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).

Acknowledgment. Financial support was provided by NIH Grants GM-06840 and GM-28352. We thank Dr. W. C. M. C. Kokke for helpful discussion, Ms. A. Wegmann for mass spectral measurements, and Dr. L. Durham for the 360-MHz NMR spectra. Use of the 360-MHz NMR spectrometer was made possible by grants from the NSF (GP-23663) and NIH (RR-0711).

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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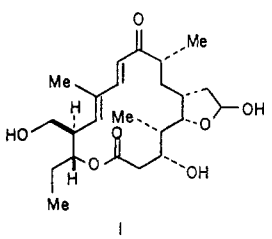
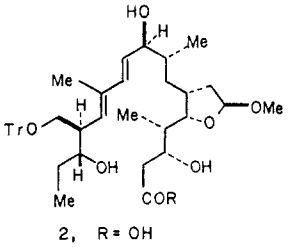
Received July 7, 1982

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]



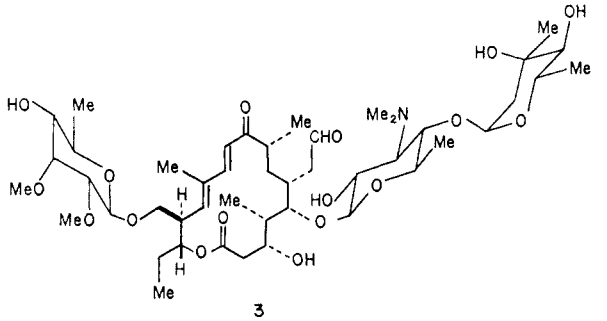
1



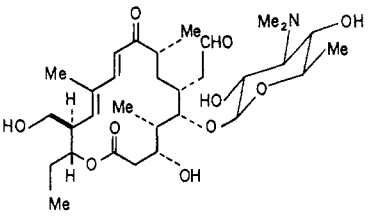
2, R = OH

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



3



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.

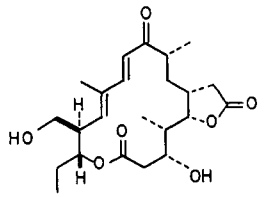
(6) Hamill, R. L.; Haney, M. E., Jr.; Stamper, M.; Wiley, P. F. *Antibiot. Chemother. (Washington, DC)* **1961**, *11*, 328. Omura, S.; Matsubara, H.; Nakagawa, A.; Furusoki, A.; Matsumoto, T. *J. Antibiot.* **1980**, *33*, 915.

(7) Morin, R. B.; Gorman, M.; Hamill, R. L.; Demarco, P. V. *Tetrahedron Lett.* **1970**, 4737.

(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.

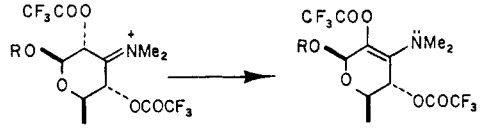
0022-3263/83/1948-0892$01.50/0

lide hemiacetal (1). Toward this end, OMT (4), readily available in ca. 65% overall yield from tylosin (3),[6] was converted into its corresponding *N*-oxide by treatment with *m*-chloroperbenzoic acid in chloroform. Crystalline OMT *N*-oxide [mp 157–159 °C; $[\alpha]_D$ +10.9° (*c* 1.00, $CHCl_3$)] was isolated in 95% yield. Subjection of OMT *N*-oxide to trifluoroacetic anhydride in tetrahydrofuran containing diisopropylethylamine (method A) afforded in 39% yield tylonolide hemiacetal as a crystalline compound, $[\alpha]_D$ +30.0° (*c* 0.32, $CHCl_3$). In addition, 10% of the known[3f] γ-lactone **5** (mp 196–197 °C) was isolated. In an



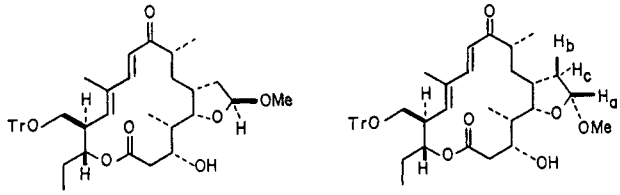
5

alternate procedure (method B) treatment of OMT *N*-oxide with chloroacetic anhydride in chloroform followed by prolonged exposure (45 h) to 0.1 N hydrochloric acid–pyridine generated tylonolide hemiacetal (1) in 30% isolated yield. The method of choice (method C) for the formation of 1 involves trifluoroacetylation of OMT *N*-oxide and subsequent treatment (65 °C, 4 h) with sodium acetate in aqueous tetrahydrofuran. As suggested previously[8a,b] from studies in the leucomycin series, the generation of 1 from OMT *N*-oxide proceeds via the intermediacy of enamine **6** which arises from imminium ion **7**.



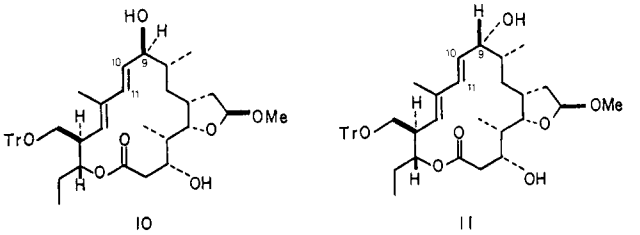
6 7

With a sufficient quantity of tylonolide hemiacetal available, we focussed our efforts on the conversion of **1** into seco acid **2**. Treatment of 1 with methanol–PPTS[9] and subsequent tritylation provided, in accord with the observation by Tatsuta,[3c] a 3:1 mixture of acetals **8** and **9**, in 70% overall yield, which were readily separated by preparative TLC.



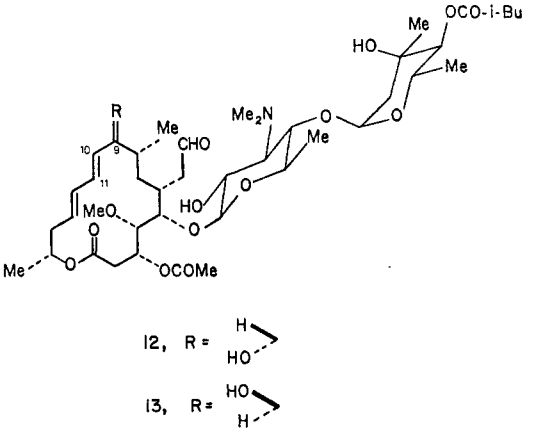
8 9

The transformation of **8** into **2** required reduction of the C(9) carbonyl and subsequent alkaline hydrolysis of the macrolide linkage. Initial attempts at reducing **8** with sodium borohydride in methanol at either −20 °C or ambient temperature provided in nearly quantitative yield a 7.7:1 mixture of allylic alcohols **10** (R_f 0.50, 3:2 ether–hexane, two developments) and **11** (R_f 0.36), respectively, which was in disagreement with the results reported in the literature.[10] No reduction products were observed at −78 °C. In sharp contrast to these results, *reduction of 8 at*



10 11

−78 °C with sodium borohydride in methanol containing cerium(III) chloride hexahydrate[11] *led (15 min) exclusively to* ***10*** *as a crystalline material in 99% yield.* The configuration at C(9) was established by correlation of the ^1H NMR spectra of **10** and **11** with those previously recorded in the literature for the closely related macrolides leucomycin A_3 (**12**) and 9-*epi*-leucomycin A_3 (**13**).[12] In



12, R =

13, R =

leucomycin A_3, the coupling constant between H_9 and H_{10} is 9.0 Hz whereas in the epi series, $J_{9,10}$ = 4.0 Hz. Examination of the ^1H NMR spectrum (220 MHz) of **10** reveals H_{10} as a doublet of doublets centered at δ 5.78 with $J_{10,11}$ = 15.8 Hz and $J_{9,10}$ = 3.6 Hz. In the case of the isomeric allylic alcohol **11**, the H_{10} proton also appears as a doublet of doublets at δ 5.66 with $J_{10,11}$ = 15.8 Hz and $J_{9,10}$ = 8.6 Hz.

Alkaline hydrolysis of **10** proceeded smoothly (97%) at 60 °C upon treatment with 1 N sodium hydroxide–methanol (1:4) for 12 h, giving rise to enantiomerically pure seco acid **2** which was characterized as its methyl ester **14** (see Experimental Section), thus completing the initial phase of our tylosin studies.

Experimental Section

Melting points were determined on a Fisher-Johns hot-stage melting point apparatus. All melting points and boiling points are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 298 grating infrared spectrometer, and nuclear magnetic resonance (NMR) spectra were recorded at either 220 (Varian HR-220) or 360 MHz (Nicolet NT-360) as indicated. Chemical shifts are reported in parts per million (δ) relative to Me_4Si (δ 0.0) as an internal standard. Rotations were carried out at 25–28 °C on a Perkin-Elmer 241 Polarimeter. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

Reactions were run under an atmosphere of nitrogen. "Dry" solvents were dried immediately before use. Tetrahydrofuran and dimethoxyethane were distilled from sodium–benzophenone. Pyridine, triethylamine, and diisopropylamine were distilled from calcium hydride. Methylene chloride was distilled from P_2O_5. Thin-layer chromatography (TLC) was carried out on Analtech (Uniplate) glass plates precoated with silica gel GF (250 μm).

***O*-Mycaminosyltylonolide *N*-Oxide (OMT *N*-Oxide).** To a stirred solution of 597 mg (1.0 mmol) of *O*-myc-

(9) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.

(10) After the completion of our studies, Professor Tatsuta informed us (private communication) that the yields reported for **28a** and **28b** in his paper[3c] should be reversed.

(11) Gamal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

(12) Freiberg, L. A.; Egan, R. S.; Washburn, W. H. *J. Org. Chem.* **1974**, *39*, 2474.

aminosyltylonolide (4)[6] in 10 mL of chloroform was added at 0 °C over a 10-min period 246 mg (1.4 mmol) of *m*-chloroperbenzoic acid in 10 mL of chloroform. After 4 h at room temperature, the reaction mixture was passed through a column of basic alumina (Woelm, activity I, 25 g). Elution with 4:1 chloroform–methanol gave 580 mg (95%) of pure OMT *N*-oxide as a white crystalline solid: mp 157–159 °C; R_f 0.72 (neutral alumina, 7:1 chloroform–methanol); $[\alpha]_D$ +10.9° (*c* 1.00, chloroform); IR ($CHCl_3$) 3600–3200, 2960, 2930, 2870, 2720, 1720, 1670, 1625, 1580, 1455, 1375, 1315, 1270, 1180, 1160, 1070, 985 cm^{-1}; NMR (220 MHz) ($CDCl_3$) δ 9.75 (s, 1 H), 7.34 (d, 1 H, *J* = 15 Hz), 6.23 (d, 1 H, *J* = 15 Hz), 5.94 (d, 1 H, *J* = 9.5 Hz), 5.07 (br t, 1 H, *J* = 9.0 Hz), 4.43 (m, 1 H), 3.47 (s, 3 H), 3.28 (s, 3 H), 1.61 (s, 3 H), 1.34 (d, 3 H, *J* = 7.0 Hz), 1.23 (d, 3 H, *J* = 7.0 Hz), 0.98 (d, 3 H, *J* = 7.0 Hz), 0.96 (t, 3 H, *J* = 7.0 Hz). Anal. Calcd for $C_{31}H_{51}NO_{11}\cdot H_2O$: C, 58.93; H, 8.46; N, 2.22. Found: C, 58.65; H, 8.53; N, 2.14.

Tylonolide Hemiacetal (1). Method A. To a solution of 580 mg (0.95 mmol) of *O*-mycaminosyltylonolide *N*-oxide in 10 mL of dry tetrahydrofuran cooled to −78 °C were added 1.04 mL (6.0 mmol) of diisopropylethylamine and 776 μL (5.49 mmol) of trifluoroacetic anhydride. After 1 h at −78 °C, the reaction mixture was warmed to room temperature where stirring was continued for 15 h. After neutralization with a saturated sodium bicarbonate solution at 0 °C, the reaction mixture was extracted with chloroform. The organic layer was washed with a saturated sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Removal of the solvent in vacuo afforded 820 mg of a drak brown oil which was passed through a column of neutral alumina (Woelm, activity I, 40 g). Elution with 8:1 chloroform–methanol gave 284 mg of a brown oil which was chromatographed on 30 g of silica gel. Elution with 3:7 benzene–ethyl acetate gave 42 mg (10%) of γ-lactone **5** as colorless prisms: mp 196–197 °C (acetone–ether–hexane) (lit.[3f] mp 186–188 °C); $[\alpha]_D$ +58.7° (*c* 0.15, $CHCl_3$); R_f 0.75 (benzene–ethyl acetate, 1:4); IR ($CHCl_3$) 3500, 2960, 2930, 2870, 1770, 1705, 1675, 1620, 1590, 1455, 1400, 1375, 1355, 1330, 1315, 1290, 1270, 1220, 1175, 1145, 1055, 995, 980, 950, 910, 875, 850, 810 cm^{-1}; NMR (220 MHz, $CDCl_3$) δ 0.97 (t, 3 H, *J* = 7.2 Hz), 1.08 (d, 3 H, *J* = 6.0 Hz), 1.28 (d, 3 H, *J* = 6.0 Hz), 1.84 (s, 3 H), 4.45 (dd, 1 H, *J* = 11.0, 4.0 Hz), 4.98 (br t, 1 H, *J* = 9.0 Hz), 5.90 (d, 1 H, *J* = 10.0 Hz), 6.40 (d, 1 H, *J* = 15.5 Hz), 7.30 (d, 1 H, *J* = 15.5 Hz). Continued elution provided 156 mg (39%) of tylonolide hemiacetal **1** as a solid: R_f 0.58; $[\alpha]_D$ +30.0° (*c* 0.32, $CHCl_3$). Repeated recrystallization from methylene chloride–hexane gave colorless needles, mp 102.5–103.5 °C (lit.[3f] mp 103–105 °C). In contrast, recrystallization (five times) from acetone–ether–hexane provided colorless needles: mp 157.5–158.5 °C (lit.[3a] mp 147–148 °C); IR ($CHCl_3$) 3590, 3500, 2970, 2935, 2880, 1710, 1675, 1625, 1595, 1455, 1400, 1375, 1355, 1320, 1270, 1245, 1180, 1130, 1055, 985, 960, 905, 880 cm^{-1}; NMR (220 MHz) ($CDCl_3$) δ 7.26 (d, 1 H, *J* = 15.5 Hz), 6.36 (d, 1 H, *J* = 15.5 Hz), 5.86 (d, 1 H, *J* = 10.0 Hz), 5.53 (m, 1 H), 4.97 (t, 1 H, *J* = 9.0 Hz), 2.86 (m, 1 H), 1.83 (s, 3 H), 1.25 (d, 3 H, *J* = 7.0 Hz), 1.01 (d, 3 H, *J* = 7.0 Hz), 0.95 (t, 3 H, *J* = 6.5 Hz). Anal. Calcd for $C_{23}H_{36}O_7\cdot H_2O$: C, 62.42; H, 8.65. Found: C, 62.75; H, 8.77.

Tylonolide Hemiacetal (1). Method B. To a solution containing 140 mg (0.23 mmol) of OMT *N*-oxide in 2.5 mL of chloroform heated to 60 °C was added 312 mg (1.82 mmol) of chloroacetic anhydride. After 15 min, the reaction was cooled to room temperature, and a solution of saturated sodium bicarbonate was added. The product was isolated by extraction with chloroform. The combined organic extracts were washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude residue was treated with 3.0 mL of pyridine–0.1 N hydrochloric acid (10:1 v/v) (pH ca. 6.5). After 45 h at room temperature, the pyridine was evaporated under reduced pressure, and the crude product was dissolved in ethyl acetate. The organic layer was washed successively with 3% phosphoric acid, water, and saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue (viscous oil) was chromatographed on 5.0 g of silica gel. Elution with a gradient of 1:3 chloroform–ether to all ether gave 29 mg (30%) of tylonolide hemiacetal which was identical in all respects with the sample of 1 obtained above.

Tylonolide Hemiacetal (1). Method C. To a stirred solution of 100 mg (0.16 mmol) of OMT *N*-oxide in 1.8 mL of chloroform was added 184 μL (1.3 mmol) of trifluoroacetic anhydride. After 20 min at room temperature, the reaction mixture was cooled to 0 °C and was quenched by the addition of a saturated sodium bicarbonate solution. The reaction mixture was extracted with chloroform, and the combined organic layers were dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was diluted with 3.0 mL of a water–tetrahydrofuran (1:4) mixture, treated with 150 mg of sodium acetate, and heated at 65 °C for 4 h. After removal of the solvent under reduced pressure, the product was extracted with ethyl acetate. The combined organic extracts were washed with saturated sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo gave a yellow oil which was chromatographed on 5.0 g of silica gel. Elution with a gradient of 1:3 chloroform–ether to all ether afforded 24 mg (35%) of tylonolide hemiacetal which was identical in all respects with the sample of 1 obtained above.

20-*O*-Methyltylonolide Hemiacetal. A solution of 25 mg (0.059 mmol) of tylonolide hemiacetal (1) in 1.2 mL of methanol containing 1.5 mg of pyridinium *p*-toluenesulfonate[9] was stirred for 5 h at room temperature. The reaction was quenched by the addition of saturated sodium bicarbonate solution. After removal of the solvent in vacuo, the crude product was isolated by extraction with ether. The combined organic extracts were washed with water, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The crude product was chromatographed on 10 g of silica gel. Elution with ether gave 25 mg (97%) of crystalline 20-*O*-methyltylonolide hemiacetal as a mixture about the anomeric carbon: R_f 0.50 (ether); IR ($CHCl_3$) 3500, 2960, 2925, 2870, 2820, 1705, 1675, 1625, 1590, 1450, 1400, 1370, 1315, 1265, 1180, 1125, 1090, 1050, 1010, 980, 955, 910, 900, 870 cm^{-1}; NMR (220 MHz, $CDCl_3$) δ 0.93 (t, 3 H, *J* = 6.5 Hz), 1.01 (d, 3 H, *J* = 6.5 Hz), 1.22 (d, 3 H, *J* = 6.5 Hz), 1.82 (s, 3 H), 3.32 (s, 3 H), 5.88 (br d, 1 H, *J* = 10.0 Hz), 6.35 (d, 1 H, *J* = 15.5 Hz), 7.25 (d, 1 H, *J* = 15.5 Hz). Recrystallization from methylene chloride–ether–hexane provided analytically pure material, mp 103–105 °C. Anal. Calcd for $C_{24}H_{38}O_7$: C, 65.73; H, 8.73. Found: C, 65.64; H, 9.03.

20-*O*-Methyl-23-*O*-trityltylonolide Hemiacetal (8). A mixture of 25 mg (0.057 mmol) of 20-*O*-methyltylonolide hemiacetal [mixture about C(20)], 47.7 mg (0.17 mmol) of trityl chloride, 0.7 mg of 4-(dimethylamino)pyridine, 26.3 μL (0.19 mmol) of triethylamine, 288 mg of sodium bicarbonate, and 200 mg of magnesium sulfate in 2.5 mL of dry methylene chloride was stirred for 24 h at room temperature. After dilution with 10 mL of ether, the reaction mixture was filtered through a pad of Celite. The filtrate was washed with a saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was chromatographed on 10 g of silica gel. Elution with 1:1 ether–hexane gave 34 mg (87%) of a mixture of trityl ethers **8** and **9** (3:1 ratio by NMR) which were separated by preparative TLC (silica gel) with 1:1 ether–hexane (three developments).

α-Isomer **9**: R_f 0.46 (ether–hexane, 2:1); mp 85–86 °C; $[\alpha]_D$ +1.4° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3510, 3080, 3060, 3000, 2970, 2935, 2880, 2830, 1705, 1675, 1625, 1595, 1490, 1445, 1400, 1375, 1355, 1320, 1270, 1180, 1150, 1125, 1070, 1005, 985, 950, 915, 895, 870, 810, 695, 625 cm^{-1}; NMR (220 MHz, $CDCl_3$) δ 0.80 (t, 3 H, *J* = 6.5 Hz), 1.03 (d, 3 H, *J* = 6.5 Hz), 1.25 (d, 3 H, *J* = 6.5 Hz), 1.80 (s, 3 H), 3.34 (s, 3 H), 3.64 (d, 1 H, *J* = 10.8 Hz), 3.85 (dd, 1 H, *J* = 10.4 Hz, *J* = 3.6 Hz), 4.93 (d, 1 H, *J* = 6.0 Hz), 5.04 (br t, 1 H, *J* = 10.0 Hz), 6.02 (d, 1 H, *J* = 10.5 Hz), 6.38 (d, 1 H, *J* = 15.5 Hz).

β-Isomer **8**: R_f 0.41; mp 131–132 °C; $[\alpha]_D$ +67.0° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3510, 3080, 3050, 2990, 2960, 2925, 2865, 2820, 1705, 1675, 1625, 1590, 1485, 1445, 1400, 1375, 1355, 1320, 1270, 1185, 1150, 1130, 1075, 1060, 1015, 1005, 985, 960, 920, 900, 880, 855, 815, 700, 630 cm^{-1}; NMR (220 MHz $CDCl_3$) δ 0.80 (t, 3 H, *J* = 6.5 Hz), 1.03 (d, 3 H, *J* = 6.5 Hz), 1.24 (d, 3 H, *J* = 6.5 Hz), 1.81 (s, 3 H), 3.34 (s, 3 H), 3.64 (d, 1 H, *J* = 10.8 Hz), 3.99 (dd, 1 H, *J* = 10.4, 3.5 Hz), 4.95–5.11 (m, 2 H), 6.02 (d, 1 H, *J* = 10.5 Hz), 6.35 (d, 1 H, *J* = 15.5 Hz). Anal. Calcd for $C_{43}H_{52}O_7$: C, 75.85; H, 7.70. Found: C, 75.97; H, 7.78.

$NaBH_4$–$CeCl_3\cdot 6H_2O$ Reduction of 20-*O*-Methyl-23-*O*-trityltylonolide Hemiacetal (8). To a cooled solution (−78 °C) of 320 mg (0.47 mmol) of ketone **8** in 18 mL of methanol containing 171 mg (0.47 mmol) of cerium chloride hexahydrate was added

17.8 mg (0.47 mmol) of sodium borohydride. After 15 min at −78 °C, the reaction was quenched by the addition of acetone. The solvent was removed under reduced pressure, and the crude product was dissolved in ethyl acetate and was washed with saturated sodium bicarbonate solution. The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. There was obtained 320 mg (100%) of crude alcohol **10** [R_f 0.47 (ether–hexane, 2:1)] as a homogeneous crystalline solid. Recrystallization from ether–hexane gave colorless needles: mp 180–181 °C; $[\alpha]_D$ +75.5° (*c* 0.70, $CHCl_3$); IR ($CHCl_3$) 3590, 3500, 3080, 3055, 3020, 3000, 2960, 2920, 2870, 2820, 1710, 1595, 1490, 1450, 1405, 1365, 1325, 1315, 1270, 1185, 1070, 1020, 1000, 980, 960, 895, 875, 700, 625 cm^{-1}; NMR (220 MHz, $CDCl_3$) δ 0.80 (t, 3 H, *J* = 6.5 Hz), 1.00 (d, 6 H, *J* = 6.5 Hz), 1.75 (s, 3 H), 3.34 (s, 3 H), 4.04 (dd, 1 H, *J* = 10.0, 5.0 Hz), 4.26 (br s, 1 H), 5.00 (m, 2 H), 5.56 (d, 1 H, *J* = 10.5 Hz), 5.78 (dd, 1 H, *J* = 15.8, 3.6 Hz), 6.46 (d, 1 H, *J* = 15.8 Hz). Anal. Calcd for $C_{43}H_{54}O_7$: C, 75.63; H, 7.97. Found: C, 75.83; H, 8.01.

Preparation of Seco Acid Derivative 2. A solution of 100 mg (0.15 mmol) of lactone **10** in 1.5 mL of methanol was treated with 340 μL (0.35 mmol) of 1 N sodium hydroxide solution. After 12 h at 60 °C, the methanol was removed under reduced pressure, and 10 mL of water was added. The alkaline solution was cooled to 0 °C, acidified (pH 4) with 3% phosphoric acid, and saturated with sodium chloride. The product was isolated by extraction with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate and evaporated in vacuo. There was obtained 95 mg (97%) of seco acid **2** as a glass which was used directly in the next reaction. For purposes of characterization, seco acid **2** was transformed into ester **14** by treatment with an ethereal solution of diazomethane. Purification on silica gel with 4:1 ether–hexane gave analytically pure **14** as colorless needles: mp 52–54 °C: R_f 0.55 (ether); $[\alpha]_D$ +43.0° (*c* 1.00, $CHCl_3$) (lit.[3c] $[\alpha]_D$ +40.0°); IR ($CHCl_3$) 3590, 3500, 3080, 3050, 2995, 2950, 2920, 2870, 2830, 1725, 1595, 1490, 1460, 1445, 1435, 1375, 1365, 1320, 1225, 1175, 1150, 1060, 1025, 970, 895, 695, 625 cm^{-1}; NMR (360 MHz, $CDCl_3$) δ 1.72 (s, 3 H), 3.33 (s, 3 H), 3.69 (s, 3 H), 4.15 (m, 1 H), 4.20 (m, 1 H), 4.28 (dd, 1 H, *J* = 7.2, 4.0 Hz), 5.01 (d, 1 H, *J* = 4.3 Hz), 5.61 (dd, 1 H, *J* = 15.5, 6.8 Hz), 5.62 (d, 1 H, *J* = 9.4 Hz), 6.29 (d, 1 H, *J* = 15.5 Hz). Anal. Calcd for $C_{44}H_{58}O_8$: C, 73.92; H, 8.18. Found: C, 73.68; H, 8.10.

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Addition Reactions of *N*-Bromoperfluoromethanamine with Some Olefins

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Perfluoro compounds containing nitrogen–bromine bonds are very rare. Only a few examples are known in the literature including *N*-bromoperfluorosuccinimide,[2] $SF_2{=}NBr$,[3] F_2NBr,[4] $(CF_3)_2C{=}NBr$,[5] and $(CF_3)_2NBr$.[6] Only the latter compound has been investigated in any detail regarding its chemistry.[7] As expected, the N–Br bond in $(CF_3)_2NBr$ is very labile, the bromine atom is electrophilic, and a variety of useful photochemical and thermal reactions can be carried out, e.g., see Scheme I.

Scheme I

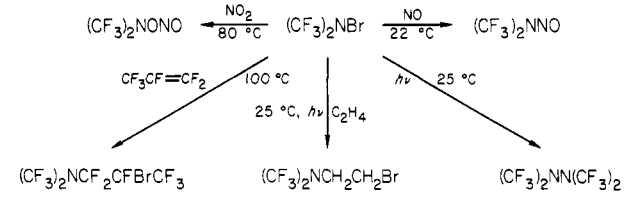

Table I. Addition Reactions of CF_3NBrF

olefin[a]	temp/time, °C/h	product (%)[c]
$CH_2{=}CH_2$	110/12	$CF_3NFCH_2CH_2Br$ (37)
$CH_2{=}CH_2$	110/5, 110/13, 125/18[b]	$CF_3NFCH_2CH_2Br$ (~90)
$CF_2{=}CH_2$	110/12	$CF_3NFCH_2CF_2Br$ (25)
$CF_2{=}CH_2$	93/10, 108/9, 150/12[b]	$CF_3NFCH_2CF_2Br$ (40)
$CF_2{=}CF_2$	122/9, 125/18[b]	$CF_3NFCF_2CF_2Br$ (90)
$CF_2{=}CF_2$	105/18	$CF_3NFCF_2CF_2Br$ (80)
$CF_2{=}CFCl$	100/9	$CF_3NFCF_2CFClBr$ (73)
$CF_2{=}CBr_2$	105/10	$CF_3NFCF_2CBr_3$ (85)
$CF_2{=}CCl_2$	109/13	$CF_3NFCF_2CCl_2Br$ (52

[a] Reactions were carried out with ~1 mmol each of olefin and CF_3NBrF. [b] Product was removed and unreacted starting materials were recycled after each temperature/time given. [c] Yield is based on starting amount of CF_3NBrF.

Recently, an excellent synthesis for CF_3NBrF from CF_2NF was found.[8]

$$CF_2{=}NF + Br_2 + KF \xrightarrow{22\ °C} CF_3NBrF + KBr$$

The surprising thermal stability of this compound facilitates an investigation of its reaction chemistry. Herein we report the thermal addition of CF_3NBrF to several olefins, which proceed in good yield with high regioselectivity.

Results and Discussion

The addition reactions of CF_3NBrF to olefins are summarized in Table I. The temperature necessary for reaction in every case was very near 100 °C. All the olefins except $CF_2{=}CBr_2$ and $CF_2{=}CCl_2$ were checked for reactivity at 22 °C, and the reactants were recovered after 1 day. In addition, $CF_2{=}CH_2$ was recovered after 10 h at 93 °C and similarly $CF_2{=}CFCl$ after 6 h at 80 °C. Even at 100 °C, the reactions are slow. Very little product was observed with $CF_2{=}CF_2$ after only 3 h at 105 °C. The yields of the reactions are not optimized, and it is clear from this survey that the yields vary with pressure and temperature. Also, side reactions were evident with $CH_2{=}CH_2$ and $CH_2{=}CF_2$, resulting in lower yields. Improved yields in these cases by removing the product after a period of time and recycling the reactants suggest that

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