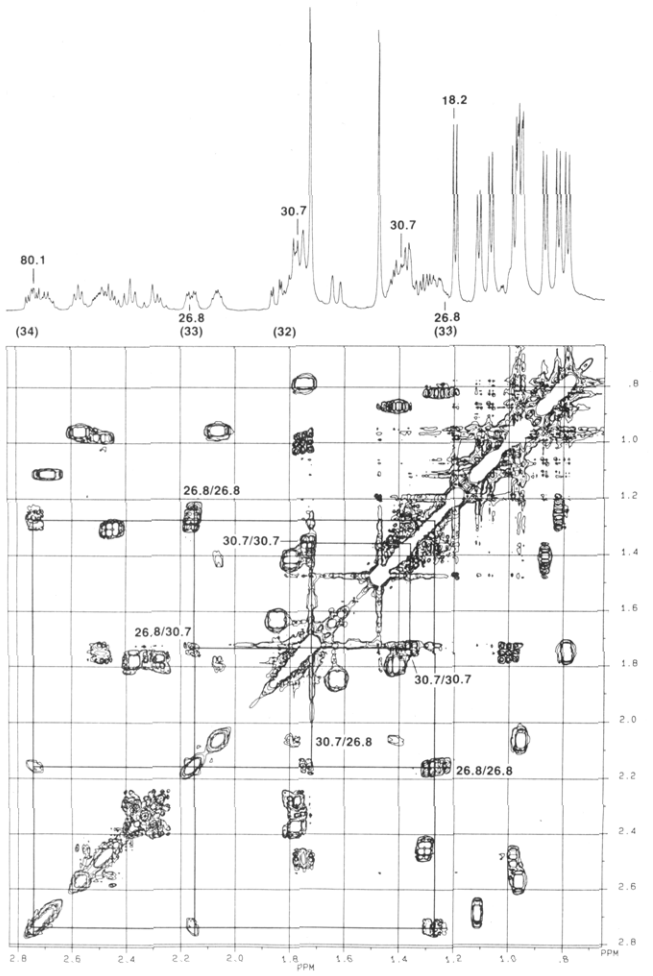

Figure 8. Expansion of Figure 7 in the range 0.8–2.8 ppm.

Experimental Section

Structural assignments were derived from a variety of one-dimensional and two-dimensional (COSY and heteronuclear ^1H–^{13}C correlated) NMR experiments carried out on a Bruker (^1H NMR, 250 MHz; ^{13}C NMR, 62.8 MHz) WH-250 spectrometer operating at ambient temperatures. The carbon type (methine, methylene, methyl, or quaternary) was determined by DEPT experiments. High-resolution electron impact mass spectra were obtained on an AEI-MS 30 spectrometer and FAB mass spectra were obtained on a VG 70/250 spectrometer. The three-dimensional structure of the Rubidium salt of 1 (crystallized from CH_3OH) was determined by X-ray crystallography with a crystal that measured 0.22 × 0.25 × 0.28 mm. A 1-Å data set (maximum $\sin\theta/\lambda = 0.5$) was collected on a Nicolet R3m/μ diffractometer, and a trial structure was obtained by direct methods revealing the following lattice parameters: a = 12.384 (3) Å, b = 16.328 (4) Å, and c = 14.190 (5) Å with α = 90.0°, β = 98.84 (2)°, and γ = 90.0°. The space group was determined to be $P2_1$ with two molecules per unit cell. The molecular formula was $C_{47}H_{77}O_{14}Rb{\cdot}2CH_3OH$ with a calculated density of 1.19 g/cm^3. There were 3054 reflections collected, and of those reflections 2848 (93%) with $I > 3.0\sigma$ were adjudged observed. This trial structure refined routinely. Hydrogen positions were calculated whenever possible. The methyl hydrogens and the hydrogens on oxygen were located by difference Fourier techniques. The shifts calculated in the final cycle of least-squares refinement were all less than 0.1 of their corresponding standard deviations. The final R index was 0.059. The absolute configuration was determined by using the anomalous dispersion of the Rb ion. The refined structure was plotted using the SHELXTL[12] plotting package (Figure 9).

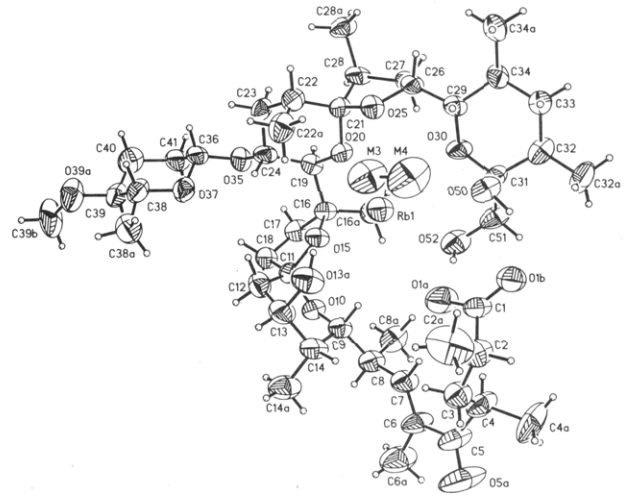

Figure 9. The computer rendering of the solid-state structure of polyether 1.

Acknowledgment. We thank R. Ware and J. Stroh for obtaining mass spectral data and D. Rescek for obtaining NMR data. The X-ray data were obtained by J. Bordner.

Supplementary Material Available: Tables containing coordinates, anisotropic temperature factors, bond distances, and torsional angles for Figure 9 (9 pages). Ordering information is given on any current masthead page.

(12) Sheldrick, G. M. SHELXTL user manual; Nicolet Instrument Co., 1981.

(13) The structure of the related 19-deoxy aglycon also has been reported; see: Westley, J. W.; et al. *J. Antibiot.* **1984**, *37*, 813.

New Synthesis from β-Pinene of Tetracyclo[6.2.1.0^{1,6}.0^{6,10}]undecanes, an Unusual Ring System

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The product (**2**) of the ene reaction between β-pinene (**1**) and acryloyl chloride cyclizes on heating at 150 °C in tributylamine to 10,10-dimethyltricyclo[7.1.1.0^{2,7}]undec-2(7)-en-6-one (**3**), 10-chloro-9,9-dimethyltricyclo-[6.2.1.0^{1,6}]undecan-5-one (**4**) of unstated stereochemistry, a number of ring-opened hydrogenated naphthalenes, and unidentified substances.[1,2] We now establish the stereochemistry of the chloro ketone (**4**), show that one of the unidentified substances is 9,9-dimethyltetracyclo-[6.2.1.0^{1,6}.0^{6,10}]undecan-2-one (**5**), and describe the preparation of this new representative of an unusual ring system from the chloro ketone (**4**).

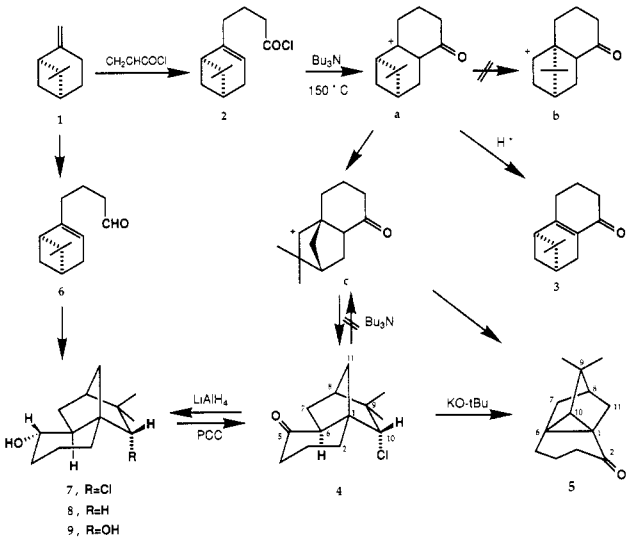
The ene reaction between (–)-β-pinene (**1**) and acryloyl chloride, followed by treatment of the crude product (**2**) with tributylamine, was carried out as described by Wolinsky et al.,[2] and products **3** and **4** were purified by chromatography in hexane–ether mixtures on silica gel. Further elution from this column after elution of the tricyclic ketone (**3**) yielded a new, optically active, ketone,

(1) (a) Krieger, H.; Yrjanheikki, E.; Huhtala, P. *Finn. Chem. Lett.* **1978**, 219. (b) Krieger, H.; Huhtala, P.; Tanninen, N. *Finn. Chem. Lett.* **1984**, *2*, 29. (c) For examples of catalyzed ene reactions of β-pinene, see: Snider, B. B. *J. Org. Chem.* **1974**, *39*, 255.

(2) Moore, L.; Gooding, D.; Wolinsky, J. *J. Org. Chem.* **1983**, *48*, 3750.

0022-3263/89/1954-3504$01.50/0

Scheme I

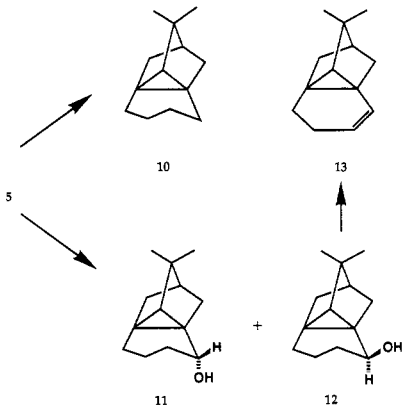


$C_{13}H_{18}O$, having no double bonds (^{13}C NMR) and with a shorter GC retention time on polar columns than the known compounds (**3** and **4**). We ascribe structure **5** to this substance. The required tetracyclic structure could arise by Wagner–Meerwein rearrangement from one of the intermediate carbocations (a) proposed by Wolinsky, either by a bornyl rearrangement (to b) or a fenchyl rearrangement (to c). That the latter occurs was shown by Wolff–Kishner reduction of **5** to the hydrocarbon, 9,9-dimethyltetracyclo[6.2.1.$0^{1,6}$.$0^{6,10}$]undecane (**10**), which has a plane of symmetry leading to simplified ^1H and ^{13}C NMR spectra. (The corresponding hydrocarbon from b has no plane of symmetry.) The structure of **5** was confirmed by a 2D INADEQUATE NMR spectrum,[3] which showed the connectivities $H_2C(3)$–$H_2C(4)$–$H_2C(5)$–C(6)–$H_2C(7)$–HC(8)–$H_2C(11)$–C(1)– with the figures ascribed to C-6 and C-1 corresponding to singlets. The connectivities between the two methyl groups and C-9 were also observed.

The endo stereochemistry of the chlorine atom in **4** was established by the observation of a long-range coupling between the exo proton at C-10 and the proton at C-8. The stereochemistry at C-6 was established by the fact that the alcohol (**7**) obtained by lithium aluminum hydride reduction of **4** had a diaxial coupling between the protons on C-5 and C-6, $J_{5,6}$ = 9 Hz. Furthermore, the equatorial orientation of the hydroxy group of **7** was consistent with the small change of the ^{13}C NMR signal for C-3 from the ketone (**4**). After removal of the chlorine atom of **7** with tributyltin hydride, the resulting alcohol (**8**) exhibited similar coupling between the protons on C-5 and C-6.

Support for the configuration of the chlorine atom in **4** was obtained from a consideration of the cyclization of the thermal addition product (**6**) of acrolein to β-pinene (**1**).[4] This compound (**6**) was found by de Boer et al. to cyclize with 10% sulfuric acid in poor yield to the diol (**9**),[4] whose configuration was established by consideration of the fact that Wagner–Meerwein rearrangements of pinene systems normally yield products with the hydroxyl group in the endo position[5] and by metal hydride reduction of the corresponding ketone, which yielded only the original

Scheme II



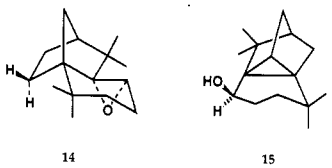
endo isomer (**9**).[4] When we carried out cyclization of the pinene–acrolein adduct (**6**) with hydrogen chloride in hexane, we obtained as the major product the same chloro alcohol (**7**) as we had from the chloro ketone (**4**), and by analogy with de Boer et al., we would expect an endo chlorine atom. Oxidation of the chloro alcohol (**7**) gave the chloro ketone (**4**).

The chloro ketone (**4**) was unchanged by tributylamine at 160 °C, but potassium *tert*-butoxide in glyme at 82 °C smoothly converted it to the tetracyclic ketone (**5**) in 90% yield.

Reduction of the tetracyclic ketone (**5**) with lithium aluminum hydride in ether gave two alcohols (**11**, **12**) in 8:3 ratio. The minor alcohol (**12**) was not obtained pure because it partially decomposed during preparative GC to the hydrocarbon (**13**) (Scheme II). The structures of these tetracyclic compounds were confirmed by the ^1H and ^{13}C NMR spectral data.

Other representatives of this tetracyclic ring system are derived from isolongicyclene and have 5,5,11,11-tetramethyl groups (cf. **15**), generally with a function at C-2.[6]

We believe that it is premature to ascribe a mechanism to the conversion of **4** to **5**, which corresponds to a "U-type" 1,3-elimination of Nickon,[7] but with an unusual C-6 syn elimination of chloride. One somewhat related reaction is the cyclization of isolongifolene epoxide (**14**)[8] in the presence of aluminum isopropoxide to alcohol **15**,[9] which was described (without supporting evidence) as occurring via "cis proton elimination at C-10".[9a]



Experimental Section

NMR spectra were measured in $CDCl_3$, at 360 MHz for ^1H NMR spectra and at 90 MHz for ^{13}C-NMR spectra, using the Bruker Software Library DISN 85, with the exception of one

(3) Bax, A.; Freeman, R.; Kempsell, S. P. *J. Am. Chem. Soc.* **1980**, *102*, 4849. The 2D INADEQUATE NMR spectrum of compound **5** was carried out on 24 mg by Dr. W. Amman, Varian AG, Zug, Switzerland, and by Dr. H. Rüegger, Spectrospin AG, Fällenden, Switzerland.

(4) Kruk, C.; v. Velzen, J. C.; de Boer, Th. J. *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 139.

(5) Geyer, S.; Zieger, W.; Mayer, R. *Z. Chem.* **1966**, *6*, 138.

(6) Goudgaon, N. M.; Reddy, R. D.; Nayak, U. R. *Ind. J. Chem.* **1984**, *24B*, 487, and references quoted therein.

(7) (a) Nickon, A.; Simons, J. R.; Ho, B. *J. Org. Chem.* **1977**, *42*, 800. (b) Werstiuk, N. H. *Chem. Commun.* **1970**, 1499.

(8) McMillan, J. A.; Paul, I. C. *Tetrahedron Lett.* **1974**, 419.

(9) (a) Eschinazi, E. H.; Shaffer, G. W.; Bartels, A. P. *Tetrahedron Lett.* **1970**, 3523. This paper uses incorrect numbering and nomenclature, but gives corrected stereochemistry from the earlier description of the reaction by (b) Santhanakrishnan, T. S.; Sobbi, R. R.; Nayak, U. R.; Dev, S. *Tetrahedron* **1970**, *26*, 657. (c) Dev, S. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Griesbach, H., Kirby, G. W., Eds.; Springer-Verlag: New York, 1981; Vol. 40.

INADEQUATE ^{13}C NMR spectrum.[3] Where attributions are given, they were confirmed by 2D COSY and ^{1}H–^{13}C correlation spectra. Mass spectra were obtained by using a Finnigan 1020 quadrupole spectrometer coupled with a gas chromatograph containing a 30-m glass capillary column coated with Supelcowax stationary phase. Exact mass measurements were made with a VG 70SE with 2000-Da resolution. Results are given as m/z (rel abundance). Petroleum ether refers to the fraction of bp 50–70 °C.

10-*endo*-Chloro-9,9-dimethyltricyclo[6.2.1.0^{1,6}]undecan-5-one (4). **A** (cf. ref 2). (−)-β-Pinene, $[\alpha]^{20}_D$ −18° (neat) (500 g), acryloyl chloride (111 g, 1.25 mol), and hydroquinone (1 g) were heated together at 90 °C for 48 h. The resulting mixture, without purification, was added dropwise to tributylamine (340 mL) heated to 150 °C, and the whole was maintained at 150 °C for 48 h. The cooled mixture was diluted with ether (300 mL), washed once with water, dried, concentrated, and distilled rapidly (Vigreux column). The excess pinenes and tributylamine (426 g, bp 35–85 °C/0.3 mm) were removed first, followed by a fraction (bp 110 °C/0.1 mm, 119.6 g) which consisted of three main peaks (GC) and a number of minor products. Collected from a preparative GC (Carbowax) column, the main products were identified as 10,10-dimethyltricyclo[7.1.1.0^{2,7}]undec-2(7)-en-6-one (**3**, 31%), having spectra identical with those described by previous workers,[1a,1b,2] followed by the title product (12%) with the following spectra (cf. ref 2): ^{1}H NMR δ 1.00, 1.07 (s, 3 H, H_2C-2), 2.06 (eq), 1.73 (ax, H_2C-3), 2.05 (eq), 1.66 (ax, H_2C-4), 2.40 (eq), 2.27 (ax, HC-6), 2.54 (H_2C-7), 1.99 (exo), 1.78 (endo, HC-8), 1.83 (HC-10), 3.72 (H_2C-11), 1.30 1.365; $J_{6,7en}$ = 7 Hz, $J_{5,6}$ = 9 Hz, $J_{ex,8}$ = 3.5 Hz, $J_{8,10}$ < 1 Hz; ^{13}C NMR q at 23.0 and 30.5, t at 28.5 (C-2), 23.0 (C-3), 41.4 (C-4), 26.4 (C-7), 37.3 (C-11), d at 46.2 (C-6), 46.5 (C-8), 77.4 (C-10), s at 58.2 (C-1), 39.9 (C-9). With a retention time shorter than that of these two products was eluted 9,9-dimethyltetracyclo[6.2.1.0^{1,6}.0^{6,10}]undecan-2-one (**5**) with spectra as described below.

Redistillation of this fraction through a column packed with glass helices enabled the purity of **3** to be raised to 93%, and of **4** to 72%. Even by chromatography over silica gel,[2] it was not possible to achieve better than 96% purity of **4**; this was the quality used in other experiments, but for analysis, the product was collected by preparative GC, when it had mp 40–41 °C, $[\alpha]^{20}_D$ +14.2° (7% in $CHCl_3$).

B. The chloro alcohol (**7**, 1.5 g, prepared as described in the next section, method B) in dichloromethane (12 mL) was treated at room temperature for 1.5 h with pyridinium chlorochromate (2 g). The mixture was filtered through a short column of Florisil, which was rinsed with ether (150 mL). After concentration of the filtrate, 1.35 g of the title product was obtained (purity 91% by GC).

10-*endo*-Chloro-9,9-dimethyltricyclo[6.2.1.0^{1,6}]undecan-5-*endo*-ol (7). A. The chloro ketone (**4**, 3 g) was treated at 0 °C with a suspension of lithium aluminum hydride (375 mg) in dry ether (10 mL). After 1.5 h, the mixture was poured onto ice and the product was extracted into ether. After washing (10% HCl, saturated $NaHCO_3$, water) and drying ($MgSO_4$), evaporation gave 2.7 g (90%) of the title product, which was recrystallized from petroleum ether; mp 120 °C; $[\alpha]_D$ +51° (1% in $CHCl_3$); ^{1}H NMR δ 0.99 and 1.06 (each s, 3 H), 2.09 (3 d, J = 13 Hz, 8 Hz, 4 Hz, H_{en}C-6), 3.26 (3 d, J = 13 Hz, 9 Hz, 4 Hz, H_{ax}C-5), 3.59 (s, HC-10); MS 137 (100), 119 (90), 91 (68), 93 (50), 77 (40), 41 and 97 (30)...228 ($M^{\cdot+}$, 13), 230 (4). Anal. Calcd for $C_{13}H_{21}ClO$: C, 68.2; H, 9.3; Cl, 15.5. Found: C, 68.4; H, 9.3; Cl, 15.5.

B. The aldehyde (**6**, 12 g, produced by the reaction of (−)-β-pinene and acrolein[4]) dissolved in hexane (25 mL) was treated with dry hydrogen chloride. The temperature rose to 65 °C and was maintained at this temperature by adjusting the rate of HCl addition. After 1.5 h there was no further rise in temperature, and the reaction mixture began to darken. Addition of HCl was stopped, and the mixture was cooled and washed with ice water. The mixture was dried ($MgSO_4$) and concentrated, and the residue was dissolved in cyclohexane/ether (3:1) and rapidly filtered through silica gel. After concentration, the residue was distilled (bp 110 °C/0.1 mm) to yield 5 g of the title product (80% pure by GC).

9,9-Dimethyltricyclo[6.2.1.0^{1,6}]undecan-5-*endo*-ol (8). A mixture of the chloro alcohol (**7**, 1.7 g) and tributylstannane (2.3 g) was heated at 150 °C for 6 h. Starting material was still present so more tributylstannane (0.7 g) was added, the heating was continued for 2 h, and the mixture was distilled (bulb tube, ca. 150 °C/0.1 mm). The first fraction gave crystals (1.6 g). After recrystallization from petroleum ether, the product still contained traces of tin compounds, so the whole was purified by flash chromatography. The title product had mp 99 °C, $[\alpha]^{20}_D$ +71° (6% in $CHCl_3$); ^{1}H NMR δ 0.92 (s, 6 H, H_2C-2), 1.62 (eq), 1.30 (ax, H_2C-3), 1.64 (eq), 1.33 (ax, H_2C-4), 1.87 (eq), 1.13 (ax, HC-5), 3.23 (HC-6), 1.08 (H_2C-7), 2.115 (exo), 1.28 (endo, HC-8), 1.75 (H_2C-10), 1.24 (exo), 0.91 (endo, H_2C-11), 1.26, 1.39; $J_{6,7en}$ = 7.5 Hz, $J_{5,6}$ = 9 Hz, $J_{4ax,5}$ = 11 Hz, $J_{7ex,7en}$ = 13 Hz, $J_{7ex,8}$ = 3 Hz; ^{13}C NMR q at 26.6 and 31.0, t at 31.0 (C-2), 22.1 (C-3), 35.1 (C-4), 32.5 (C-7), 54.5 (C-10), 38.9 (C-11), d at 77.1 (C-5), 48.7 (C-6), 48.7 (C-8), s at 49.8 (C-1), 36.2 (C-9); MS 119 (100), 91 (78), 137 (52), 79 (48), 120 (45)...176 (12), 179 (4), 194 ($M^{\cdot+}$, 18). Anal. Calcd for $C_{13}H_{22}O$: C, 80.3; H, 11.4. Found: C, 80.2; H 11.3.

9,9-Dimethyltetracyclo[6.2.1.0^{1,6}.0^{6,10}]undecan-2-one (5). Potassium *tert*-butoxide was made from potassium (2 g) and *tert*-butyl alcohol (30 mL), and the excess *tert*-butyl alcohol was distilled off and replaced with 1,2-dimethoxyethane (30 mL dried over grade I alumina). The chloro ketone (**4**, 10 g) in 1,2-dimethoxyethane (30 mL) was added, and the mixture was heated at 80 °C for 12 h, cooled, and poured into water. The title product was isolated in pentane, which was washed (water), dried ($MgSO_4$), and concentrated to yield 7.3 g (90%) of the title product practically pure (GC). Collected from GC on Carbowax, it had the following properties: mp 34–35 °C, $[\alpha]^{20}_D$ −12° (1% in $CHCl_3$); ^{1}H NMR δ 0.93, 0.97 (s, 3 H), 1.29 and 1.90 (AB system, J = 10 Hz, H_2C-7), 1.32 and 2.10 (AB system, J = 10 Hz, H_2C-11), 1.52 (s, HC-8), 1.86 (s, HC-10), multiplets centered on 1.68 and 1.78 (H_2C-4), 1.80 and 2.10 (HC-5), 2.06 and 2.29 (HC-3); ^{13}C NMR q at 22.3 (double), t at 20.8 (C-4), 23.4 (C-5), 31.4 (C-11), 37.0 (C-3), 37.3 (C-7), d at 38.3 (C-10), 40.6 (C-8), s at 35.2 (C-6), 40.1 (C-1), 44.0 (C-9), 209.1 (C-2); MS 190 ($M^{\cdot+}$, 100), 91 and 161 (92), 119 (90), 175 (68), 105 and 147 (62), 41 (58), 148 (50), 77 (45), 133 (43). Anal. Calcd for $C_{13}H_{18}O$: C, 82.1; H, 9.5. Found: C, 82.0; H, 9.4.

This material was identical with that obtained on chromatography of the chloro ketone (**4**) described above, after **4** and the unsaturated ketone (**3**) had been eluted.

9,9-Dimethyltetracyclo[6.2.1.0^{1,6}.0^{6,10}]undecan-2-ols (11 and 12). The tetracyclic ketone (**5**, 4.7 g) was treated in ether (30 mL) with lithium aluminum hydride (574 mg) at 0 °C for 1.5 h. The solution was poured into water, and the ethereal phase was washed (10% HCl, saturated $NaHCO_3$, water), dried ($MgSO_4$), and concentrated to yield 4.6 g of a mixture (8:3) of two alcohols, containing no olefinic material (by ^{1}H NMR spectra). These were separated by preparative GC on Carbowax into the minor (exo) isomer (**12**) having the shorter retention time: ^{1}H NMR δ 0.91, 0.92 (s, 3 H), 0.80 (s, HC-10), 1.18 and 1.78 (AB system, J = 10 Hz, H_2C-7), 1.13 and 1.97 (AB system, J = 10 Hz, H_2C-11), 1.38 (s, HC-8), 4.07 (t, J = 8 Hz, HC-2); ^{13}C NMR (observed as impurity in the ^{13}C NMR of **11**) q at 23.2, t at 21.4 (C-4), 24.4 (C-5), 31.9 (C-3), 35.6 (C-11), 38.0 (C-7), d at 35.6 (C-11), 41.6 (C-8), s at 43.7 (C-9), 69.3 (C-2); the signals for C-1 and C-6 were not visible; MS 131 (100), 91 (70), 145 (56), 117 (50), 159 (46), 77 and 118 (33), 105, 107, 115 and 174 (30)...192 ($M^{\cdot+}$, 7); exact mass calcd for $C_{13}H_{20}O$ 192.1514, found 192.1511. The endo isomer (**11**) had a longer retention time on the Carbowax column, and after collection had the following properties: ^{1}H NMR δ 0.89 (s, 6 H), 0.45 (s, HC-10), 1.18 and 1.73 (AB system, J = 10 Hz, H_2C-7), 1.33 and 1.73 (AB system, J = 10 Hz, H_2C-11), 1.39 (br s, HC-8), 4.26 (t, J = 4.5 Hz, HC-2); ^{13}C NMR q at 22.8, 23.0, t at 16.8 (C-4), 24.3 (C-5), 31.2 (C-3), 33.4 (C-11), 38.3 (C-7), d at 33.4 (C-10), 41.6 (C-8), 67.1 (C-2), s at 23.7 (C-6), 28.9 (C-1), 44.0 (C-6); the MS of **11** was practically the same as that of **12**, but with a more important fragment at m/z 174 (35); exact mass calcd for $C_{13}H_{20}O$ 192.1514, found 192.1510. Collection of **12** by preparative GC caused for formation of a new peak at much shorter retention time, and this, when collected, had spectra consistent with **9,9-dimethyltetracyclo[6.2.1.0^{1,6}.0^{6,10}]undec-2-ene (13)**: ^{1}H NMR δ 0.90 (s, 6 H), 1.14 (s, HC-10), 1.105, 1.81, and 1.41 (ABX system, J_{AB} = 10, J_{AX} = ca. 0, J_{BX} = 5 Hz, H_2C-7 and HC-8), 1.20, 1.83 (AB system, J = 10 Hz, H_2C-11, B also coupled with HC-8, J = 5 Hz), 5.45 (4 d, J = 10, 7, 3, 2 Hz, HC-3), 6.08 (dd, J = 10, 3 Hz, HC-2);

^{13}C NMR q at 22.6, 23.1, t at 21.0 (C-4), 23.4 (C-5), 35.2 (C-11), 37.0 (C-7), d at 35.1 (C-10), 42.1 (C-8), 123.0 (C-3), 129.2 (C-2), s at 24.2 (C-6), 28.3 (C-1), 43.8 (C-9); MS 131 (100), 91 (80), 145 (60), 117 (55), 159 (50), 118 and 174 ($M^{+\cdot}$, 43), 105 (32), 77 and 115 (28); exact mass calcd for $C_{13}H_{18}$ 174.1408, found 174.1433.

9,9-Dimethyltetracyclo[6.2.1.0^{1,6}.0^{6,10}]undecane (13). A mixture of 9,9-dimethyltetracyclo[6.2.1.0^{1,6}.0^{6,10}]undecan-2-one (**5**, 0.6 g), hydrazine hydrate (6 mL), diethylene glycol (12 mL), and ethanol (12 mL) was heated at reflux for 15 min. Potassium hydroxide pellets (3 g) were added, and heating at reflux was continued for 1 h. The mixture was then distilled very slowly, allowing the temperature to rise over 3 h. The distillate was extracted with water and pentane, and the residue in the distillation flask was extracted with pentane. The combined pentane phases were washed (10% HCl, water) and concentrated carefully with a distillation column. The residue (0.5 g) consisted mainly of the title product and was purified by preparative GC on Carbowax: $[\alpha]^{20}_D$ 0° (10% in $CHCl_3$); ^1H NMR δ 0.87 (s, 6 H), 0.46 (s, 1 H, HC-10), 1.09 and 1.69 (each 2 H, AB system, J = 10 Hz, H_2C-7 and H_2C-11), 1.26 (HC-8) overlapping with 1.15 and 1.26 (mult, H_2C-3 and H_2C-4), 1.73 and 1.80 (each 2 H, mult, H_2C-2 and H_2C-5); ^{13}C NMR q at 23.3, t at 23.0 (C-3, C-4), 25.8 (C-2, C-5), 38.4 (C-7, C-11), d at 33.8 (C-10), 42.0 (C-8), s at 23.2 (C-1, C-6), 44.2 (C-9); MS 91 (100), 133 (78), 176 ($M^{+\cdot}$) and 105 (40), 119 (38), 161 (35), 41, 79, 93 (21); exact mass calcd for $C_{13}H_{20}$ 176.1564, found 176.1490.

15-Membered Macrolides via Translactonization in 14-Hydroxy-6-*O*-methylerythromycin A

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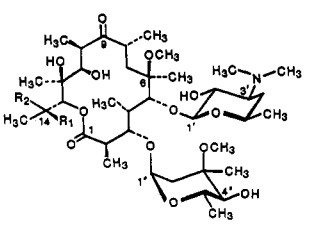
In our previous studies on the metabolism of 6-*O*-methylerythromycin A (**1**), a new semisynthetic macrolide antibiotic, several metabolites were isolated from human urine.[1] Among them, active metabolites M-5 (**2**) and M-6 (**3**) were determined to be (14*R*)- and (14*S*)-14-hydroxy-6-*O*-methylerythromycins A, respectively.[2]

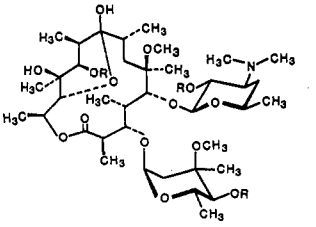
During the isolation and identification of the metabolites of **1**, **3** was found to be converted to a new polar compound when dissolved in protic solvents, methanol, or acetone–water, etc. This compound was identical with M-7 (**4**), previously isolated from human urine,[1] whose structure still remained to be identified. The latter has been determined to be a novel 15-membered macrolide having the 9,13-hemiketal structure, derived by a translactonization between the 14-hydroxyl and the lactone group. The translactonization from **3** to **4** is accelerated by reaction of **3** with potassium carbonate in methanol. The above results let us convert **2**, an epimer of **3** at C-14, into another type of translactonization product. The desired 15-membered macrolide **5** could readily be obtained from **2** by the use of potassium carbonate and exists as two tautomers having the 9-carbonyl (**5A**) and the 9,12-hemiketal (**5B**) structures. This paper describes the structure determination of the two novel 15-membered macrolides, **4** and **5**.

Results and Discussion

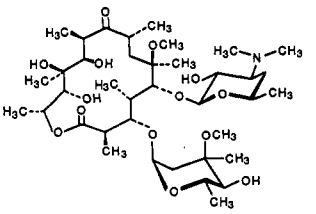
The molecular formula of **5** was determined as $C_{38}H_{69}NO_{14}$ from the elemental analysis and mass and ^{13}C NMR



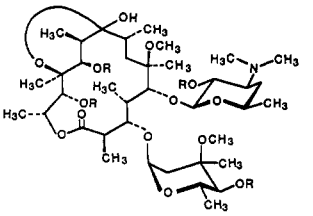
1 R_1 = H R_2 = H
2 R_1 = OH R_2 = H
3 R_1 = H R_2 = OH



4 R = H
7 R = Ac



5A



5B R = H
6 R = Ac

spectra, which is the same as that of **2**. The ^1H NMR spectrum of **5** in deuteriochloroform indicates that **5** contains two components (**5A** and **5B**, ca. 2:1, respectively) from several pairs of signals for H-1′, H-1″, H-14, 3″-OCH_3, 6-OCH_3, etc. In the ^{13}C NMR spectrum of **5** in deuteriochloroform, C-9 resonates at 222.4 ppm (**5A**, major) and 107.3 ppm (**5B**, minor), and these signals are ascribed to carbonyl and hemiketal structures at C-9, respectively. Compound **5** showed absorption at 1683 cm^{-1} in the IR spectrum and absorption around 280 nm (shoulder) in the UV spectrum, consistent with a 9-carbonyl group. When the ^1H NMR spectrum of **5** was measured in deuteriopyridine, several pairs of signals converged. The signal of C-9 resonates only at 107.5 ppm, indicating that **5** exists as the hemiketal structure (**5B**) in deuteriopyridine. The ^1H NMR spectrum of the sample recovered from the solution of deuteriopyridine was measured in deuteriochloroform, and the same ^1H NMR spectrum as originally measured in deuteriochloroform was obtained. Therefore **5A** and **5B** are interconvertible tautomers.

Unambiguous NMR assignments of **5A** were made by means of homonuclear ^1H–^1H and heteronuclear ^1H–^{13}C 2D NMR spectroscopy. Tables I and II show that the chemical shifts of protons and carbons assigned to cladinose and desosamine were similar in **5A** and **2**. However, the chemical shifts of the aglycons are considerably different between **5A** and **2**. The signal of H-13 in **5A** is 1.71 ppm upfield from that in **2**, whereas H-14 and C-14 in **5A** resonate at lower field by 0.66 and 6.0 ppm, respectively, than those in **2**. The chemical shifts of H-14 (4.79 ppm) and C-14 (72.5 ppm) in **5A** are similar to those of H-13 (4.94 ppm) and C-13 (74.5 ppm) in **2**, respectively. These spectral data clearly indicate that **5A** is a 15-membered macrolide derived from **2** by a translactonization between the 14-hydroxyl and the lactone group.

The chemical shifts of protons and carbons of **5B** in deuteriopyridine were compared with those of **2**. The ^1H and ^{13}C NMR spectra of **2** were also measured in deuteriopyridine. The upfield shift of H-13 (−1.10 ppm) and the downfield shifts of H-14 (+1.19 ppm) and C-14 (+6.6 ppm) in **5B** with respect to **2** shows that **5B** is also a translactonization product between the 14-hydroxyl and the lactone group. The chemical shift of C-9 (107.5 ppm) indicates a hemiketal structure. In order to confirm the hemiketal structure, the hydroxy protons of **5B** were assigned. The signals at 8.04, 5.81, 5.55, and 5.06 ppm are

(1) Adachi, T.; Morimoto, S.; Watanabe, Y.; Sota, K. *Chemotherapy* **1988**, *36*(S-3), 264.
(2) Adachi, T.; Morimoto, S.; Kondoh, H.; Nagate, T.; Watanabe, Y.; Sota, K. *J. Antibiot.* **1988**, *41*, 966.

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