1,4-dihydro-3*H*-pyran-1-yl]-2(*R*)-methylpentane-1,3(*R*)-diol. Copper bromide–dimethyl sulfide complex (7.53 g, 36.6 mmol) was suspended in 15 mL of ether with stirring and was cooled to 0 °C. To this mixture was added in portions a 1.5 M solution of methyllithium in ether until the yellow precipitate that formed had almost completely disappeared. After this mixture had stirred for 5 min, 1.31 g (3.60 mmol) of the epoxy alcohol **15** was dissolved in 5 mL of ether and added to the cuprate solution. The yellow suspension was stirred 4 h at 0 °C and then quenched carefully with saturated copper sulfate solution (15 mL). This mixture was stirred for 1 h, diluted with ether (300 mL), and separated. The ether solution was washed with 100 mL of water and then with 100 mL of brine and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the crude crystalline triol, which was used without further purification in most cases.

2(*R*)-[(1*R*)-4(*R*)-[(Benzyloxy)methyl]-4-hydroxy-3(*R*),8(*S*)-dimethyl-2,9-dioxabicyclo[3.3.1]non-5(*Z*)-en-1-yl]propan-1-ol (16). The crude triol from the above reaction was dissolved in 50 mL of chloroform, and a few crystals of *p*-toluenesulfonic acid (approximately 10 mg, anhydrous) were added. The reaction mixture was stirred at ambient temperature, and the reaction appeared complete by TLC after 30 min. Potassium bicarbonate (0.5 g) was then added to quench the acid, and the suspension was stirred for 5 min. It was then filtered through Celite, the solvent was removed on a rotary evaporator, and the crude crystalline material was chromatographed on 125 g of silica, eluting with 40% ethyl acetate/petroleum ether. The major product (851 mg, 68% from the epoxide **15**) was separated from the methyl epimer, which had been carried along from the Claisen rearrangement. A mixture of minor products (120 mg) was also isolated; it consisted primarily of this methyl epimer. Analysis and spectral data: R_f 0.30 (ethyl ether); IR ($CHCl_3$) 3500, 1090, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (d, 3 H, J = 7 Hz), 1.01 (d, 3 H, J = 8 Hz), 1.47 (s, 3 H), 1.6 (br s, 1 H), 1.7 (m, 1 H), 2.3 (m, 1 H), 2.71 (s, 1 H), 3.3–3.6 (m, 4 H), 3.8 (m, 1 H), 4.25 (t, 1 H, J = 4 Hz), 4.57 (d, 2 H, J = 1.5 Hz), 5.96 (dd, 1 H, $J_{5,6}$ = 4 Hz, $J_{6,7}$ = 10 Hz), 6.21 (d, 1 H, J = 10 Hz), 7.32 (s, 5 H); mp 106–108 °C; $[\alpha]^{23}_D$ +104° (c 4.28, $CHCl_3$). Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.97, H, 8.02.

Ethyl 4(*R*)-[(1*R*)-4(*R*)-[(Benzyloxy)methyl]-4-hydroxy-3(*R*),8(*S*)-dimethyl-2,9-dioxabicyclo[3.3.1]non-5(*Z*)-en-1-yl]-2-methylpent-2(*E*)-enoate (18). The crystalline bicyclic alcohol **16** (832 mg, 2.39 mmol) was dissolved in 10 mL of dichloromethane; 2.65 g (12.3 mmol) of pyridinium chlorochromate (PCC) was then added with stirring. The reaction mixture turned brown and then black, and the solids produced interfered with stirring within 5 min. After 45 min, the suspension was poured into 350 mL of ether, and the solids were rinsed repeatedly with dichloromethane, which was added to the ether solution. This solution was extracted with 50-mL portions of water, saturated sodium bicarbonate (twice), and brine. It was then dried over magnesium sulfate and filtered, and 3.42 g (9.4 mmol) of (carbethoxyethylidene)triphenylphosphorane was added. The volume of the solution was reduced to about 25 mL on a rotary evaporator, 20 mL of benzene was added, and the volume was again reduced to about 20 mL. More benzene (20 mL) was added, and the volume of the solution was reduced to about 15 mL. This solution was then heated in a 75 °C oil bath overnight. Most of the solvent was then removed and the cride mixture loaded onto a column of 70 g of silica and eluted with 20% ethyl acetate/petroleum ether. In this manner the following products were obtained: 50 mg of **17** from chromate rearrangement[14] (5%), 23 mg of an unidentified product (2%), 617 mg of the major product (**18** 61%), 93 mg of (apparently *Z*-olefin) (9%). Analysis and spectral data: R_f 0.54 (3:2 petroleum ether/ethyl acetate); IR ($CHCl_3$) 3520, 1695, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.65 (d, 3 H, J = 7 Hz), 0.93 (d, 3 H, J = 7 Hz), 1.26 (t, 3 H, J = 6 Hz), 1.50 (s, 3 H), 1.80 (s, 3 H), 1.8 (m, 1 H), 2.5 (m, 1 H), 2.68 (s, 1 H), 3.48 (q, 2 H, J = 10 Hz), 4.2 (m, 3 H), 4.57 (AB, 1 H, J = 9 Hz), 4.65 (AB, 1 H, J = 9 Hz), 5.97 (dd, 1 H, $J_{5,6}$ = 4 Hz, $J_{6,7}$ = 10 Hz), 6.21 (d, 1 H, J = 10 Hz), 6.87 (br d, 1 H, J = 10 Hz), 7.35 (s, 5 H); $[\alpha]^{22}_D$ +95.0° (c 2.82, $CHCl_3$). Anal. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.68; H, 7.91.

4(*R*)-[(1*R*)-4(*R*)-[(Benzyloxy)methyl]-4-hydroxy-3(*R*),8(*S*)-dimethyl-2,9-dioxabicyclo[3.3.1]non-5(*Z*)-en-1-yl]-2-methylpent-2(*E*)-en-1-ol. The ester from the Wittig reaction (538 mg, 1.30 mmol) was dissolved in 10 mL of ether and cooled to −78 °C. The solution was stirred, while 5.0 mL of 1 M DIBAL-H/hexane was added slowly. After 1 h, the reaction was allowed to warm to 0 °C and quenched with 1 mL of methanol. It was then stirred with 10 mL of 0.5 M sodium potassium tartrate for 3 h at room temperature, separated, dried ($MgSO_4$), and flash chromatographed with 60% ethyl acetate/petroleum ether. This resulted in isolation of 478 mg of the desired alcohol (95% yield) as a colorless oil. Analysis and spectral data: R_f 0.15 (3:2 petroleum ether/ethyl acetate); IR ($CHCl_3$) 3500, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) 0.68 (d, 3 H, J = 7 Hz), 0.90 (d, 3 H, J = 7 Hz), 1.45 (s, 3 H), 1.64 (s, 3 H), 1.8 (m, 1 H), 2.5 (m, 2 H), 3.4 (m, 2 H), 3.46 (q, 2 H, J = 10 Hz), 3.98 (s, 2 H), 4.16 (t, 1 H, J = 4 Hz), 4.57 (d, 2 H, J = 2 Hz), 5.53 (br d, 1 H), J = 10 Hz), 5.93 (dd, 1 H, $J_{5,6}$ = 4 Hz, $J_{6,7}$ = 10 Hz), 6.21 (d, 1 H, J = 10 Hz), 7.35 (s, 5 H); $[\alpha]^{22}_D$ +92.0° (c 0.65, $CHCl_3$). Anal. see following compound (silyl ether).

1-[(*tert*-Butyldimethylsilyl)oxy]-4(*R*)-[(1*R*)-4(*R*)-[(benzyloxy)-methyl]-4-hydroxy-3(*R*),8(*S*)-dimethyl]-2,9-dioxabicyclo[3.3.1]non-5-(*Z*)-en-1-yl]-2-methylpent-2(*E*)-ene. Silylation of the alcohol was accomplished as follows: the alcohol (434 mg, 1.12 mmol) was dissolved in 4.0 mL of DMF. To this was added 181 mg of imidazole (2.7 mmol) followed by 224 mg of (TBS)Cl (1.49 mmol). The reaction was complete in 30 min (judged by TLC), and after 30 min more it was diluted with 120 mL of ether. This solution was washed with three 25-mL portions of water and dried over magnesium sulfate. Flash chromatography of the residue gave 521 mg of clear oil for a 93% yield of the desired silyl ether product. Analysis and spectral data: R_f 0.76 (3:2 petroleum ether/ethyl acetate); IR ($CHCl_3$) 3520 (br), 1090, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.07 (s, 6 H), 0.65 (d, 2 H, J = 7 Hz), 0.88 (d, 3 H, J = 7 Hz), 0.93 (s, 9 H), 1.44 (s, 3 H), 1.55 (s, 3 H), 1.8 (m, 1 H), 2.5 (m, 1 H), 2.60 (s, 1 H), 3.38 (d, 1 H, J = 9 Hz), 3.48 (q, 2 H, J = 10 Hz), 4.00 (s, 2 H), 4.15 (t, 1 H, J = 4 Hz), 4.58 (d, 2 H, J = 2 Hz), 5.49 (br d, 1 H, J = 10 Hz), 5.95 (dd, 1 H, $J_{5,6}$ = 4 Hz, $J_{6,7}$ = 10 Hz), 6.20 (d, 1 H, J = 10 Hz), 7.35 (s, 5 H); $[\alpha]^{22}_D$ +501° (c 1.03, $CHCl_3$). Anal. Calcd for $C_{29}H_{46}O_5Si$: C, 69.28; H, 9.22. Found: C, 69.30; H, 9.25.

1-[(*tert*-Butyldimethylsilyl)oxy]-4(*R*)-[(1*R*)-4(*R*)-(hydroxymethyl)-4-hydroxy-3(*R*),8(*S*)-dimethyl-2,9-dioxabicyclo[3.3.1]non-5-(*Z*)-en-1-yl]-2-methylpent-2(*E*)-ene (19). Lithium di-*tert*-butylbiphenyl radical anion solution was prepared as described above, starting with 4.2 g of di-*tert*-butylbiphenyl (16 mmol) and 140 mg of lithium wire (20 mmol) in 100 mL of THF.[9] The benzyl ether above (501 mg, 1.00 mmol) was dissolved in 12 mL of THF and cooled to −78 °C. The radical anion solution was then added dropwise until the dark green color persisted in the reaction. An additional 1 mL of the reagent solution was then added, and the reaction was stirred 1 min more and quenched at −78 °C with aqueous ammonium chloride. The suspension was then allowed to warm to room temperature, diluted with ether (100 mL), and extracted with brine. The organic layer was dried over $MgSO_4$, the solvent was removed under reduced pressure, and the crude product was purified by flash chromatography (eluting with 35% ethyl acetate/petroleum ether) to yield 386 mg (94%) of the deprotected alcohol **19** as a clear oil. Analysis and spectral data: R_f 0.41 (3:2 petroleum ether/ethyl acetate); IR ($CHCl_3$) 3530, 3450 (br), 828 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.10 (s, 6 H), 0.67 (d, 3 H, J = 7 Hz), 0.91 (s, 9 H), 0.96 (d, 3 H, J = 7 Hz), 1.42 (s, 3 H), 1.58 (s, 3 H), 2.0 (m, 1 H), 2.2 (br s, 1 H), 2.4 (m, 1 H), 3.5 (m, 3 H), 3.99 (s, 2 H), 4.13 (t, 1 H, J = 4 Hz), 5.50 (br d, 1 H, J = 9 Hz), 5.96 (dd, 1 H, $J_{5,6}$ = 4 Hz, $J_{6,7}$ = 10 Hz), 6.26 (d, 1 H, J = 10

Hz). $[\alpha]^{22}_D$ +93.5° (c 0.43, $CHCl_3$). Anal. Calcd for $C_{22}H_{40}O_5Si$: C, 64.04; H, 9.77. Found: C, 63.91; H, 9.62.

1-[(*tert*-Butyldimethylsilyl)oxy]-4(*R*)-[(1*R*)-3(*R*),8(*S*)-dimethyl-4-(*R*)-(methyleneoxy)-2,9-dioxabicyclo[3.3.1]non-5(*Z*)-en-1-yl]-2-methylpent-2(*E*)-ene (20). The above diol **19** (298 mg, 0.723 mmol) was dissolved in 15 mL of THF and cooled to 0 °C. Sodium hydride (150 mg of a 50% oil dispersion, 3.1 mmol) was added, and the mixture was stirred for 10 min. (*p*-Tolylsulfonyl)imidazolide (342 mg, 1.54 mmol) was dissolved in 3.0 mL of the THF, and the solution was added dropwise to the reaction over 5 min.[17] By TLC, the reaction was not quite complete after 2 h, so it was stirred for 30 min at room temperature and then carefully quenched with methanol. The mixture was diluted with 250 mL of ether and extracted with 100-mL portions of brine, then water, and then brine. Brief drying over $MgSO_4$ was followed by filtration and solvent removal (rotary evaporator). The crude material was flash chromatographed with 9% ethyl acetate/petroleum ether to provide 273 mg (96% yield) of the epoxide **20**, which was pure by TLC and NMR. Analysis and spectral data: R_f 0.78 (4:1 petroleum ether/ethyl acetate); IR ($CHCl_3$) 995, 828 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (s, 6 H, 0.65 (d, 3 H, J = 7 Hz), 0.92 (s, 9 H), 0.96 (d, 3 H, J = 7 Hz), 1.19 (s, 3 H), 1.60 (s, 3 H), 2.0 (m, 1 H), 2.5 (m, 1 H), 3.53 (dd, 1 H, $J_{3,4}$ = 10 Hz, $J_{3,4'}$ = 2 Hz), 3.75 (d, 1 H, J = 5 Hz), 3.92 (d, 1 H, J = 5 Hz), 4.00 (s, 2 H), 4.29 (t, 1 H, J = 4 Hz), 5.49 (br d, 1 H, J = 9 Hz), 5.57 (d, 1 H, J = 10 Hz), 6.30 (dd, 1 H, $J_{5,6}$ = 4 Hz, $J_{6,7}$ = 10 Hz); $[\alpha]^{22}_D$ +154° (c 0.75, $CHCl_3$). Anal. see following compound (desilyated).

4(*R*)-[(1*R*)-4(*R*)-(Methyleneoxy)-3(*R*),8(*S*)-dimethyl-2,9-dioxabicyclo[3.3.1]non-5(*Z*)-en-1-yl]-2-methylpent-2(*E*)-en-1-ol. The epoxide **20** (91 mg, 0.23 mmol) was dissolved in 2.0 mL of the THF and cooled to 0 °C. A 1 M THF solution of tetra-*n*-butylammonium fluoride (1 mL) was added, and the reaction was stirred for 1 h, at which time it was judged complete by TLC. The solution was diluted with 100 mL of ether and extracted with 25 mL of brine. The organic layer was then dried over magnesium sulfate and filtered, and the solvent was removed under reduced pressure. Flash chromatography of the residue gave 63 mg (97%) of white crystalline alcohol. Analysis and spectral data: R_f 0.30 (7:3 petroleum ether/ethyl acetate); IR ($CHCl_3$) 3540, 3460 (br), 992 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.66 (d, 3 H, J = 7 Hz), 0.99 (d, 3 H, J = 7 Hz), 1.21 (s, 3 H), 1.68 (s, 3 H), 1.7 (br s, 1 H), 2.0 (m, 1 H), 2.5 (m, 1 H), 2.76 (d, 1 H, J = 5 Hz), 2.97 (d, 1 H, J = 5 Hz), 3.58 (dd, 1 H, $J_{3,4}$ = 10 Hz, $J_{3,4'}$ = 2 Hz), 4.01 (s, 2 H), 4.32 (t, 1 H, J = 4 Hz), 5.52 (br d, 1 H, J = 9 Hz), 5.59 (d, 1 H, J = 10 Hz), 6.37 (dd, 1 H, $J_{5,6}$ = 4 Hz, $J_{6,7}$ = 10 Hz); $[\alpha]^{23}_D$ +193° (c 0.859, $CHCl_3$). Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.63; H, 8.60.

Streptolic Acid Ethyl Ester (21). Dichloromethane (2.0 mL) was cooled to −78 °C and 30 mL (0.34 mmol) of oxalyl chloride was added followed by 30 mL (0.42 mmol) of DMSO. After the resultant mixture was stirred for 15 min, the above alcohol was added in 1.0 mL of dichloromethane and rinsed in with 1 mL more of dichloromethane. This was stirred for 30 min, and 0.15 mL (0.84 mmol) of Hunig's base was added. It was then allowed to warm to room temperature, and 318 mg (0.91 mmol) of (carbethoxymethylene)triphenylphosphorane was added. This reaction mixture was stirred overnight at room temperature. It was then diluted with 100 mL of dichloromethane and extracted with brine followed by sodium bicarbonate. The solution was dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. Chromatography on 8 g of silica, eluting with 7% ethyl acetate/petroleum ether, gave 49 mg of the ethyl ester **21** (74%). Analysis and spectral data: R_f 0.43 (4:1 petroleum ether/ethyl acetate). IR ($CHCl_3$) 1690, 1622 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.70 (d, 3 H, J = 7 Hz), 1.03 (d, 3 H, J = 7 Hz), 1.23 (s, 3 H), 1.31 (t, 3 H, J = 7 Hz), 1.80 (s, 3 H), 1.9 (s, 1 H), 2.7 (m, 1 H), 2.78 (d, 1 H, J = 5 Hz), 2.98 (d, 1 H, J = 5 Hz), 3.62 (dd, 1 H, $J_{3,4}$ = 10 Hz, $J_{3,4'}$ = 2 Hz), 4.20 (q, 2 H, J = 7 Hz), 4.33 (t, 1 H, J = 4 Hz), 5.69 (d, 1 H, 10 Hz), 5.88 (d, 1 H, J = 16 Hz), 6.06 (br d, 1 H, J = 9 Hz), 6.33 (dd, 1 H, $J_{5,6}$ = 4 Hz, $J_{6,7}$ = 10 Hz), 7.34 (d, 1 H, J = 16 Hz), 7.34 (d, 1 H, J = 16 Hz); $[\alpha]^{23}_D$ +140° (c 0.75, $CHCl_3$). Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.87; H, 8.07.

Streptolic Acid (2). A 19-mg sample of the ester **21** (0.055 mmol) in 5 mL of methanol was treated with 3 mL of 10% aqueous sodium hydroxide. After being stirred for 2 h, the mixture was diluted with sodium bicarbonate solution, extracted with 15 mL of petroleum ether, acidified to about pH 2 with 10% HCl, and extracted with three 25-mL portions of chloroform. The chloroform solution was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. Drying under vacuum resulted in crystallization of the residue (17.6 mg, 100% crude yield). After three recrystallizations (benzene/petroleum ether) the pure material (15 mg, 86%) was judged identical with streptolic acid (**2**) (from degradation of streptolydigin) by comparisons of melting point, ^1H NMR, IR, and specific rotation.[3] Analysis and spectral data: R_f 0.30 (ethyl acetate); IR ($CHCl_3$) 3000 (br), 1672, 1617 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.66 (d, 3 H, J = 7 Hz), 1.02 (d, 3 H, J = 7 Hz), 1.20 (s, 3 H), 1.79 (s, 3 H), 1.8 (m, 1 H), 2.7 (m, 1 H), 2.76 (d, 1 H, J = 5 Hz), 2.95 (d, 1 H, J = 5 Hz), 3.6 (dd, 1 H, $J_{3,4}$ = 10 Hz, $J_{3,4'}$ = 2 Hz), 4.30 (t, 1 H, J = 5 Hz), 5.59 (d, 1 H, J = 10 Hz), 5.78 (d, 1 H, J = 16 Hz), 6.09 (br d, 1 H, J = 10 Hz), 6.31 (dd, 1 H, $J_{5,6}$ = 5 Hz, $J_{6,7}$ = 10 Hz), 7.40 (d, 1 H, J = 16 Hz); mp 168-169 °C (lit.[2] 168-170 °C); $[\alpha]^{22}_D$ +138° (c 0.55, 95% EtOH) [lit.[2] $[\alpha]^{25}_D$ +147° (c 1.21, 95% EtOH). Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.35; H, 7.71.

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Kinetic Investigation of the Type 2 Intramolecular Diels-Alder Cycloaddition

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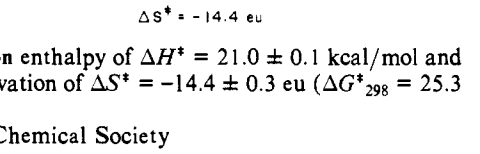
Abstract: Rate constants and activation energy parameters for the type 2 intramolecular Diels-Alder cycloaddition of a series of dienyne esters have been determined. It is noted that the point of substitution of an oxygen atom in the tether joining diene and dienophile results in substantial rate differences. An analysis of these rate differences has provided a transition-state model for the type 2 intramolecular cycloaddition. Variation of the tether length from five to seven atoms produces changes in both the enthalpy and entropy of activation, but no systematic trend in rate is observed. The EM (effective molarity) for the type 2 intramolecular Diels-Alder cycloaddition of dienyne ester **4** was determined to be 0.4-0.5 M.

The intramolecular Diels-Alder reaction has played an important role in the recent advances of synthetic organic chemistry.[1] Despite this fact there has been relatively little effort directed toward developing a quantitative understanding of the rates of intramolecular Diels-Alder reactions. In an important early investigation, Gschwend and co-workers reported the activation energy for intramolecular Diels-Alder cycloaddition of several triene amides. A kinetic analysis of the cycloaddition (eq 1)



(1)

afforded a reaction enthalpy of $\Delta H^{\ddagger} = 21.0 \pm 0.1$ kcal/mol and an entropy of activation of $\Delta S^{\ddagger} = -14.4 \pm 0.3$ eu ($\Delta G^{\ddagger}_{298} = 25.3$

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