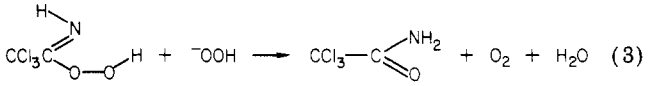
of an oxygen-transfer reagent is its ability to epoxidize a weakly nucleophilic terminal alkene. Our data also demonstrate that **6** has chemoselectivity of practical value to the synthetic chemist. The deactivated double bonds of α,β-unsaturated carbonyls are epoxidized, although 2-cyclohexenone failed to react under our typical reaction conditions. No products derived from a Baeyer–Villiger oxidation were in evidence. The carbon–carbon double bond in 6-methyl-5-hepten-2-one was also selectively epoxidized. Another unique characteristic of this oxidant is its capacity to epoxidize 1-cyclopenteneacetonitrile without disturbing the nitrile functional group. The reaction is also stereospecific as evidenced by the formation of only cis epoxide from *cis*-stilbene and the trans epoxide from *trans*-cinnamyl alcohol, *trans*-stilbene, and *trans*-cyclooctene.

We propose a bimolecular mechanism involving nucleophilic attack of the alkene HOMO on the antibonding orbital of the O–O bond.[15b] The equilibrium constant for formation of **6** is quite low (i.e., $k_{-1} \gg k_1$). The rate expression consistent with this suggestion is rate = $K_{eq}k_2$-$[CCl_3CN][H_2O_2]$[alkene]. Consequently, the rate of reaction may be increased by increasing the ratio of coreactants to alkene. An increase in pH favors formation of **6**, but a competing reaction with the anion of H_2O_2 reduces the concentration of active oxygen by a direct nucleophilic displacement on the peroxide bond (eq 3).[19] The reaction times may be reduced by carrying out the reaction at reflux (~40 °).



The reaction may also be accomplished in methanol as the solvent, where the relative rates of epoxidation with benzonitrile and trichloroacetonitrile are comparable. However, under our biphasic conditions employing CH_2Cl_2 solvent, benzonitrile did not afford a detectable amount of epoxide. We made similar observations earlier where we noted that methanol solvent was required when acetonitrile was employed as the coreactant.[13b] We attribute these observations to a lack of solubility of the peroxyimidic acids (1; R = CH_3, Ph) in a nonpolar solvent.

We conclude that the trichloroacetonitrile–H_2O_2 system provides the versatility, specificity, ease of preparation, and mild reaction conditions required of an epoxidizing agent. This reagent should provide a practical substitute for MCPBA in many instances.

Experimental Section

6-Methyl-5,6-epoxyheptan-2-one. To a stirring solution of trichloroacetonitrile (8.5 g, 0.059 mol) and 6-methyl-5-hepten-2-one (3.72 g, 0.0294 mol) in 40 mL of methylene chloride was added dropwise 5.0 mL of 30% H_2O_2 (0.044 mol). The H_2O_2 was adjusted to pH 6.8 by the addition of 2.25 g of K_2HPO_4 prior to addition. The biphasic mixture was magnetically stirred at room temperature while the depletion of alkene was monitored by GLC (6-ft column, 10% UCW on Chromosorb W, 130 °C). After 3 h, 25 mL of pentane was added, and the precipitated trichloroacetamide was removed by filtration through a fritted disk and washed with pentane. The filtrates were washed with water (20 mL), cold 3% Na_2SO_3 solution (25 mL), and brine (25 mL) and dried ($MgSO_4$). The solvents were removed by aspiration, and the yellow residue was fractionally distilled to afford 3.35 g (80%) of epoxide, bp 42–42.5 °C (20 mm).

Acknowledgment. We gratefully acknowledge support from the National Science Foundation (Grant No. CHE-81-06520) and the National Institutes of Health (Grant No. ES00761-09).

Registry No. Cl_3CCN, 545-06-2; H_2O_2, 7722-84-1; cyclohexene, 110-83-8; cyclohexene oxide, 286-20-4; 1-methylcyclohexene, 591-49-1; 1-methylcyclohexene oxide, 1713-33-3; *cis*-cyclooctene, 931-87-3; *cis*-cyclooctene oxide, 4925-71-7; *trans*-cyclooctene, 931-89-5; *trans*-cyclooctene oxide, 57378-33-3; norbornene, 498-66-8; norbornene epoxide, 278-74-0; 1-nonene, 124-11-8; 1-nonene oxide, 28114-20-7; *cis*-stilbene, 645-49-8; *cis*-stilbene oxide, 1689-71-0; *trans*-stilbene, 103-30-0; *trans*-stilbene oxide, 1439-07-2; *trans*-cinnamyl alcohol, 4407-36-7; *trans*-cinnamyl alcohol epoxide, 40641-81-4; 2-isopropylidene-5-methylcyclohexanone, 15932-80-6; 2-isopropylidene-5-methylcyclohexanone epoxide, 17677-87-1; 6-methyl-5-hepten-2-one, 110-93-0; 6-methyl-5,6-epoxyheptan-2-one, 16262-93-4; 1-cyclopenteneacetonitrile, 22734-04-9; 1-cyclopenteneacetonitrile epoxide, 84694-14-4; peroxytrichloroacetimidic acid, 84694-15-5.

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(24*S*)-24*H*-Isocalysterol: A New Steroidal Cyclopropene from the Marine Sponge *Calyx niceaensis*[1]

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Calysterol [23,28-cyclostigmasta-5,23(24)-dien-3β-ol, **N1**],[3,4] the principal sterol component of the sponge *Calyx niceaensis*, possesses one of the most intriguing functionalities, a cyclopropene ring, among the great variety of unusual side-chain substituents of marine sterols.[5] Recently we determined the absolute configuration (28*R*) of calysterol and isolated a novel steroidal cyclopropene, (23*R*)-23*H*-isocalysterol [(23*R*)-23,28-cyclostigmasta-5,24(28)-dien-3β-ol, **N2**] from *C. niceaensis*.[4] Our continuing study of the sterols of this sponge has now led to the isolation and characterization of a third steroidal cyclopropene, (24*S*)-24*H*-isocalysterol [(24*S*)-23,28-cyclostigmasta-5,23(28)-dien-3β-ol, **N3**] which forms the subject of this paper; in addition we have isolated two members of the rare class of Δ^{23}-unsaturated sterols, viz., (23*E*)- (**N4**) and (23*Z*)-stigmasta-5,23-dien-3β-ol (**N5**).

Reverse-phase HPLC of the sterol mixture of *C. niceaensis* yielded **N3** [M^+, m/z 410 ($C_{29}H_{46}O$); mp 111–113 °C; $[\alpha]^{20}_D$ −26° (*c* 0.007, CCl_4)]. The 360-MHz ^1H NMR spectrum (C_6D_6) showed the following side-chain signals: δ 1.020 (3 H, d, J = 6.8 Hz), 1.033 (3 H, d, J = 6.8 Hz), 1.092 (3 H, d, J = 6.6 Hz), 1.547 (1 H, d, J = 4.1 Hz), 1.70 (1 H, m), 1.975 (3 H, t, J = 1.4 Hz), 2.316 (1 H, ddd, J = 1.2, 7.9, 16.2 Hz), 2.473 (1 H, ddd, J = 1.9, 3.2, 16.2 Hz), besides signals arising from the usual Δ^5-3β-hydroxy sterol nucleus[6] [δ 0.659 (3 H, s, C-18), 0.931 (3 H, s, C-19), 3.38 (1 H, m, C-3α), 5.34 (1 H, m, C-6)]. Irradiation at δ 1.020,

(1) Minor and Trace Sterols in Marine Invertebrates. 36. For part 35 in this series, see: Itoh, T.; Sica, D.; Djerassi, C. *J. Chem. Soc. Perkin Trans. 1*, in press.

(2) Istituto di Chimica Organica dell'Università di Napoli, Naples, Italy.

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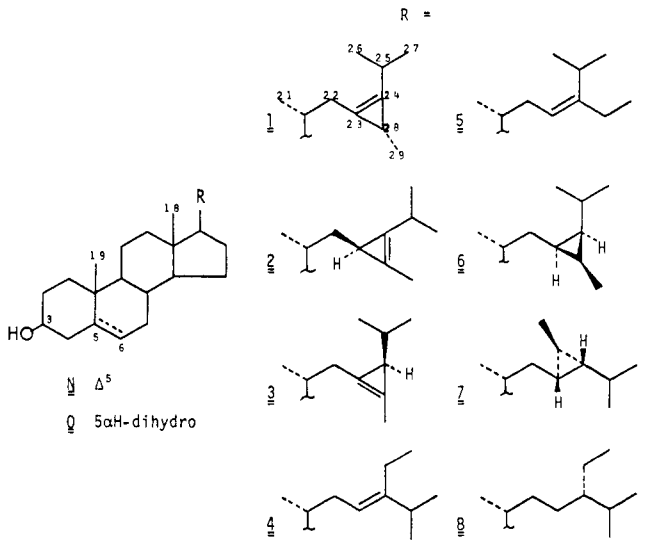

1.033, or 1.547 simplified the multiplet at δ 1.70, while irradiation of the δ 1.70 signal collapsed the former three doublets into singlets. This experiment allowed the assignment of the doublets at δ 1.020 and 1.033 to the C-26 and C-27 isopropyl methyls, the doublet at δ 1.547 to the C-24 H, and the multiplet at δ 1.70 to the C-25 H. The chemical shift of the highly deshielded olefinic methyl triplet (δ 1.975) suggests that the triplet is associated with the C-29 methyl group which is linked to the cyclopropene functionality.[4] The magnitude of the coupling constant (J = 1.4 Hz) of the triplet is consistent with that of ^5J (H—C—C=C—C—H) coupling. Irradiation of the δ 1.975 signal simplified the methylene (ddd, each 1 H) signals into dd signals [δ 2.316 (J = 7.9, 16.2 Hz), 2.473 (J = 3.2, 16.2 Hz)], indicating that the coupling partner of the methyl triplet is the C-22 methylene group. The remaining methyl doublet (δ 1.092) must then be ascribed to the C-21 methyl substituent. Taking into consideration that there is no olefinic signal, aside from C-6 H, in the NMR spectrum, the 23,28-cyclostigmasta-5,23(28)-dien-3β-ol (24*H*-isocalysterol, **N3**) structure can be proposed for this sterol.

The mass spectral data are consistent with this structure: the base peak at m/z 367 originates from an allylic cleavage of the 24–25 bond, while the diagnostically significant ion of mass 300 is due to a McLafferty rearrangement[7] involving cleavage of the 20–22 bond with one H transfer from C-17. The presence of the Δ5-3β-hydroxy sterol nucleus was substantiated by the typical fragments at m/z 325, 299, 271, 253, 231, and 213.[8] For establishment of the stereochemistry (24*S*) of cyclopropene **N3**, this sterol was subjected to catalytic hydrogenation over platinum oxide. Assuming syn hydrogenation to be operative on both sides of the double bond of **N3**, one will encounter two possible diastereoisomeric cyclopropanes, (23*R*,24*S*,28*S*)- (**O6**) and (23*S*,24*S*,28*R*)-23,24-dihydrocalystanol (**O7**). On the assumption that steric factors (hydrogen attack opposite the C-24 alkyl rest) would play the dominant stereochemical role,[9] the all-cis-substituted cyclopropane **O6** would be expected to be the kinetically controlled major product. On hydrogenation, cyclopropene **N3** yielded cyclopropane **O6** (23*R*,24*S*,28*S*) as the major (65%) product accompanied by the cyclopropane **O7** (23*S*,24*S*,28*R*, 16%) and a ring-opened product, (24*S*)-5α-stigmastan-3β-ol (**O8**, 19%), thus demonstrating that the new marine sterol has the (24*S*)-24*H*-isocalysterol (**N3**) structure.

In addition to the new steroidal cyclopropene **N3**, we isolated both the 23*E* (**N4**) and 23*Z* (**N5**) epimers of stigmasta-5,23-dien-3β-ol from the sponge and characterized them by comparison of their spectroscopic data with those of their 24-methyl analogues.[10] A stigmasta-5,23-dien-3β-ol has previously been isolated from this sponge,[11] but the stereochemistry at C-23 remained undetermined.

Experimental Section

General Methods. Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Specific rotation was measured on a Perkin-Elmer 141 polarimeter. GLC was performed on a Hewlett-Packard 402 A chromatograph equipped with a flame-ionization detector (carrier gas He, temperature 260 °C). A glass column (1.8 m × 2 mm i.d.) containing 3% OV-17/GCQ was used. Relative retention times (RRT) were expressed relative to cholesterol (1.00). Low-resolution mass spectra were recorded on a Varian MAT-44 GLC/MS system at 70 eV by using a 3% OV-17/GCQ column (1.8 m × 2 mm i.d.). High-resolution mass spectra were recorded on a Varian MAT-711 double-focusing spectrometer equipped with a PDP-11/45 computer. ^{1}H NMR spectra were recorded on a Bruker HXS-360 (360 MHz) spectrometer in $CDCl_3$ or in C_6D_6 with $SiMe_4$ as an internal standard. Preparative HPLC was carried out on a Waters Associates HPLC system (M 6000 pump, R 403 differential refractometer) with two different reverse-phase columns: Whatman Partisil M9 10/50 ODS-2 (50 cm × 9 mm i.d.) with absolute methanol as the mobile phase; Altex Ultrasphere ODS 5 μm (25 cm × 10 mm i.d., two columns in series) with methanol–water (95:5) as the eluent. The RRT was expressed relative to (28*R*)-calysterol (**N1**).

Extraction, Sterol Isolation, and Fractionation. The *Calyx niceaensis* sponge, collected in the Bay of Naples (Italy) in 1981, was extracted with $CHCl_3$–MeOH (1:1). Prior to use for sterol isolation, the extract was kept under argon at −10 °C in the same solvent system as above containing 0.002% of butylated hydroxytoluene. In order to remove the phospholipids from the extract, the solvent was concentrated in vacuo at room temperature to a small volume, a 20-fold excess of acetone was added to the extract, and it was cooled to below 10 °C for 3 h. The bulky phospholipid precipitate was removed by centrifugation. After evaporation of acetone in vacuo, the phospholipid-free lipids (dissolved in a small amount of toluene) were chromatographed on Florisil, with the sterols being eluted with *n*-hexane–diethyl ether (3:1). The sterol mixture was initially fractionated by HPLC on an ODS-2 column which yielded fractions A [42% of the total sterols, RRT (ODS-2) = 1.00] and B (2%, RRT = 1.46) in addition to several other fractions. Fraction A, consisting mainly of (28*R*)-calysterol (**N1**), was fractionated further by HPLC on an Altex Ultrasphere ODS column, giving **N1** [RRT (Altex) = 1.00] and a new steroidal cyclopropene, (24*S*)-24*H*-isocalysterol [**N3**, 3.9% of the total sterols, HPLC (Altex) RRT = 0.98, GLC RRT = 1.30]. HPLC separation of fraction B on an Altex column afforded (23*E*)-stigmasta-5,23-dien-3β-ol [**N4**, 0.04% of the total sterols, HPLC (Altex) RRT = 1.30, GLC RRT = 1.59], (23*Z*)-stigmasta-5,23-dien-3β-ol [**N5**, 0.6% HPLC RRT = 1.34, GLC RRT = 1.64], and several other sterols.

Catalytic Hydrogenation of (24*S*)-24*H*-Isocalysterol (N3). The steroidal cyclopropene **N3** (3 mg) was hydrogenated in EtOH (4 mL) over PtO_2 catalyst (20 mg) at atmospheric pressure and temperature for 16 h. The reaction product was subjected to HPLC separation on an Altex column, affording three 24*S* compounds: (23*R*,24*S*,28*S*)-23,24-dihydrocalystanol [**O6**, 65% of the reaction mixture, HPLC (Altex) RRT = 1.85, GLC RRT = 1.27], (23*S*,24*S*,28*R*)-23,24-dihydrocalystanol (**O7**, 16%, HPLC RRT = 1.93, GLC RRT = 1.42), and (24*S*)-5α-stigmastan-3β-ol (**O8**, 19% HPLC RRT = 2.16, GLC RRT = 1.59). Identification of

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these three sterols, **O6–O8**, was accomplished by direct comparison of their chromatographic and spectroscopic properties with those of authentic sterols.[4]

Physical Data. The 360-MHz ^{1}H NMR data ($CDCl_3$, J values in hertz) and the mass spectral (MS) data [m/z (assignment, relative intensity)] of the three sterols **N3–N5** are given below.

(24*S*)-24*H*-Isocalysterol (N3): NMR δ 0.703 (3 H, s, C-18), 1.011 (3 H, s, C-19), 0.968 (3 H, d, J = 6.6, C-21), 0.785 and 0.792 (each 3 H, d, J = 6.8, C-26, C-27), 2.021 (3 H, t, J = 1.4, C-29), 1.168 (1 H, d, J = 4.4, C-24), 3.53 (1 H, m, C-3α), 5.35 (1 H, m, C-6); MS, m/z 410.352 23 (M^+, $C_{29}H_{46}O$, 6; calcd 410.354 84), 395.331 49 ($C_{28}H_{43}O$, 3), 392.344 64 ($C_{29}H_{44}$, 2), 377.317 77 ($C_{28}H_{41}$, 1), 367.298 89 ($C_{29}H_{39}O$, 100), 349.291 48 ($C_{26}H_{37}$, 5), 325.249 63 ($C_{23}H_{33}O$, 5), 300.244 54 ($C_{21}H_{32}O$, 9), 299.272 82 ($C_{22}H_{35}$, 2), 271.206 12 ($C_{19}H_{27}O$, 32), 267.211 84 ($C_{20}H_{27}$, 6), 253.193 37 ($C_{19}H_{25}$, 9), 231.174 06 ($C_{16}H_{23}O$, 9), 213.163 30 ($C_{16}H_{21}$, 8).

(23*E*)-Stigmasta-5,23-dien-3β-ol (N4): NMR δ 0.688 (3 H, s, C-18), 1.006 (3 H, s, C-19), 0.893 (3 H, d, J = 6.5, C-21), 0.997 (6 H, d, J = 7.1, C-26, C-27), 0.946 (3 H, t, J = 7.7, C-29), 5.076 (1 H, dd, J = 6.4, 7.6, C-23), 3.52 (1 H, m, C-3α), 5.35 (1 H, m, C-6), 2.23 (1 H, m, C-25); MS, m/z 412.370 50 (M^+, $C_{29}H_{48}O$, 40; calcd. 412.370 49), 397 (7), 394 (6), 379 (3), 314 (43), 301 (17), 300 (17), 299 (27), 296 (8), 283 (55), 271 (100), 255 (10), 253 (14), 241 (7), 229 (6), 215 (20).

(23*Z*)-Stigmasta-5,23-dien-3β-ol (N5): NMR δ 0.687 (3 H, s, C-18), 1.007 (3 H, s, C-19), 0.901 (3 H, d, J = 6.5, C-21), 0.958 (6 H, d, J = 6.9, C-26, C-27), 1.007 (3 H, t, J = 7.4, C-29), 5.006 (1 H, dd, J = 6.6, 7.9, C-23), 2.818 (1 H, septet, J = 6.9, C-25), 3.52 (1 H, m, C-3α), 5.35 (1 H, m, C-6); MS, m/z 412 (M^+, 13), 397 (25), 394 (1), 379 (1), 314 (13), 301 (8), 300 (13), 299 (13), 283 (16), 271 (100), 255 (6), 253 (7), 241 (8).

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Registry No. **N3**, 84582-62-7; **N4**, 77715-86-7; **N5**, 84621-35-2; **O6**, 83542-18-1; **O7**, 83542-20-5; **O8**, 55529-51-6.

Macrolide Antibiotics: Chemical Transformations in the Tylosin Series

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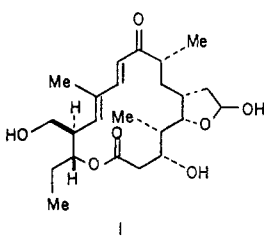
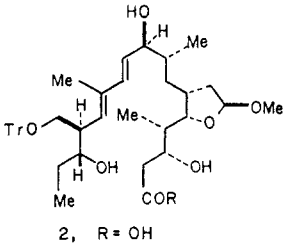
In connection with our synthetic objectives in the 16-membered-ring macrolide area, we required a sample of tylonolide hemiacetal (**1**)[1] in order to (1) permit full characterization[2] and (2) provide access to the seco acid derivative **2**.[3] The ready availability of **2** was required so that an investigation into the critical macrocyclization process could be examined prior to the realization of totally synthetic **2** in chiral form.[4]



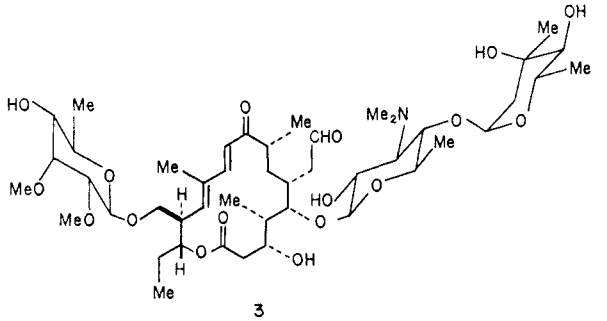
1



2, R = OH

14, R = OMe

Our first objective necessitated, in view of the low yields associated with the transformation of the N-oxide of O-mycaminosyltylonolide into tylonolide hemiacetal (**1**),[5] the development of an improved procedure for the cleavage of the glycosidic linkage in O-mycaminosyltylonolide (OMT, **4**). In contrast to the other glycosidic linkages in



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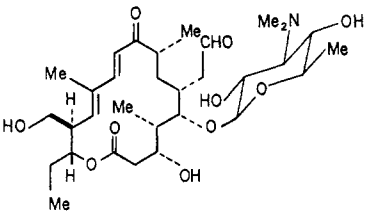

4

tylosin which are easily cleaved under acid hydrolysis, the amino sugar present in **4** resists acid hydrolysis. It has previously been established that hydrolysis of **4** under acid catalysis results in extensive destruction of the aglycon.[7] Previous degradation studies in the leucomycin series[8] and more recently in the tylosin area[3a,f] have successfully cleaved the amino sugar residue by subjecting the corresponding N-oxide to a modified Polonovski reaction.

During our degradation studies, we examined three sets of conditions for the transformation of OMT into tylono-

(1) Tylonolide hemiacetal is the aglycon of the 16-membered macrolide tylosin which is used therapeutically for the treatment of chronic respiratory diseases in chickens: McGuire, J. M.; Bonieces, W. S.; Higgins, C. E.; Hoehn, M. M.; Stark, W. M.; Westhead, J.; Wolfe, R. N. *Antibiot. Chemother. (Washington, DC)* **1961**, *11*, 320.

(2) Despite the fact that tylonolide hemiacetal (1) has been prepared by degradation[3a,f] and partial synthesis,[3a] the $[\alpha]_D$ has never been recorded in the literature. Note the structure proposed in ref 3a for tylonolide hemiacetal has the wrong configuration about C(14).

(3) For synthetic studies in the tylosin series see: (a) Masamune, S.; Hayase, Y.; Chan, W. K.; Sobczak, R. L. *J. Am. Chem. Soc.* **1976**, *98*, 7874. (b) Nagel, A. A.; Vincent, L. A. *J. Org. Chem.* **1979**, *44*, 2050. (c) Tatsuta, K.; Amemiya, Y.; Kanemura, Y.; Kinoshita, M. *Tetrahedron Lett.* **1981**, *22*, 3997. (d) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *J. Am. Chem. Soc.* **1982**, *104*, 2027. Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *Ibid.* **1982**, *104*, 2030. (e) Lu, L.D.-L. *Tetrahedron Lett.* **1982**, *23*, 1867. (f) Matsubara, H.; Miyano, K.; Nakagawa, A.; Omura, S. *Chem. Pharm. Bull.* **1982**, *30*, 97. (g) Grieco, P. A.; Inanaga, J.; Lin, N.-H.; Yanami, T. *J. Am. Chem. Soc.* **1982**, *104*, 5781.

(4) Since completion of our initial degradation studies, the macrocyclization of seco acid **2** has been reported (see ref 3c,g).

(5) Omura reports a 10% yield for the transformation of the N-oxide of O-mycaminosyl tylonolide into 1 (Omura, S.; Nakagawa, A.; Machida, M.; Imai, H. *Tetrahedron Lett.* **1977**, 1045). For complete experimental details see ref 3f above. Masamune, in his degradation studies,[3a] claims, without experimental details, yields as high as 50% for the preparation of 1 from the N-oxide of OMT.

(6) Hamill, R. L.; Haney, M. E., Jr.; Stamper, M.; Wiley, P. F. *Antibiot. Chemother. (Washington, DC)* **1961**, *11*, 328. Omura, S.; Matsubara, H.; Nakagawa, A.; Furusoki, A.; Matsumoto, T. *J. Antibiot.* **1980**, *33*, 915.

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(8) (a) Moura, S.; Nakagawa, A.; Suzuki, K.; Hata, T.; Jakuboski, A.; Tishler, M. *J. Antibiot.* **1974**, *27*, 147. (b) Girotra, N. N.; Wendler, N. L. *Tetrahedron Lett.* **1975**, 227. (c) Also see: Ganguly, A. K.; Liu, Y.-T.; Same, O.; Jaret, R. S.; McPhail, A. T.; Onan, K. K. *Ibid.* **1980**, *21*, 4699.

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