Photosensitized Oxygenation of Labda-8(17),12-diene, Labda-8(17),13-diene, and the Biformenes. Synthesis of Pumiloxide[1]

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Reactions of the title compounds with singlet oxygen were studied. In labda-8(17),12-diene (**2**; 7:3 mixture of *E* and *Z* isomers), syn addition leading to **7** (58%) was predominant. Smaller amounts of **8** (20%) by syn addition to (*E*)-**2** or anti addition to (*Z*)-**2**, **9** (5%), **10** (2.5%), and **11** (1.5%) were also formed. (*E*)-Labda-8-(17),13-diene ((*E*)-**3**) gave 29% **12** and 40% **13** by syn addition, whereas (*Z*)-**3** gave 57% **12** by syn addition and 19% **13** by anti addition. In *trans*-biformene (**5**) syn attack at C-12 to give **15** (27%), **16** (10%), **18** (12%), and **19** (4%) was greatly preferred to syn attack at C-13 to give **17** (6%). In *cis*-biformene (**6**) syn attack at C-13 to give **17** (39%) predominated slightly over anti attack at C-12 to give **15** (13%), **16** (8%), **18** (4%), and **19** (4%). Diels–Alder reactions with singlet oxygen leading to epidioxides **20** and **21** were relatively unimportant (7% from **5**, 5% from **6**). The epidioxides were converted to the naturally occurring furanolabdane pumiloxide (**22**).

In our study of biomimetic cyclizations in the diterpene series we had need of labda-8(17),13-dien-12-ol (**1**;[2] see Chart I). A possible route to this epimer mixture which seemed more convenient than the one adopted previously[2] was the reaction of labda-8(17),12-diene (**2**) with singlet oxygen. The present report describes the results of this as well as related work on photosensitized oxygenation of the labdadiene isomers **3** and the biformenes **5** and **6**. The results are of interest in the larger context of ene reactions with singlet oxygen.[3-7]

Labda-8(17),12-diene (**2**; 7:3 mixture of *E* and *Z* isomers), labda-8(17),13-diene (**3**; 1:1 mixture of *E* and *Z* isomers), and labda-8(17),13(16)-diene (**4**) were prepared by dehydration of 14,15-dihydromanool and subsequent separation by high-pressure LC.[8] Photosensitized oxygenation of **2** (CH_2Cl_2–5% MeOH, rose bengal) followed by reduction with triethyl phosphite and high-pressure LC gave as major products 58% of (11*E*)-labda-8(17),11-dien-13-ol (**7**) and 20% of (12*R*)-labda-8(17),13(16)-dien-12-ol (**8**) but no **1**. Minor products were the 12*S* epimer **9** of **8** (5%), (12*R*)-labda-8(17),14-diene-12,13-diol (**10**, 2.5%), and (11*E*)-14,15-bisnorlabda-8(17),11-dien-13-one (**11**, 1.5%).

That **7** was a mixture of C-13 epimers was evident from the ^{1}H NMR spectrum (270 MHz) which exhibited two sets of almost superimposed signals for H-11, H-12, H-16, and H-17; the magnitude of $J_{11,12}$ (16 Hz) showed that the 11,12 double bond was trans. The ^{1}H NMR spectra of **8** and **9** were very similar except for the chemical shifts of H-17 (5.01 and 4.49 ppm for **8**, 4.91 and 4.69 ppm for **9**) which permitted assignment of the 12*R* configuration to the epimer formed in larger amount.[10] Also noteworthy was the difference in coupling constants involving H-12 (J = 8.5, 1.5 Hz for **8**; J = 8.5, 6 Hz for **9**).[13] Substance **10** was also a mixture of epimers as evidenced by the duplication of signals for H-12, H-14, H-15, and H-17; the chemical shifts of H-17a (4.44 ppm in both isomers) and H-17b (4.84 and 4.82 ppm, respectively) indicated that both components of the mixture had the 12*R* configuration and were therefore C-13 epimers.

Compounds **7**–**9** are clearly products of ene reactions. The favored ene reaction leading to **7** involves attack of singlet oxygen at C-13 and migration of hydrogen from C-11, with substance **11** likely to derive from Hock cleavage[14] of the resulting hydroperoxide. The less favored ene reaction leading to **8** and **9** involves attack at C-12 and hydrogen migration from C-16 rather than C-14. The latter process is quite unimportant, as indicated by the very small yield of **10** which is obviously formed by further reaction of singlet oxygen with the 12β-hydroperoxide corresponding to **1**. Preference for the 12*R* configuration resulting from the less favored process can be rationalized in terms of conformational arguments presented previously.[12,15,16]

The availability of **3** (1:1 mixture of *E* and *Z*) also prompted a study of its reaction with singlet oxygen. Reduction with triethyl phosphite and high-pressure LC gave only two fractions: a 5:4 mixture (38% yield) of manool (**12a**) and 13-epimanool (**12b**) and a 1:1 mixture (33%) of the C-14 epimers of labda-8(17),13(16)-dien-14-ol (**13**).[2] Hydrogen abstraction from C-12 during the attack at C-14 was not observed.

The results from **2** are in harmony with the recent generalization that singlet oxygen abstracts hydrogen preferentially from the more crowded side of trisubstituted olefins,[17] **7** being formed by syn addition[18,19] to both *E* and *Z* isomers. Either syn addition to (*E*)-**2** or anti addition to (*Z*)-**2** could be responsible for **8** and the small yield of **9**, whereas the small amounts of **10** and **11** could derive from anti addition to (*E*)-**2** or syn addition to (*Z*)-**2**. In

(1) Supported in part by a grant (CHE-7801191) from the National Science Foundation.

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(10) In (12*R*)-labd-8(17)-en-12-ols, $\Delta\delta$ for H-17a and H-17b is more than twice than $\Delta\delta$ in the 12*S* epimers.[2,11,12]

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(13) The preferred conformation of the 12*R* epimers which gives rise to one large and one small coupling constant has been discussed in ref 12. To judge by the coupling constants involving H-12, one observes that the preferred conformation of the 12*S* epimers appears to be essentially that resulting from interchange of 12-OH and C-13 in the preferred conformation of the 12*R* epimers.

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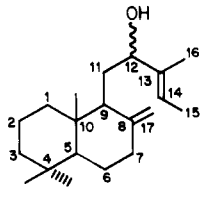
Chart I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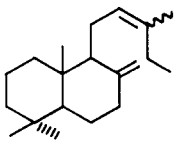
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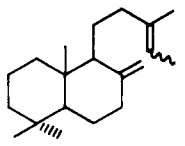
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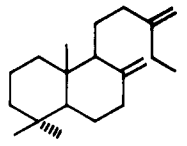
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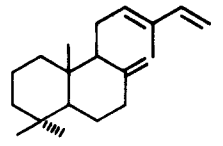
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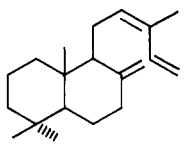
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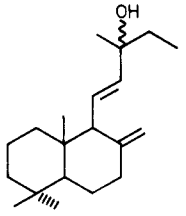
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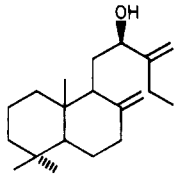
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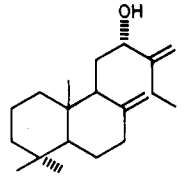
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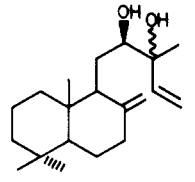
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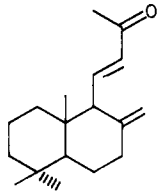
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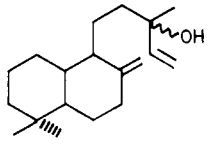
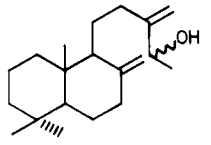

12a, β-OH
b, α-OH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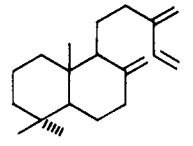
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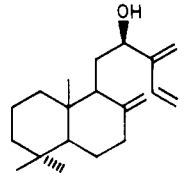
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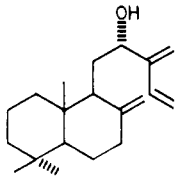
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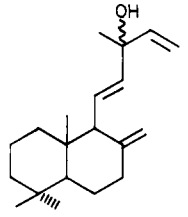
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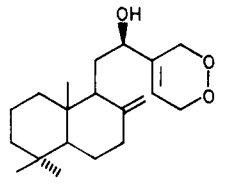
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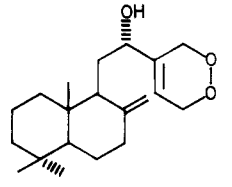
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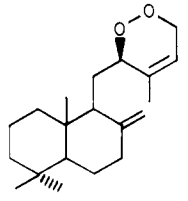
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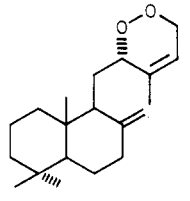
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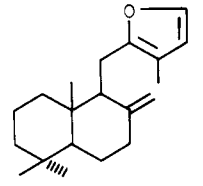
22

the case of **3**, the results, while seemingly supporting the generalization, were not as definite. While **12** was obviously formed only by syn addition [to (*E*)-**3** and/or (*Z*)-**3**], the composition of starting material and product was such that the appreciable yield of **13** might have been derived entirely from anti addition to (*Z*)-**3** although it seemed likely that syn addition to (*E*)-**3** contributed.

To settle this ambiguity, we separated (*E*)-**3** and (*Z*)-**3** by further high-pressure LC using the peak shaving–recycle technique, and each compound was individually subjected to the photooxygenation reaction. Assignment of stereochemistry was based on the ^{13}C NMR spectra (Table I), with C-12 of the *E* isomer appearing 8.4 ppm downfield and C-16 at 7.7 ppm upfield from the shifts of C-12 and C-16 of the *Z* isomer.[20] In accordance with the generalization, (*E*)-**3** furnished 39% of a 5:4 mixture of **12a** and **12b** and 40% of a 9:8 mixture of **13** epimers, both by syn addition, whereas (*Z*)-**3** gave 57% of a 7:5 mixture of **12a** and **12b** by syn addition and 19% of a 3:4 mixture of **13** epimers by anti addition.

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The results described so far made it desirable to reexamine our earlier work[12] on photosensitized oxygenation of *trans*-biformene (**5**) in a search for minor products and to extend the study to *cis*-biformene (**6**). In the interval Wahlberg and co-workers[15,16] have carried out similar studies on the closely related (12*E*)- and (12*Z*)-abienols.

Dehydration of manool by the literature method[9] and separation by high-pressure LC[8] gave pure **5**, **6**, and **14** in vastly improved yields of 48%, 10%, and 24%. Photosensitized oxygenation of **5** (CH_2Cl_2–5% MeOH, rose bengal) followed by reduction with triethyl phosphite and separation of the crude product by TLC gave 27% of the previously reported major product **15**[12] and the following minor products: **16** (10%), **17** (1:1 mixture of epimers, 6%), **18** (12%), **19** (4%), **20** (4%), **21** (3%). Epimers **15** and **16**, which are formed by attack of singlet oxygen at C-12 and hydrogen abstraction from C-16, were differentiated by the chemical shift differences for H-17a and H-17b (4.87 and 4.53 ppm for **15**, 4.89 and 4.74 ppm for **16**) as in the case of **8** and **9**.[10] The same technique was also applicable to the previously reported[12] **18** (4.87 and 4.43 ppm) and the new **19** (4.89 and 4.67 ppm) which are formed by further reaction of **15** and **16** with singlet oxy-

Table I. ^{13}C NMR Spectra[a]

carbon	(E)-3	(Z)-3[b]	4
1	39.12 t	39.03 t	39.12 t
2	19.48 t	19.45 t	19.45 t
3	42.29 t	42.25 t	42.27 t
4	33.56	33.63	33.63
5	55.63 d	56.17 d	55.61 d
6	24.53 t	24.53 t	24.52 t
7	38.44 t	38.42 t	38.42 t
8	148.45	148.81	148.70
9	56.39 d	56.37 d	56.47 d
10	39.61	39.61	39.68
11	22.11 t	21.43 t	21.99 t
12	38.64 t	30.23 t	35.18 t
13	136.31	136.57	152.28
14	117.86 d	119.10 d	28.92 t
15	13.32 q	13.25 q	12.44 q
16	15.70 q	23.35 q	107.22 t
17	106.29 t	106.13 t	106.18 t
18	21.76 q	21.75 q	21.76 q
19	33.64 q	33.63 q	33.63 q
20	14.54 q	14.54 q	14.54 q

[a] Run in $CDCl_3$ at 67.9 MHz with Me_4Si as internal standard. Frequencies are in parts per million. Unmarked signals are singlets. Assignments are based on comparisons with data in the literature [e.g.: Wehrli, F. W.; Nishida, T. *Fortschr. Chem. Org. Naturst.* **1979**, 36, 1] and predicted shifts. [b] Values from spectrum of a mixture of (Z)-3 and 4.

gen. Product **17** was a mixture of (11*E*)-labda-8-(17),11,14-trien-13-ols as shown by broadening of the signals for H-11, H-12, H-16, and H-17, the magnitude of $J_{11,12}$ (16 Hz), and the chemical shift of H-16 (1.30 ppm).

That compounds **20** and **21** were epimeric epidioxides formed by 1,4-addition of singlet oxygen to the diene system was evident from the ^1H NMR spectra which displayed signals characteristic of a vinylic proton (H-14) at 5.59 ppm (or 5.56 ppm), a vinylic methyl proton (H-16) at 1.81 ppm (or 1.79 ppm), and multiplets characteristic of H-12 (4.16 or 4.21 ppm) and H-15 (4.68, 4.31 and 4.56, 4.41 ppm). Assignment of the 12*R* configuration to **20** and the 12*S* configuration to **21** was again based on the chemical shifts of H-17 (4.86 and 4.50 ppm for **20**, 4.87 and 4.73 ppm for **21**).

Photooxygenation of *cis*-biformene (**6**) followed by reduction with triethyl phosphite gave the same products **15–21**, but in different proportions. Attack of singlet oxygen at C-13 and hydrogen abstraction from C-12 leading to **17** (39%) predominated, whereas the fraction of products resulting from attack at C-12 and hydrogen abstraction from C-16 declined to 13% for **15**, 8% for **16**, 4% for **18**, and 4% for **19**. The amount of **20** (3%) and **21** (2%) was not changed significantly.

Photooxygenation of **5** and **6** thus involves preferential ene reaction with the more heavily substituted double bond of the conjugated system and is in keeping with the previously proposed[12] order of reactivity of olefins toward singlet oxygen: tetrasubstituted monoolefins > trisubstituted monoolefins > 1,3-diene ≫ disubstituted monoolefins and monosubstituted olefin. Only a small part of the product, **20** and **21**, represents 1,4-addition of singlet oxygen to the *s-cis*-1,3-diene systems of **5** and **6**. The conformational factors probably responsible for predominant formation of the 12*R* epimers in the ene addition at C-12 have been discussed.[12,15,16]

Among the two possible syn ene additions in **5**, that leading to **15** and **16** (and thence to **18** and **19**) greatly predominates over that leading to **17** (53% vs. 6%), somewhat more so than for (12*E*)-abienol.[16] Syn ene addition in **6** can occur only at C-13 to give **17** (39%), and hence anti addition leading to **15** and **16** (and thence **18** and **19**) becomes more competitive (29%). These yields differ somewhat from those reported for (12*Z*)-abienol where syn vs. anti addition was 68% vs. 3%.[15]

The 12*R* and 12*S* epimers **20** and **21** were converted to the same furan, **22**, on treatment with aqueous $FeSO_4$.[12] The product had properties similar to those reported[21] for a diterpene pumiloxide from the oleoresin of *Pinus pumila* to which the same formula has been attributed. Our work thus constitutes a partial synthesis of pumiloxide.

Experimental Section

IR spectra were recorded on neat samples with a Perkin-Elmer 257 spectrophotometer. NMR spectra were run at 270 MHz on a Bruker HX-270 spectrometer in $CDCl_3$ solution with Me_4Si as internal standard. Mass spectra were obtained on an AEI MS-902 instrument at 70 eV. High-pressure LC separations were carried out on a Waters ALC 202 liquid chromatograph equipped with differential refractometer R 401 and using three 4 ft × $^3/_8$ in. Porasil B columns or a Waters Prep LC/System 500 liquid chromatograph using two 5.7 × 30 cm Prep Pak 500/Silica cartridges. Silica gel used for TLC was silica gel 60 PF 254+366 (EM Reagents). Silica gel used for flash chromatography was silica gel 60 (230–460 mesh, EM Reagents).

Photolyses were carried out by irradiating solutions of the olefin and sensitizer with two Quartzline lamps (DVY 650 W) as external light source. The lamps were operated at 70 V and cooled with a stream of air. A stream of oxygen was bubbled through the reaction mixture which was cooled by a cooling jacket surrounding the reaction vessel.

14,15-Dihydromanool. To a mixture of 6.5 g of manool and 8.8 g of tosylhydrazide in 200 mL of methyl Cellosolve was added 10 g of saturated K_2CO_3 solution. After being heated at 95–100 °C for 45 h, the mixture was cooled, diluted with water, and extracted with ether. The washed and dried ether extract was evaporated, and the residue (6.8 g) was purified by preparative high-pressure LC to give 3.84 g of dihydromanool: NMR signals at 4.80 and 4.53 (both br, H-17), 1.13 (H-16), 0.88 (t, J = 7 Hz, H-15), and 0.86, 0.81, and 0.70 ppm (C-4 and C-10 Me).

Dehydration of 14,15-Dihydromanool. A solution of 3.35 g of 14,15-dihydromanool in 60 mL of pyridine was stirred at 0 °C with 20 mL of $POCl_3$ in pyridine for 24 h, poured into ice-cold sodium bicarbonate solution, and extracted with *n*-hexane. Flash chromatography of the extract over silica gel gave 2.7 g of a mixture of labdatrienes **2–4**. Separation of the mixture by preparative high-pressure LC using the peak shaving–recycle technique[8] gave the following. (A) Labda-8(17),12-diene (**2**) as a 7:3 mixture of *E* and *Z* isomers: 0.47 g; IR 3075, 1640, 890 cm^{-1}; NMR 5.04 (br t, J = 6 Hz, H-12), 4.81 (br, H-17a), 4.50 (br, H-17b of *Z* isomer), 4.48 (br, H-17b of *E* isomer), 1.66, 1.00 (t, J = 7 Hz, C-13 and C-14 Me of *Z* isomer), 1.63, 0.97 (t, C-13 and C-14 Me of *E* isomer), 0.89, 0.83, and 0.73 ppm (C-4 and C-10 Me). (B) Labda-8(17),13-diene (**3**) as a 1:1 mixture of *E* and *Z* isomers, 0.35 g. (C) Labda-8(17),13(16)-diene (**4**): 0.07 g; IR 3075, 1640, 890 cm^{-1}; NMR 4.86 and 4.59 (both br, H-17), 4.70 (br, H-16), 1.03 (t, J = 7 Hz, C-14 Me), 0.89, 0.82, and 0.69 ppm (C-4 and C-10 Me); ^{13}C NMR spectrum in Table I. The mixture of (*E*)-**3** and (*Z*)-**3** was further separated by high-pressure LC (Prep LC/system 500, two Prep PAC-500/SILICA cartridges) employing peak shaving from the seventh recycle onward and using 8 L of *n*-hexane in 15 recycles (104 min) which afforded 0.06 g of the *Z* isomer and 0.15 g of the *E* isomer. (*Z*)-**3** had the following: IR 3075, 1640, 890 cm^{-1}; NMR 5.20 (q, J = 7 Hz, H-14), 4.85 and 4.59 (both br, H-17), 1.56 (C-13 Me), 1.53 (d, J = 7 Hz, C-14 Me), 0.87, 0.80, and 0.68 ppm (C-4 and C-10 Me); ^{13}C NMR spectrum in Table I. (*E*)-**3** had the following: IR 3075, 1640, 890 cm^{-1}; NMR 5.17 (q, J = 7 Hz, H-14), 4.82 and 4.53 (both br H-17), 1.60 (C-13 Me), 1.57 (d, J = 7 Hz, C-14 Me), 0.87, 0.80, and 0.68 ppm (C-4 and C-10 Me); ^{13}C NMR spectrum in Table I.

Photooxygenation of 2. A solution of 0.2 g of **2** in CH_2Cl_2–5% MeOH was reacted with singlet oxygen (10 mg of rose bengal as sensitizer) for 2 h. After addition of 0.2 g of triethyl phosphite, the solvent was removed at reduced pressure. Flash chromatography of the residue over silica gel and high-pressure LC (Waters ALC 202) gave 122 mg (58%) of **7**, 42 mg (20%) of **8**,

10 mg (5%) of **9**, 5 mg (2.5%) of **10**, and 3 mg (1.5%) of **11**.

(11*E*)-Labda-8(17),11-dien-13-ol (**7**, 1:1 mixture of epimers at C-13): IR 3425, 3075, 1640, 985, 890 cm^{-1}; NMR 5.68 and 5.67 (dd, J = 16, 10 Hz, H-11), 5.50 and 5.49 (2 d, J = 16 Hz, H-12), 4.75, 4.75 and 4.50, 4.49 (all br, H-17), 1.30 and 1.29 (C-13 Me), 0.90 (t, J = 7 Hz, C-14 Me of both epimers), 0.90, 0.85, and 0.82 ppm (C-4 and C-10 Me of both epimers).

Anal. Calcd for $C_{20}H_{34}O$: mol wt 290.2609. Found: mol wt (mass spectroscopy) 290.2630 (2%).

(12*R*)-Labda-8(17),13(16)-dien-12-ol (**8**): IR 3435, 3075, 1640, 890 cm^{-1}; NMR 5.01 and 4.49 (both br, H-17), 4.85 and 4.80 (2 d, J = 1.5 Hz, H-16), 4.41 (dd, J = 8.5, 1.5 Hz, H-12), 1.09 (t, J = 7 Hz, C-14 Me), 0.87, 0.81, and 0.68 ppm (C-4 and C-10 Me).

Anal. Calcd for $C_{20}H_{34}O$: mol wt 290.2609. Found: mol wt (mass spectroscopy) 290.2613 (1%).

(12*S*)-Labda-8(17),13(16)-dien-12-ol (**9**): IR 3350, 3075, 1640, 895 cm^{-1}; NMR 4.91 and 4.69 (both br, H-17), 4.86 and 4.84 (2 d, J = 1 Hz, H-16), 4.19 (dd, J = 8.5, 6 Hz, H-12), 1.09 (t, J = 7 Hz, C-14 Me), 0.87, 0.80, and 0.69 ppm (C-4 and C-10 Me).

Anal. Calcd for $C_{20}H_{34}O$: mol wt 290.2609. Found: mol wt (mass spectroscopy) 290.2582 (1%).

(12*R*)-Labda-8(17),14-diene-12,13-diol (**10**, 5:4 mixture of epimers at C-13): IR 3420, 3075, 1640, 920, 890 cm^{-1}; NMR 5.96 and 5.94 (both dd, J = 17, 10.5 Hz, H-14), 5.36 (d, J = 17 Hz, H-15$_{trans}$ of both epimers) 5.24 and 5.21 (2 d, J = 10.5 Hz, H-15$_{cis}$), 4.84 and 4.82 (both br, H-17a), 4.44 (br, H-17b of both epimers), 3.50 and 3.48 (both dd J = 10, 1.5 Hz, H-12), 1.35 and 1.29 (C-13 Me), 0.89, 0.83, and 0.69 ppm (C-4 and C-10 Me of both epimers). The mass spectrum did not exhibit the molecular ion.

Anal. Calcd for $C_{20}H_{32}O$: m/e 288.2453 ($M^+ - H_2O$). Found: mass spectrum, m/e 288.2474 ($M^+ - H_2O$, 2%).

(11*E*)-14,15-Bisnorlabda-8(17),11-dien-13-one (**11**): mp 128–129 °C (not recrystallized because of the smallness of the sample); IR 3075, 1665, 1650, 1640, 995, 900 cm^{-1}; NMR 6.87 (dd, J = 16, 10 Hz, H-11), 6.07 (d, J = 16 Hz, H-12), 4.79 and 4.41 (both br, H-17), 2.28, 0.90, 0.86, and 0.86 ppm (C-13, C-4), and C-10 Me).

Anal. Calcd for $C_{18}H_{28}O$: mol wt 260.2139. Found: mol wt (mass spectroscopy) 260.2139 (9.4%).

Photooxygenation of 3. (a) Reaction of 0.1 g of **3** (1:1 mixture of *E* and *Z* isomers) in CH_2Cl_2–5% MeOH with singlet oxygen (5 mg of rose bengal) for 90 min, addition of 0.1 g of triethyl phosphite, workup in the manner described previously, and high-pressure LC (Waters ALC 202) gave 40 mg of a 5:4 mixture of **12a** and **12b**: IR 3410, 1075, 1640, 995, 920, 890 cm^{-1}; NMR 5.91 (dd, J = 17.5, 10.5 Hz, H-14 of both epimers), 5.21 and 5.20 (both d, J = 17.5 Hz, H-15$_{trans}$), 5.05 and 5.04 (2 d, J = 10.5 Hz, H-15$_{cis}$), 4.80 (br, H-17a of both epimers), 4.51 and 4.47 (both br, H-17b), 1.27, 0.87, 0.80, and 0.67 ppm (C-13, C-4, and C-10 Me of both epimers). A 35-mg (33%) amount of a 1:1 mixture of labda-8(17),13(16)-dien-14-ols (**13**) was also obtained: IR 3350, 3075, 1460, 890 cm^{-1}; NMR 5.03 (br, H-17a of both epimers), 4.52 and 4.50 (both br, H-17b), 4.83 (br, H-16 of both epimers), 4.24 and 4.23 (both br q, J = 7 Hz, H-14), 1.28 (d, J = 7 Hz, H-15 of both epimers), 0.87, 0.81, and 0.70 ppm (C-4 and C-10 Me of both epimers).

(b) Reaction of 0.14 g of pure (*E*)-**3** with singlet oxygen in the manner described above (8 mg of rose bengal, 90 min) followed by the usual workup and separation by preparative TLC gave 58 mg (39%) of a 5:4 mixture of **12a** and **12b** and 59 mg (40%) of a 9:8 mixture of the epimers of **13**.

(c) Reaction of 50 mg of pure (*Z*)-**3** with singlet oxygen in the manner described above (5 mg of rose bengal, 60 min) followed by the usual workup and separation by preparative TLC gave 30 mg (57%) of a 7:5 mixture of **12a** and **12b** as well as 10 mg (19%) of a 3:4 mixture of the epimers of **13**.

Dehydration of Manool. Dehydration of 1.0 g of manool by the literature procedure[9] and flash chromatography over silica gel gave 0.80 g of an oil. High-pressure LC of 0.75 g of this material gave[8] 0.17 g of sclarene (**14**), 0.07 g of *cis*-biformene (**6**), and 0.34 g of *trans*-biformene (**5**). Sclarene had the following: IR 3075, 1640, 1595, 990, 895 cm^{-1}; NMR 6.37 (dd, J = 17.5, 11 Hz, H-14), 5.23 (d, J = 17.5 Hz, H-15$_{trans}$), 5.05 (d, J = 11 Hz, H-15$_{cis}$), 5.00 and 4.99 (both br, H-16), 4.85 and 4.56 (both br, H-17), 0.90, 0.83, and 0.70 (C-4 and C-10 Me). *trans*-Biformene had the following: IR 3075, 1640, 1605, 985, 890 cm^{-1}; NMR 6.34 (dd, J = 17.5, 11 Hz, H-14), 5.43 (br t, J = 7 Hz, H-12), 5.05 (d, J = 17.5 Hz, H-15$_{trans}$), 4.48 (d, J = 11 Hz, H-15$_{cis}$), 4.82 and 4.46 (both br, H-17), 1.78 (d, J < 1 Hz, H-16), 0.90, 0.85, and 0.75 ppm (C-4 and C-10 Me). *cis*-Biformene had the following: IR 3075, 1640, 1595, 985, 895 cm^{-1}; NMR 6.81 (dd, J = 17.5, 11 Hz, H-14), 5.33 (br t, J = 7 Hz, H-12), 5.19 (d, J = 17.5 Hz, H-15$_{trans}$), 5.10 (d, J = 11 Hz, H-15$_{cis}$), 4.84 and 4.49 (both br, H-17), 1.81 (d, J = 1 Hz, H-16), 0.91, 0.85, and 0.76 ppm (C-4 and C-10 Me).

Photooxygenation of 5. A solution of 0.3 g of *trans*-biformene (**5**) in CH_2Cl_2–5% MeOH was reacted with singlet oxygen (14 mg of rose bengal) for 75 min. After addition of 0.3 g of triethyl phosphite, flash chromatography over silica gel and separation by preparative TLC gave 80 mg (27%) of **15**, 29 mg (10%) of **16**, 17 mg (6%) of **17**, 36 mg (12%) of **18**, 12 mg (4%) of **19**, 13 mg (4%) of **20**, and 8 mg (3%) of **21** as well as 16 mg of starting material **5**.

(12*R*)-Labda-8(17),13(16),14-trien-12-ol (**15**):[12] mp 65–67 °C; IR 3415, 3075, 1640, 890, 760 cm^{-1}; NMR 6.35 (dd, J = 17.5, 10.5 Hz, H-14), 5.43 (d, J = 17.5 Hz) and 5.13 (d, J = 10.5 Hz, H-15$_{trans}$ and H-15$_{cis}$), 5.22 and 5.15 (both br, H-16), 4.87 and 4.53 (both br, H-17), 4.41 (dd, J = 6.5, 5 Hz, H-12), 0.90, 0.83, and 0.69 ppm (C-4 and C-10 Me).

(12*S*)-Labda-8(17),13(16)-14-12-ol (**16**): IR 3385, 3075, 1640, 890, 760 cm^{-1}; NMR 6.36 (dd, J = 17.5, 10.5 Hz, H-14), 5.43 (d, J = 17.5 Hz) and 5.13 (d, J = 10.5 Hz, H-15$_{trans}$ and H-15$_{cis}$), 5.18 and 5.15 (both br, H-16), 4.89 and 4.74 (both br, H-17), 4.44 (dd, J = 8, 5.5 Hz, H-12), 0.88, 0.81, and 0.71 ppm (C-4 and C-10 Me). The mass spectrum did not exhibit the molecular ion peak.

Anal. Calcd for $C_{20}H_{30}$: m/e 270.2347 (M^+ – 18). Found: mass spectrum, m/e 270.2329 (M^+ – 18, 1%).

(11*E*)-Labda-8(17),11,14-trien-13-ol (**17**, 1:1 mixture of 13-epimers): IR 3410, 3075, 1640, 990, 920, 890 cm^{-1}; NMR (peaks of two epimers almost coincident) 5.99 (dd, J = 17.5, 11 Hz, H-14), 5.72 (dd, J = 16, 9.5 Hz, H-11), 5.57 (d, J = 16 Hz, H-12), 5.25 (d, J = 17.5 Hz) and 5.06 (d, J = 11 Hz, H-15$_{trans}$ and H-15$_{cis}$), 4.74 and 4.46 (both br, H-17), 1.40 (C-13 Me), 0.90, 0.85, and 0.82 ppm (C-4 and C-10 Me).

Anal. Calcd for $C_{20}H_{32}O$: mol wt 288.2453. Found: mol wt (mass spectroscopy) 288.2480 (3%).

(12*R*)-15,16-Epidioxylabda-8(17),13-dien-12-ol (**18**):[12] IR 3440, 3065, 1640, 890, 760 cm^{-1}; NMR 5.89 (H-14), 4.87 and 4.43 (both br, H-17), 4.67 (br, H-16), 4.65 and 4.50 (both br dd, J = 17, 3 Hz, H-15), 4.21 (br t, J = 6 Hz, H-12), 0.90, 0.83, and 0.70 ppm (C-4 and C-10 Me).

(12*S*)-15,16-Epidioxylabda-8(17),13-dien-12-ol (**19**): IR 3405, 3065, 1640, 890, 760 cm^{-1}; NMR 5.83 (m, H-14), 4.89 and 4.67 (both br, H-17), 4.68 and 4.53 (dq, J = 16.5, 2.5 Hz, H-15), 4.67 (br, H-16), 4.29 (br dd, J = 9, 6 Hz, H-12), 0.89, 0.82, and 0.71 ppm (C-4 and C-10 Me). The mass spectrum did not exhibit the molecular ion peak.

Anal. Calcd for $C_{20}H_{30}O_2$: m/e 302.2245 (M^+ – 18). Found: m/e 302.2233 (M^+ – 18, 7%).

(12*R*)-12,15-Epidioxylabda-8(17),13-diene (**20**): IR 3075, 1635, 885 cm^{-1}; NMR 5.59 (m, H-14), 4.86 and 4.50 (both br H-17), 4.68 and 4.31 (both br dd, J = 15.5, 2.5 Hz, H-15), 4.16 (br dd, J = 10, 2 Hz, H-12), 1.81 (br, H-16), 0.90, 0.83, and 0.72 ppm (C-4 and C-10 Me). The mass spectrum did not exhibit the molecular ion peak.

Anal. Calcd for $C_{20}H_{30}O$: m/e 286.2296 (M^+ – 18). Found: m/e 286.2277 (M^+ – 18, 13%).

(12*S*)-12,15-Epidioxylabda-8(17),13-diene (**21**): IR 3075, 1640, 895 cm^{-1}; NMR 5.56 (m, H-14), 4.87 and 4.73 (both br, H-17), 4.56 and 4.41 (both dq, J = 15.5, 2 Hz, H-15), 4.21 (br t, J = 6.5 Hz, H-12), 1.79 (d, J = 2 Hz, H-16), 0.90, 0.83, and 0.71 ppm (C-4 and C-10 Me).

Anal. Calcd for $C_{20}H_{32}O_2$: mol wt 304.2401. Found: mol wt (mass spectroscopy) 304.2361 (0.3%).

Photooxygenation of 6. Reaction of 0.1 g of **6** in CH_2Cl_2–5% MeOH with singlet oxygen (5 mg of rose bengal) for 45 min, addition of 0.1 g of triethyl phosphite, flash chromatography over silica gel, and preparative TLC gave 14 mg (13%) of **15**, 8 mg (8%) of **16**, 41 mg (39%) of **17**, 4 mg (4%) of **18**, 4 mg (4%) of **19**, 3 mg (3%) of **20**, and 2 mg (2%) of **21**.

Conversion of 20 and 21 to Pumiloxide (22). A solution of 10 mg of **20** in 2 mL of tetrahydrofuran was stirred with 10 mg of $Fe_2SO_4 \cdot 7H_2O$ in 2 mL of water for 1 h and concentrated in vacuo. The residue was diluted with H_2O and extracted with ether.

Evaporation of the washed and dried ether extract followed by TLC of the residue gave 8 mg of 12,15-epoxylabda-8(17),12,14-triene (**22**): mp 85–86 °C (not recrystallized because of sample size) (lit.[21] mp 88–89 °C); IR 3075, 1640, 1620, 1510, 885, 725 cm^{-1}; NMR 7.18 (d, J = 2 Hz, H-15), 6.12 (d, J = 2 Hz, H-14), 4.78 and 4.59 (both br, H-17), 2.00 (H-16), 0.92, 0.86, and 0.86 ppm (C-4 and C-10 Me).

Anal. Calcd for $C_{20}H_{30}O$: mol wt 286.2296. Found: mol wt (mass spectroscopy) 286.2296 (15.6%).

Reaction of 5 mg of **21** with $FeSO_4 \cdot 7H_2O$ in the same manner gave 3 mg of **22** after purification by TLC.

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Registry No. (*E*)-**2**, 76467-03-3; (*Z*)-**2**, 76467-04-4; (*E*)-**3**, 10483-51-9; (*Z*)-**3**, 10395-41-2; **4**, 76498-70-9; **5**, 10395-42-3; **6**, 17990-20-4; **7** (isomer 1), 76467-05-5; **7** (isomer 2), 76497-67-1; **8**, 76467-06-6; **9**, 76467-07-7; **10** (isomer 1), 76467-08-8; **10** (isomer 2), 76497-68-2; **11**, 76497-69-3; **12a**, 596-85-0; **12b**, 1438-62-6; **13** (isomer 1), 61091-79-0; **13** (isomer 2), 61091-80-3; **14**, 511-02-4; **15**, 76467-09-9; **16**, 76467-10-2; **17** (isomer 1), 76467-11-3; **17** (isomer 2), 76497-70-6; **18**, 61604-71-5; **19**, 76467-12-4; **20**, 76467-13-5; **21**, 76467-14-6; **22**, 67779-53-7; manool, 596-85-1; 14,15-dihydromanool, 40768-86-3.

Supplementary Material Available: Mass spectral data (2 pages). Ordering information is given on any current masthead page.

Synthesis of 7,9-Di-*O*-methyl-11-oxosibiromycinone

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The synthesis of 7,9-di-*O*-methyl-11-oxosibiromycinone (**8**) is described. Nitration of methyl 4-methyl-3,5-dimethoxybenzoate (**18**) gave the corresponding nitro derivative **20** which was converted to 4-methyl-3,5-dimethoxy-2-nitrobenzoyl chloride (**24**). Ethyl 4-formylpyrrole-2-carboxylate (**10**) was treated with ethylmagnesium bromide and the resulting secondary alcohol **25** heated in dimethyl sulfoxide to afford ethyl (*E*)-4-(1-propenyl)pyrrole-2-carboxylate (**26**). Amide bond formation between acid chloride **24** and the sodium salt of pyrrole derivative **26** gave **29**. Reduction of the nitro group of **29** with triirondodecacarbonyl gave the corresponding amine **31** which cyclized to the desired compound **8** on heating with *p*-toluenesulfonic acid in toluene. Preliminary attempts to convert **8** to sibiromycinone were unsuccessful.

Introduction

Sibiromycin (**1**)[1] is a naturally occurring antitumor antibiotic first isolated[2] in the Soviet Union from *Streptosporangium sibiricum*.[3] It binds strongly to DNA and is active against a number of tumor cells, including transplanted solid tumors in mice. Its biological activity has been attributed to covalent binding to DNA through the electrophilic N(10)–C(11) carbinolamine[4].

Sibiromycin is characterized by a number of structural features which present challenges to chemical synthesis, especially when compared to other pyrrolo[1,4]benzodiazepine antibiotics such as anthramycin (**2**).[5,6] Sibiromycin (**1**) differs from **2** in that not only is **1** the glycoside of a branched-chain amino sugar (sibirosamine) but it also incorporates an aromatic pyrrole ring into its structure as opposed to the dihydropyrrole found in **2**. Both **1** and **2** undergo ready dehydration to the corresponding imines anhydrosibiromycin (**3**) and anhydroanthramycin (**4**) (see Scheme I). While the carbinolamine–imine interconversion is readily reversible for anthramycin,[7] the equilibrium is strongly biased toward the conjugated imine **3** for **1**.[2] Anhydrosibiromycin (**3**) is biologically inactive.[2] Another significant difference is that the amide bond to the pyrrole ring nitrogen in **1** is less stable toward nucleophilic cleavage than is the corresponding amide bond in **2**.

The labile carbinolamine function apparently presents the major obstacle to any synthesis of **1** or of its aglycon sibiromycinone (**5**). In a recent synthetic effort, Parker[8] found that dehydration of 7,9-di-*O*-methylsibiromycinone (**6**) occurred spontaneously under the cyclization conditions used for its formation, giving, as the only isolable product, 7,9-di-*O*-methylanhydrosibiromycinone (**7**). An alternative approach would be to introduce the carbinolamine functionality in a separate reduction step following construction of the pyrrolo[1,4]benzodiazepine skeleton, analogous to the approach taken by Leimgruber in the synthesis of **2**.[9] We report here the synthesis of the key intermediate required to pursue this approach, 7,9-di-*O*-methyl-11-oxosibiromycinone (**8**).

Results and Discussion

The synthetic plan is outlined in Scheme II. The diazepine ring is constructed in two stages: first, amide formation between 4-methyl-3,5-dimethoxy-2-nitrobenzoyl chloride (**24**) and ethyl (*E*)-4-(1-propenyl)pyrrole-2-

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