Oxidation and Alkylation of Spectinomycin Derivatives: Synthesis of Trospectomycin from Spectinomycin

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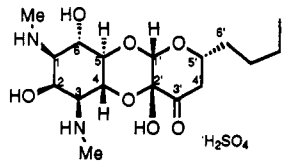
Trospectomycin can be prepared in five steps from spectinomycin. The overall yield of the process is 13.3%. The synthesis involves a new oxidation of silyl enol ether **4** to enone **5** by use of an alkyl hydroperoxide. This reaction is mild and very selective, giving excellent yields. The synthesis also involves a γ-alkylation of enone **5** activated by a β-oxygen. This alkylation is unusual in that no alkylation is seen at the α (4′) carbon.

Introduction

Trospectomycin sulfate (6′-*n*-propylspectinomycin) **1** is an aminocyclitol antibiotic under development as a broad spectrum antibiotic for treatment of sexually transmitted diseases. Trospectomycin, which is a semisynthetic derivative of spectinomycin **2**, is the only aminocylitol antibiotic which has activity against anaerobic bacteria.



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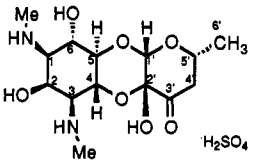

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The molecule was originally prepared by White, Maring, and Cain.[1a] White and Cain subsequently reported an improved synthesis.[1b] This report addresses an effective large-scale oxidation to the key enone **5** and a one-step addition of the desired three-carbon side chain.

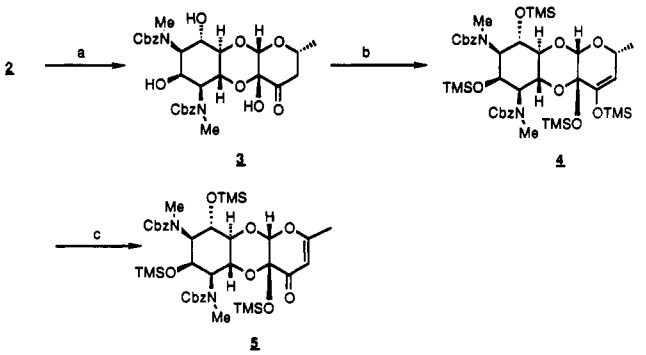
Results and Discussion

In order to access the 6′ center of spectinomycin **2** it is preferred to activate that site by formation of a double bond at the 4′–5′ position. We therefore began our study with the preparation of the key enone **5**. We reasoned that oxidation of silyl enol ether **4** would afford **5** by a number of known methods.[2]

Preparation of Enone 5. Preparation of **4** was accomplished by protection of the nitrogens with carbobenzyloxy groups[3] followed by exhaustive silylation with TMSCl and TEA at 55–60 °C (Scheme I). We were able to purify the enol ether by chromatography over silica gel. The yield from spectinomycin **2** to enol ether **4** was 58% after chromatography.

Examination of most of the known methods for oxidation of silyl enol ethers resulted in low yields or no reaction at all. Based on White's oxidation of analogous enol acetate **6**,[1b] we concluded that we needed a mild radical source to effect the desired transformation. However, the photochemical method employed by White was not acceptable for large-scale production.

Scheme I[a]



[a] (a) Benzyl chloroformate, $NaHCO_3$, acetone, water; (b) TEA, TMSCl, acetonitrile; (c) *tert*-butyl hydroperoxide, $CuCl_2$, acetonitrile.

The metal-catalyzed decomposition of peroxides is reported to be a convenient and controllable source of radicals.[4] Reaction of enol ether **4** with a variety of peroxides and metals provided the desired product **5** in varying yields (Scheme I). This result was somewhat surprising in light of the report by Kaneda et al. that enol ethers react with $MoO_2(acac)_2$ to give bond-cleavage products.[5] We examined several peroxides (di-*tert*-butyl peroxide, decanoyl peroxide, benzoyl peroxide, lauroyl peroxide, cumene hydroperoxide, *tert*-butyl hydroperoxide, and hydrogen peroxide) with copper metal catalysis, and the only one that gave no reaction was hydrogen peroxide (Table I). We chose to work with *tert*-butyl hydroperoxide (tbhp) because the di-*tert*-butyl peroxide required too high an initiation temperature and the acyl peroxides had nonproductive routes of decomposition (leading to the need for several equivalents for complete reaction). Additionally the byproducts were difficult to remove from the reaction mixture. Similarly we found that cumenyl hydroperoxide gave a faster reaction than tbhp but that the byproduct was difficult to remove.

We also examined several different metals for use as catalysts in this reaction (CuCl, $CuCl_2$, $Cu(OAc)_2$, AgOAc, $CoCl_2$, $Mn(OAc)_2$, $Ni(OAc)_2$, $CeCl_3$, $Cr(OAc)_3$) with only silver failing to give any reaction (Table II), with the best catalysts being either CuCl or $CuCl_2$. It is likely that both

(1) (a) White, D. R.; Maring, C. J.; Cain, G. A. *J. Antibiot.* **1983**, *36*, 339. (b) White, D. R.; Cain, G. A. *Tetrahedron Lett.* **1989**, *30*, 1469.

(2) (a) For a review of silyl enol ether oxidations, see: Brownbridge, P. *Synthesis* **1983**, 1. (b) Tsuji, J.; Shimizu, I.; Minami, I. *Tetrahedron Lett.* **1983**, *24*, 1797. (c) Baba, T.; Nakano, K.; Nishiyama, S.; Tsuruya, S.; Masai, M. *J. Chem. Soc., Chem. Commun.* **1989**, 1697.

(3) Wiley, P. F.; Argoudelis, A. D.; Hoeksema, H. *J. Am. Chem. Soc.* **1963**, *85*, 2652.

(4) (a) Beckwith, A. L. J.; Zavitsas, A. A. *J. Am. Chem. Soc.* **1985**, *108*, 8230. (b) Kharasch, M. S.; Pauson, P.; Nudenberg, W. *J. Org. Chem.* **1953**, *18*, 322.

(5) Kaneda, K.; Kii, N.; Jitsukawa, K.; Teranishi, S. *Tetrahedron Lett.* **1981**, *22*, 2595.

0022-3263/93/1958-0678$04.00/0

Table I. Oxidation of 4 with Various Peroxides and 0.1 equiv of $CuCl_2$

peroxide	equiv	solvent	temp, °C	% yield
di-*tert*-butyl peroxide	1.0	toluene	100	62
decanoyl peroxide	2.0	CH_2Cl_2	55	67
benzoyl peroxide	2.0	CH_2Cl_2	55	71
lauroyl peroxide	2.0	$ClCH_2CH_2Cl$	65	61
cumyl hydroperoxide	1.3	CH_2Cl_2	35	78
tert-butyl hydroperoxide	1.3	CH_2Cl_2	35	81
hydrogen peroxide	3.0	CH_2Cl_2	55	0

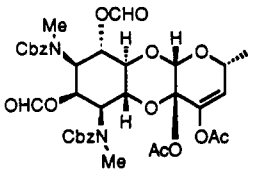
Table II. Reaction of 4 with tbhp in CH_2Cl_2 at 35 °C with Metal Catalyst

catalyst	after 4 h	after 18 h
$Cu(OAc)_2$	36%	62%
AgOAc	no reactn	no reactn
$CoCl_2$	55%	complete reactn
$Mn(OAc)_2 \cdot 4H_2O$	23%	90% complete
$Ni(OAc)_2 \cdot 4H_2O$	10%	50% complete
$CeCl_3 \cdot 7H_2O$	23%	82% complete
$Cr(OAc)_3$	34%	complete reactn
CuCl	84%	complete reactn
$CuCl_2$	82%	complete reactn

of these materials undergo the same catalytic cycle (Cu(I), Cu(II)). The amount of catalyst was varied from 0.5% up to 10%, and the optimum amount was shown to be 3%. The solvent was also found to be important. The reaction worked well in halogenated solvents (CH_2Cl_2, $CHCl_3$, dichloroethane, etc.) or acetonitrile.

An interesting dependence on light was observed in attempting to scale-up reactions using $Cu(OAc)_2$. On a small scale (≤1 g) the reaction was over in about 2 h. When the reaction was scaled up to 10 g, with all concentrations being the same, the reaction took 10 h and on a 100-g scale the reaction took >48 h. The limiting factor in this scale-up was the amount of light available to the reaction. When a 1-g reaction was run in the dark it was only 62% complete after 18 h, while a 100-g reaction which was irradiated by a 400-W halogen lamp was complete in about 4 h. This unusual photoactivation was observed for all catalysts examined with Cu–O bonds but not for any other catalysts.

Two byproducts were seen in this reaction. The major byproduct is the less polar product which result from the addition of *tert*-butoxy to the 5′-position (7). The other



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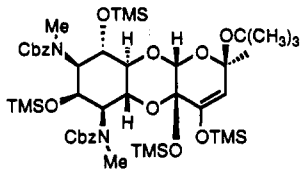

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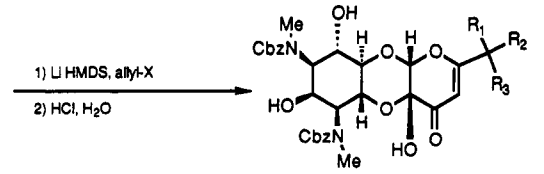
byproduct is unstable, decomposing to the desired product on attempted isolation. These byproducts are minimized by slow addition of peroxide to the reaction mixture and thereby minimizing concentration of radicals in the reaction mixture. The enone 5 was easily purified by chromatography and could be obtained in 71% purified yield from enol ether 4.

Attempts to explore the scope of the reaction have been disappointing. Treatment of the enol ether of cyclopentanone and cyclohexanone with tbhp and $CuCl_2$ in methylene chloride or acetonitrile provided 20–40% yields of the desired enones with ketone being the major product. We believe it is necessary to have heteroatom activation at the β(5′)-position to achieve high yields in this reaction.

Scheme II



8 $R_1 = R_2 = R_3 = H$
9 $R_1 = R_2 = H$ $R_3 = CH_2CH{=}CH_2$
10 $R_1 = H$ $R_2 = R_3 = CH_2CH{=}CH_2$
11 $R_1 = R_2 = R_3 = CH_2CH{=}CH_2$

Alkylation of Enone 5. Introduction of the three-carbon side chain had previously been accomplished in a two-stage manner.[1] We were hoping to achieve this transformation in a single process. While most α,β-unsaturated ketones undergo alkylation at the α-position,[6] there are some examples of γ-alkylations.[7] We reasoned that in this case the dienolate formed by deprotonation would closely resemble the dianion of a 1,3-dicarbonyl and some selectivity at the 6′-carbon could be expected.

Deprotonation of 5 with 1.05 equiv of LDA in THF at −78 °C followed by treatment with *n*-propyl iodide or allyl bromide resulted in none of the desired product. Only starting material and polar degradation products were recovered. Warming the reactions from −78 °C to 0 °C or 15 °C had the same result. Changing bases to LHMDS gave better results. Using 1.5 equiv of base and 5.0 equiv of alkylating reagent, at −78 °C alkylation still did not proceed, but after warming to 30 °C alkylation occurred with allyl bromide, but not with propyl iodide.

After removal of the TMS protecting groups, HPLC examination of the products revealed four very similar products. NMR showed the products to be the deprotected starting material 8, the desired monoallylated product 9, the diallylated product 10, and the triallylated product 11 (Scheme II). These products were isolated in a ratio of 2:12:5:1, respectively. Lowering the amount of base to 1.0 equiv changed the ratio to 3:20:2:1. None of the 4′-alkylated product was observed in any of these alkylations.

Alkylation was clearly slower than proton transfer, and so a more active alkylating agent was used. Using allyl iodide the alkylation took place at lower temperature, and the triallyl product 11 was no longer formed. Under optimized conditions this reaction gave a ratio of 2:20:1, 8:9:10. The desired product could be isolated from this mixture in a yield of 52% after chromatography. Performing the reaction by slow addition of the dienolate to an excess of alkylating reagent did not alter this ratio. Addition of metals such as copper and cerium also had little or no affect on the outcome (Table III).

Palladium-Catalyzed Reaction of Dienol Carbonate 12. Another approach to this problem was to use the allylation method of Tsujii.[8] Preparation of dienol allyl

(6) (a) For a review of alkylation of α,β-unsaturated enones, see: Zimmerman, H. E. In *Molecular Rearrangements*; de Mayo, P., Ed.; Interscience: New York, 1963; p 345. (b) Rathke, M. W.; Sullivan, D. *Tetrahedron Lett.* **1972**, 4249. (c) de Graf, S. A. G.; Osterhoff, P. E. R.; van der Gen, A. *Tetrahedron Lett.* **1974**, 1653.

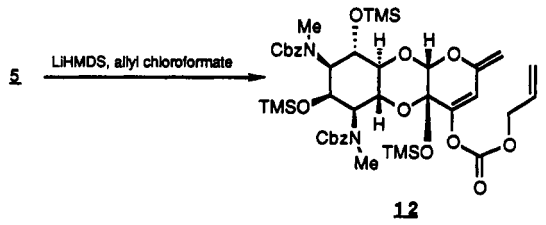
(7) (a) Katzenellenbogen, J. A.; Crumrine, A. L. *J. Am. Chem. Soc.* **1974**, *96*, 5662. (b) Katzenellenbogen, J. A.; Crumrine, A. L. *J. Am. Chem. Soc.* **1976**, *98*, 4925. (c) Katzenellenbogen, J. A.; Savu, P. M. *J. Org. Chem.* **1981**, *46*, 239. (d) Majewski, M.; Mpango, G. B.; Thomas, M. T.; Wu, A.; Snieckus, V. *J. Org. Chem.* **1981**, *46*, 2029. (e) Smith, A. B. III; Scarborough, R. M., Jr. *Tetrahedron Lett.* **1978**, 4193.

(8) (a) Tsujii, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 1793. (b) Tsujii, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 1797. (c) Tsujii, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 5635.

Table III. Alkylation of 5 with Base and Electrophile

base	equiv	electrophile	temp, °C	8	9	10	11	solvent	additive
LiHMDS	1.3	allyl Br	20	5	5	3	1	THF	
LiHMDS	1.8	allyl Br	40	2	12	5	1	THF	
LiHMDS	1.3	allyl I	15	2	20	1	0	THF	
LiHMDS	1.3	allyl I	15	22	51	1	0	toluene	
LiHMDS	1.3	allyl I	15	15	5	1	0	DME	
LiHMDS	1.3	allyl I	0	3	9	1	0	THF	CuI
LiHMDS	1.3	allyl I	0	10	22	1	0	THF	CuCN
LiHMDS	1.3	allyl I	0	18	32	1	0	THF	$CeCl_3$
LiHMDS	1.3	allyl I	0	25	27	1	0	THF	$(MeO)_3B$
NaHMDS	1.3	allyl I	15	2	18	1	0	THF	
KHMDS	1.3	allyl I	15	2	15	1	0	THF	

Scheme III



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carbonate 12 proceeded in good yield from enone 5 (Scheme III). This material was treated with palladium under Tsujii's conditions without further purification. Rapid reaction occurred with evolution of gas, and after removal of the silyl protecting groups the result was a 3:14:2 mixture of 8:9:10. None of the 4'-alkylated product was observed in this reaction. Changing palladium sources and ligands did little or nothing to affect this ratio. Overall yields of the desired product from 5 were 45–50% after purification.

Preparation of Trospectomycin. Conversion of 9 to trospectomycin was accomplished in a single step. Reduction of 9 under 50 psig of hydrogen with 5 wt % of palladium on alumina in aqueous methanol provided a solution of trospectomycin free base. Addition of sulfuric acid to pH 3.7 followed by cooling to −20 °C crystallized the product. Trospectomycin was purified by recrystallization from aqueous methanol to afford pure product in 62% yield from 9.

Conclusions

Trospectomycin can be prepared in five steps from spectinomycin. The key step of the synthesis is a new oxidation of a silyl enol ether to an enone by use of an alkyl hydroperoxide. This reaction is mild and very selective, giving excellent yields. Although this reaction was not found to be generally useful (20–40% yields in most cases), it performs very well with the 5'-oxygen in the system.

This synthesis also involves a γ-alkylation of an enone activated by a β-oxygen. This alkylation is unusual in that no alkylation is seen at the 4'-carbon. The alkylation reaction is somewhat slow, and polyalkylation is a problem. Optimization of the reaction conditions has minimized this problem. Overall yield of the process is 13.3%.

Experimental Section

General. Reagents and solvents were reagent grade and used as received unless otherwise noted. ^{1}H NMR spectra were obtained at 300 MHz and are reported in parts per million (ppm) downfield from TMS. ^{13}C spectra were measured at 75.4 MHz. Infrared spectra were obtained as mineral oil mulls and are reported in wavenumbers (cm^{-1}). Mass spectra were obtained as FAB, electron impact (EI), or chemical ionization (CI) as indicated. Molecular masses are given in atomic mass units (amu), followed by percent intensity relative to the most abundant ion. Flash chromatography was carried out using Merck 230–400-mesh silica gel from EM reagents.

Bis-Cbz-spectinomycin (3). Spectinomycin sulfate tetrahydrate (100.5 g, 0.2 mol, MW = 502.5, 1 equiv) was dissolved in water (400 mL), and the solution was cooled to 16 °C (pH = 3.5). Sodium bicarbonate (72 g, 0.86 mol, MW = 84.01, 4.3 equiv) was then added (pH = 7.0). A solution of benzyl chloroformate (71.6 g, 60 mL, d = 1.195, MW = 170.5, 0.42 mol, 2.1 equiv) in acetone (250 mL) was added (pH = 6.8) and rinsed in with acetone (50 mL, total acetone = 300 mL). The slurry was stirred at <20 °C for 2 h and then stirred at 23 °C for 2.5 h. H_2SO_4 (2.5 mL, 18 M in water) was added, and the pH dropped to 5.4. Ethyl acetate (350 mL) was added, and the phases separated. The aqueous phase was back-washed with ethyl acetate (150 mL). The organic phases were combined and concentrated to a foam on the rotovap and then placed on a vacuum line for 16 h. This procedure provided 118 g of solid containing 108.6 g of 3, 90.3% chem yield (expected yield 120 g, MW = 600.6). TLC procedure: Dilute 0.5 mL of reaction mixture with 2.0 mL of ethyl acetate and 2.0 mL of water. Spot 5 μL of each phase on a small plate. Elute with 5% methanol/CH_2Cl_2. Visualize by short-wave UV and H_2SO_4 char. Alternatively develop plate in 1% TEA/methanol with spectinomycin as standard. Visualize by H_2SO_4 char. IR: 3422, 2954, 2923, 1738, 1686, 1456, 1408, 1379, 1345, 1210, 1167, 1124, 1057, 958, 771, 738, 698. ^{1}H NMR ($CDCl_3$): 7.32 (m, 10 H), 5.10 (m, 4 H), 4.69 (s, 2 H), 4.61 (m, 1 H), 4.49 (m, 1 H), 4.37 (m, 1 H), 4.16 (m, 1 H), 4.00 (m, 1 H), 3.36 (m, 2 H), 3.07 (s, 3 H), 2.97 (s, 3 H), 2.80 (m, 2 H), 2.41 (d, J = 14 Hz, 2 H), 1.36 (d, J = 6 Hz, 3 H). ^{13}C NMR ($CDCl_3$): 156.3 (s), 136.7 (s), 128.2 (d), 127.9 (d), 127.8 (d), 127.7 (d), 100.7 (s), 92.2 (d), 89.2 (s), 78.9 (s), 73.5 (d), 67.9 (d), 66.9 (t), 64.2 (t), 60.0 (d), 56.3 (d), 31.5 (q), 31.0 (q), 25.8 (q). MS (CI, CH_4): 633 (8), 601 (28), 557 (18), 467 (12), 245 (9), 181 (7), 133 (12), 91 (100). UV (EtOH): λ_{max} 212 (18 400); $[\alpha]_D$ −3°. Anal. Calcd for $C_{30}H_{36}N_2O_{11}$: C, 59.99; H, 6.04; N, 4.66. Found: C, 59.70; H, 6.03; N, 4.51.

Bis-Cbz Silyl Enol Ether (4). 3 (118 g, 0.196 mol, MW = 600.6) was dissolved in acetonitrile (500 mL), and triethylamine (101.2 g, 140 mL, d = 0.726, 1.0 mol, MW = 101.2) was added all in one portion. Trimethylsilyl chloride (108.6 g, 127 mL, d = 0.856, 1.0 mol, MW = 108.6) was added over a period of 1 h such that the temperature rose to 50 °C. When the addition was complete the mixture was warmed to 50 °C for a further 3 h. The reaction was distilled under vacuum at 50 °C to a thick slurry, acetonitrile (250 mL) was added, and the distillation was continued to a thick slurry. Acetonitrile (300 mL) was added and the slurry cooled to <20 °C. The slurry was filtered and concentrated to a thick oil. The crude product was purified by chromatography over 1.5 kg of silica gel using 25% ethyl acetate/75% heptane as solvent. Concentration of product-containing fractions provided 103 g of purified enol ether 4. IR: 2955, 2925, 2854, 1710, 1455, 1407, 1376, 1340, 1251, 1152, 1057, 956, 844, 753, 697. ^{1}H NMR ($CDCl_3$): 7.39 (m, 10 H), 5.20 (m, 5 H), 4.86 (s, 2 H), 4.61 (m, 1 H), 4.49 (m, 1 H), 4.37 (m, 1 H), 4.16 (m, 2 H), 4.00 (m, 1 H), 3.00 (br s, 6 H), 1.36 (d, J = 4.3 Hz, 3 H), 0.18 (m, 18 H), 0.17 (s, 9 H), 0.08 (s, 9 H). ^{13}C NMR ($CDCl_3$): 157.8 (s), 148.7 (s), 136.7 (s), 128.5 (d), 128.1 (d), 127.9 (d), 127.7 (d), 112.7 (d), 95.8 (d), 89.9 (s), 74.9 (d), 69.2 (d), 68.1 (t), 65.8 (d), 61.2 (d), 57.7 (d), 57.3 (d), 33.1 (q), 33.0 (q), 23.2 (q), 2.6 (q), 2.3 (q), 1.5 (q), 1.3 (q). MS (FAB): 889 (13), 799 (61), 709 (23), 629 (26), 493 (32), 359 (34), 91 (100). UV ($CHCl_3$): λ_{max} 268 (222).

$[\alpha]_D$ +18°. Anal. Calcd for $C_{42}H_{68}N_2O_{11}Si_4$: C, 56.72; H, 7.71; N, 3.15. Found: C, 56.68; H, 7.70; N, 3.15.

Typical Procedure for Oxidation of Enol Ether 4 with Peroxide and $CuCl_2$. Enol ether 4 (1.0 g, 11.6 mmol, MW = 889) was dissolved in 6.00 mL of solvent. The $CuCl_2$ (1.16 mmol) was added and the mixture stirred to dissolve the solids. The mixture was protected from the light by wrapping the vessel in aluminum foil. Peroxide (11.6–34.8 mmol) was added and the mixture warmed to the appropriate temperature (see Table I). Completion of reaction was determined by HPLC analysis of the reaction mixture.

Typical Procedure for Oxidation of Enol Ether 4 with *tert*-Butyl Hydroperoxide and Metal Catalyst. Enol ether 4 (1.0 g, 11.6 mmol, MW = 889) was dissolved in 6.00 mL of methylene chloride. The catalyst (1.16 mmol) was added and the mixture stirred to dissolve the solids. The mixture was protected from the light by wrapping the vessel in aluminum foil. *tert*-Butyl hydroperoxide (70% aqueous, 11.6 mmol) was added and the mixture warmed to 35 °C. Completion of reaction was determined by HPLC analysis of the reaction mixture.

Oxidation of Enol Ether 4 with *tert*-Butyl Hydroperoxide and $Cu(OAc)_2$ with Light. Enol ether 4 (100 g, 0.112 mol, MW = 889) was dissolved in 600 mL of methylene chloride. $Cu(OAc)_2$ (2.0 g, 0.011 mol) was added and the mixture stirred to dissolve the solids. *tert*-Butyl hydroperoxide (70% aqueous, 0.319 g, 20.5 mL, d = 0.940, MW = 90.12, 0.15 mol) was added and the mixture irradiated with a 400-W flood light. After 4 h the reaction was compete. Aqueous sodium bisulfite (10%) (100 mL) was added, and the mixture was stirred for 30 min. The phases were separated, and the organic phase was washed with saturated NaCl (100 mL) The organic phase was concentrated to a oil at 50 °C under vacuum. Heptane (500 mL) was added and the mixture concentrated to an oil. Heptane (500 mL) was added and the mixture filtered through 50 g of silica gel. The cake was washed with heptane (100 mL). The filtrate and washes were combined and concentrated to a foam on the rotovap and then placed on a high-vacuum line overnight. The crude product was purified by chromatography over 800 g of silica gel using 25% ethyl acetate/75% heptane as solvent. Concentration of product-containing fractions provided 67 g (77%) of purified product. TLC procedure: Dilute 0.5 mL of reaction mixture in 2.0 mL of MTBE and 2.0 mL of water. Spot 5 μL of upper phase on a small plate. Elute with 25% ethyl acetate/75% heptane. Visualize with short-wave UV and H_2SO_4 char.

Trisilyl-bis-Cbz Enone (5). Enol ether 4 (103 g, 0.116 mol, MW = 889) was dissolved in 600 mL of acetonitrile. Copper(II) chloride dihydrate (0.60 g, 0.0035 mol, MW = 170.5) was added and the mixture stirred to dissolve the solids. *tert*-Butyl hydroperoxide 70% in water (19.3 g, 20.5 mL, d = 0.940, MW = 90.12, 0.15 mol) was added in five equal portions (4 mL each) every 30 min. The temperature was maintained between 28 and 33 °C. After the last addition the mixture was stirred for 1 h and 10% aqueous sodium bisulfite (100 mL) was added and the mixture stirred for 30 minutes. The phases were separated, and the organic phase was washed with saturated NaCl (100 mL). The organic phase was concentrated to a oil at 50 °C under vacuum. Heptane (500 mL) was added and the mixture concentrated to an oil. Heptane (500 mL) was added and the mixture filtered through 50 g of silica gel. The cake was washed with heptane (100 mL). The filtrate and washes were combined and concentrated to a foam on the rotovap and then placed on a high-vacuum line overnight. The crude product was purified by chromatography over 800 g of silica gel using 25% ethyl acetate/75% heptane as solvent. Concentration of product-containing fractions provided 76 g (81%) of purified product. TLC procedure: Dilute 0.5 mL of reaction mixture in 2.0 mL of MTBE and 2.0 mL of water. Spot 5 μL of upper phase on a small plate. Elute with 25% ethyl acetate/75% heptane. Visualize with short-wave UV and H_2SO_4 char. IR: 2955, 2923, 2868, 2854, 1706, 1694, 1620, 1456, 1400, 1378, 1344, 1250, 1185, 1137, 1107, 1064, 950, 878, 697. ^{1}H NMR ($CDCl_3$): 7.39 (m, 10 H), 5.20 (m, 5 H), 4.86 (s, 2 H), 4.61 (m, 1 H), 4.49 (m, 1 H), 4.37 (m, 1 H), 4.16 (m, 2 H), 4.00 (m, 1 H), 3.00 (br s, 6 H), 1.86 (s, 3 H), 0.18 (m, 18 H), 0.17 (s, 9 H). ^{13}C NMR ($CDCl_3$): 157.8 (s), 148.7 (s), 136.7 (s), 128.5 (d), 128.1 (d), 127.9 (d), 127.7 (d), 112.7 (d), 95.8 (d), 89.9 (s), 74.9 (d), 69.2 (d), 68.1 (t), 65.8 (d), 61.2 (d), 57.7 (d), 57.3 (d), 33.1 (q), 33.0 (q), 23.2 (q), 2.6 (q), 2.3 (q), 1.5 (q), 1.3 (q). MS (CI, CH_4): 833 (1.1), 816 (6.34), 215 (30.9), 199 (100), 183 (52.3), 166 (31.5). UV (EtOH): λ_{max} 268 (9920). $[\alpha]_D$ −58°. Anal. Calcd for $C_{39}H_{58}N_2O_{11}Si_3$: C, 57.47; H, 7.17; N, 3.44. Found: C, 57.22; H, 7.26; N, 3.44. Also isolated from this reaction was 0.62 g of compound 7 as a less polar material. IR: 2953, 2927, 2872, 1703, 1451, 1407, 1378, 1342, 1246, 1152, 1057, 955, 841, 756. ^{1}H NMR ($CDCl_3$): 7.32 (m, 10 H), 5.18 (m, 5 H), 4.92 (s, 2 H), 4.66 (m, 1 H), 4.43 (m, 1 H), 4.35 (m, 1 H), 3.98 (m, 3 H), 2.96 (br s, 6 H), 1.42 (s, 3 H), 1.10 (s, 9 H), 0.18 (m, 18 H), 0.17 (s, 9 H), 0.08 (s, 9 H). ^{13}C NMR ($CDCl_3$): 156.3 (s), 149.3 (s), 136.9 (s), 128.2 (d), 127.7 (d), 127.6 (d), 127.5 (d), 109.9 (d), 101.2 (s), 93.7 (d), 89.4 (s), 74.1 (d), 73.5 (d), 67.8 (d), 66.8 (t), 64.0 (d), 60.5 (d), 56.2 (d), 31.5 (q), 31.0 (q), 26.7 (q), 21.6 (q), 2.1 (q), 1.7 (q), 1.00 (q), 0.8 (q). MS(FAB): 962 (2.3), 906 (5.4), 888 (100), 815 (32), 800 (35), 630 (53), 494 (21). HRMS: calcd for $C_{46}H_{76}N_2O_{12}Si_4$ 960.4475, found 960.4397.

Typical Procedure for Alkylation of Enone 5. The trisilyl-bis-Cbz enone 5 (30 g) was dissolved in THF (60 mL) and the solution degassed by evacuating and flushing with N_2 gas. The solution was then cooled to −20 °C, and LiHMDS (1.0 M in THF, 44 mL) was added over a period of 5 min. The resulting red-brown solution was then warmed to 10 °C and allyl bromide (4.45 g, filtered through 0.5 g of basic alumina prior to use) added all in one portion. The mixture was stirred at 20–25 °C for 1 h, and then methanol (30 mL) and 6 N HCl (30 mL) were added. The yellow solution was then stirred at room temperature for 1 h. Ethyl acetate (60 mL) and water (30 mL) were then added. The phases were separated, and the organic layer was washed with saturated salt water and concentrated to dryness under vacuum. This procedure provided 23.1 g of impure 9. Purification of the crude material was accomplished by chromatography over 1 kg of silica gel using 40% ethyl acetate/60% heptane as eluent provided 8.0 g of 8. IR: 3404, 2955, 2923, 2868, 2854, 1682, 1610, 1455, 1408, 1378, 1346, 1260, 1166, 1128, 1056, 1037, 770, 738, 698. ^{1}H NMR ($CDCl_3$): 7.30 (m, 10 H), 5.41 (s, 1 H), 5.31 (s, 1 H), 5.14 (m, 5 H), 4.79 (m, 1 H), 4.52 (m, 1 H), 4.40 (m, 1 H), 4.23 (m, 2 H), 3.96 (m, 2 H), 3.01 (s, 3 H), 2.96 (s, 3 H), 2.10 (s, 3 H). ^{13}C NMR ($CDCl_3$): 187.0 (s), 175.6 (s), 157.8 (s), 136.7 (s), 128.5 (d), 128.1 (d), 127.9 (d), 127.7 (d), 101.1 (d), 98.1 (d), 86.3 (s), 74.9 (d), 69.2 (d), 68.1 (t), 65.8 (d), 61.2 (d), 57.7 (d), 57.3 (d), 33.1 (q), 33.0 (q), 21.6 (q). MS (FAB): 599 (7), 555 (4.8), 475 (2.4), 178 (4.3), 105 (3.8), 91 (100). UV (EtOH): λ_{max} 268 (6950). $[\alpha]_D$ −44°. Anal. Calcd for $C_{30}H_{34}N_2O_{11}$: C, 60.19; H, 5.72; N, 4.68. Found: C, 60.23; H, 5.76; N, 4.64. 7.8 g of 9. IR: 3404, 2955, 2923, 2868, 2854, 1682, 1610, 1455, 1408, 1378, 1346, 1260, 1166, 1128, 1056, 1037, 770, 738, 698. ^{1}H NMR ($CDCl_3$): 7.30 (m, 10 H), 5.75 (m, 1 H), 5.42 (s, 1 H), 5.29 (s, 1 H), 5.11 (m, 7 H), 4.72 (m, 1 H), 4.57 (m, 1 H), 4.40 (m, 1 H), 4.28 (m, 2 H), 3.99 (m, 2 H), 3.07 (s, 3 H), 2.98 (s, 3 H), 2.41 (m, 2 H), 2.34 (m, 2 H). ^{13}C NMR ($CDCl_3$): 187.2 (s), 177.9 (s), 158.2 (s), 136.4 (s), 135.8 (d), 128.5 (d), 128.1 (d), 127.9 (d), 127.7 (d), 116.4 (t), 100.6 (d), 98.1 (d), 86.4 (s), 75.5 (d), 73.7 (d), 67.4 (t), 65.8 (d), 64.4 (d), 58.4 (d), 34.4 (t), 32.8 (q), 30.1 (t). MS (FAB): 639 (5.1), 595 (4.6), 505 (1.4), 181 (2.2), 91 (100). UV (EtOH): λ_{max} 271 (10 100). $[\alpha]_D$ −52°. Anal. Calcd for $C_{33}H_{38}N_2O_{11}$: C, 62.06; H, 6.00; N, 4.39. Found: C, 62.14; H, 5.98; N, 4.34. 4.6 g of 10. IR: 3404, 2955, 2923, 2868, 2854, 1682, 1610, 1455, 1408, 1378, 1346, 1260, 1166, 1128, 1056, 1037, 770, 738, 698. ^{1}H NMR ($CDCl_3$): 7.30 (m, 10 H), 5.70 (m, 2 H), 5.40 (s, 1 H), 5.26 (s, 1 H), 5.08 (m, 9 H), 4.83 (m, 1 H), 4.57 (m, 1 H), 4.38 (m, 1 H), 4.25 (m, 2 H), 3.89 (m, 4 H), 3.08 (s, 3 H), 2.98 (s, 3 H), 2.43 (m, 1 H), 2.32 (m, 4 H). ^{13}C NMR ($CDCl_3$): 187.2 (s), 177.9 (s), 158.4 (s), 136.5 (s), 134.7 (d), 134.5 (s), 128.5 (d), 128.1 (d), 127.9 (d), 127.7 (d), 117.5 (t), 101.0 (d), 98.0 (d), 86.5 (s), 75.7 (d), 73.7 (d), 67.4 (t), 65.8 (d), 64.4 (d), 58.4 (d), 45.5 (d), 36.3 (d), 31.1 (q). MS (FAB): 679 (4.6), 635 (3.4), 545 (1.4), 181 (1.4), 91 (100). UV (EtOH): λ_{max} 269 (10 900). $[\alpha]_D$ −50°. Anal. Calcd for $C_{36}H_{42}N_2O_{11}$: C, 63.71; H, 6.24; N, 4.13. Found: C, 63.64; H, 6.21; N, 4.12. 1.2 g of 11. IR: 3404, 2955, 2923, 2868, 2854, 1682, 1610, 1455, 1408, 1378, 1346, 1260, 1166, 1128, 1056, 1037, 770, 738, 698. ^{1}H NMR ($CDCl_3$): 7.30 (m, 10 H), 5.70 (m, 3 H), 5.40 (s, 1 H), 5.28 (s, 1 H), 5.08 (m, 11 H), 4.76 (m, 1 H), 4.57 (m, 1 H), 4.38 (m, 1 H), 4.28 (m, 2 H), 3.92 (m, 4 H), 3.03 (s, 3 H), 2.96 (s, 3 H), 2.37 (t, J = 7.4 Hz, 6 H). ^{13}C NMR ($CDCl_3$): 187.2 (s), 180.9 (s), 156.4 (s), 136.8 (s), 132.3 (d), 128.5 (d), 128.1 (d), 127.9 (d), 127.7 (d), 119.1 (t), 100.8 (d), 98.0

(d), 86.2 (s), 75.7 (d), 73.7 (d), 67.4 (t), 65.8 (d), 60.0 (d), 56.3 (d), 47.2 (s), 38.6 (d), 31.5 (q). MS (FAB): 719 (4.1), 675 (3.8), 585 (1.2), 91 (100). UV (EtOH): λ_{max} 268 (10 900). $[\alpha]_D$ −53°. Anal. Calcd for $C_{39}H_{46}N_2O_{11}$: C, 65.17; H, 6.45; N, 3.90. Found: C, 65.04; H, 6.41; N, 3.92.

Preparation of Dienol Carbonate 12. The trisilyl-bis-Cbz enone **5** (1.63 g) was dissolved in THF (8 mL), and the solution was degassed by evacuating and flushing with N_2 gas. The solution was then cooled to −70 °C and LiHMDS (1.0 M in THF, 2.2 mL) was added over a period of 5 min. Allyl chloroformate was added all in one portion and the solution stirred at −70 °C for 1 h. The resulting solution was poured into a mixture of methyl *tert*-butyl ether (20 mL) and 1 N HCl (20 mL). The phases were separated, and the organic phase was washed with saturated NaCl (20 mL), dried over Na_2SO_4, and concentrated to give 1.71 g of a pale yellow foam. This material was used without purification in the next reaction. ^{1}H NMR ($CDCl_3$): 7.30 (m, 10 H), 6.18 (m, 1 H), 5.78 (m, 2 H), 5.28 (m, 4 H), 5.08 (m, 3 H), 4.76 (m, 1 H), 4.57 (m, 1 H), 4.38 (m, 1 H), 4.28 (m, 2 H), 3.92 (m, 4 H), 2.80 (s, 3 H), 2.78 (s, 3 H), 0.06 (s, 9 H), 0.03 (s, 9 H), 0.02 (s, 9 H). ^{13}C NMR ($CDCl_3$): 156.4 (s), 153.2 (s), 149.5 (s), 136.8 (s), 132.3 (d), 128.5 (d), 128.1 (d), 127.9 (d), 127.7 (d), 119.4 (t), 113.4 (d), 97.6 (t), 94.4 (d), 89.2 (s), 75.7 (d), 73.7 (d), 69.2 (t), 67.0 (t), 65.8 (d), 60.0 (d), 56.3 (d), 31.3 (q), 1.8 (q), 1.2 (q), 0.8 (q).

Reaction of 12 with Palladium. Preparation of 8, 9, and 10. $Pd_2(DBA)_3$ (0.13 g) was dissolved in THF (20 mL), and 1.07 g of triphenylphosphine was added. The mixture was stirred at room temperature for 30 min, and a solution of 10 g of dienol carbonate **12** in THF (20 mL) was added over 5 min. The solution evolved gas immediately upon addition of **12**. After 30 min 6 N HCl (50 mL) was added, and the mixture was stirred for 2 h. Methyl *tert*-butyl ether (100 mL) was added followed by water (100 mL). The phases were separated, and the organic phase was washed with water (100 mL) and saturated NaCl (100 mL). The organic phase was concentrated to provide 6.91 g of a yellow foam. Analysis of the crude material by HPLC showed a 3:14:2 mixture of **8**:**9**:**10**.

Preparation of Trospectomycin. Purified enone **9** (20 g) was dissolved in 100 mL of methanol, and 3.2 mL of acetic acid was added. One gram of 5% Pd on alumina was then added. The slurry was stirred or shaken under an atmosphere of H_2 at 50 psi until hydrogen uptake stops (should take about 5–6 h). It is best to check reaction completeness by TLC. TLC procedure: 0.1 mL of reaction mixture is diluted by 3 mL of MeOH, and 2 μL is spotted on a silica gel plate. Elute with 1% TEA in MeOH. Visualize by UV (should be very little or no UV activity) and H_2SO_4 char. When complete, the slurry was filtered through a pad of solka flok to remove the catalyst and the cake washed with MeOH (40 mL). The pH at this point was between 6.1 and 6.5. H_2SO_4 (50%) was added dropwise to adjust the pH to 2.0–2.2. Crystallization began at this point. The mixture was cooled to −10 °C and allowed to crystallize for several hours. The slurry was filtered and washed with cold 10% aqueous methanol, and the solids were dried in a vacuum oven at 60 °C for 8 h. This provided 8.9 g of trospectomycin identical to that prepared by White.[1b] IR: 3300, 3125, 2953, 2926, 2867, 2855, 1613, 1463, 1378, 1137, 1121, 1085, 1072, 1049, 1038, 712. ^{1}H NMR (D_2O): 4.9 (s, 1 H), 4.90 (m, 1 H), 4.45 (dd, J = 10.2, 10.6 Hz, 1 H), 4.14 (m, 1 H), 4.08 (m, 1 H), 3.97 (m, 1 H), 3.61 (dd, J = 8.9 Hz, 1.2 Hz, 1 H), 3.37 (dd, J = 7.4, 1.2 Hz, 1 H), 2.97 (s, 3 H), 2.95 (s, 3 H), 1.96 (m, 2 H), 1.70 (m, 2 H), 1.45 (m, 4 H), 1.00 (t, J = 5.3 Hz, 3 H). ^{13}C NMR (D_2O): 96.33 (d), 96.28 (s), 94.6 (s), 74.55 (d), 72.5 (d), 68.63 (d), 68.29 (d), 64.27 (d), 62.41 (d), 61.33 (d), 42.10 (t), 36.14 (t), 33.45 (q), 33.01 (q), 29.01 (t), 24.63 (t), 15.88 (q). $[\alpha]_D$ +19°.