1600, 1448, 1275, 1210, 1150, 1100, 1040, 1010, 958, 910, 740, 685 cm^{-1}. Anal. Calcd for $C_{27}H_{18}O_4$: C, 79.80; H, 4.43. Found: C, 79.77; H, 4.70.

Dispiro[cyclohexane-1,3'-(1',2',4'-trioxolane)-5',9''-(10''-oxo-9'',10''-dihydrophenanthrene)] (22): mp 95–96 °C dec (from methanol); ^{13}C NMR δ 23.67–41.98 (5 C), 102.39, 113.00, 123.33–136.07 (12 C), 192.11; IR 2935, 2860, 1715, 1605, 1455, 1278, 1175, 1095, 1020, 982, 920, 760 cm^{-1}. Anal. Calcd for $C_{20}H_{18}O_4$: C, 74.53; H, 5.59. Found: C, 74.22; H, 5.66.

Preparation of Dispiro[(3-phenyl-1,2,4-trioxolane)-5,1'-cyclohexane-2',5''-(3''-phenyl-1'',2'',4''-trioxolane)] (33). A solution of benzylidenecyclohexanone (**25**; 186 mg, 1 mmol) in ether (15 mL) was treated with 1 mmol of O_3 at −70 °C. Then, vinyl ether **1b** (268 mg, 2 mmol) dissolved in ether (5 mL) was added, and the mixture was treated with 2 mmol of O_3 at the same temperature. After evaporation of the solvent, the products were triturated with ether/hexane to give the diozonide **33** (206 mg, 58%) as a ca. 1:1 mixture of two isomers. Recrystallization from ethyl acetate yielded a ca. 3:2 mixture, but further separation of each isomer failed. This mixture showed the following physical properties: mp 95–100 °C; ^1H NMR δ 1.4–3.0 (m, 8 H), 6.14 (s, CH, minor), 6.35 (s, CH, major), 7.3–8.4 (m, 10 H); ^{13}C NMR (major) δ 21.94, 22.58, 32.82, 34.18, 104.25, 104.94, 108.29, 109.01, 128.01–130.98 (12 C); ^{13}C NMR (minor) δ 22.07 (2 C), 34.53 (2 C), 105.10 (2 C), 108.52 (2 C), 127.94–131.13 (12 C); IR 2950, 2920, 1460, 1390, 1320, 1180, 1110, 1040, 1010, 760, 700 cm^{-1}. Anal. Calcd. for $C_{20}H_{20}O_6$: C, 67.41; H, 5.62. Found: C, 67.42; H, 5.63.

Ozonolysis of Vinyl Ether in the Presence of α-Keto Ester. The ozonolysis of a mixture of vinyl ether **1b** and ethyl pyruvate (**34**) is representative. A solution of **1b** (134 mg, 1 mmol) and **34** (116 mg, 1 mmol) in ether (15 mL) was treated with 1 mmol of O_3 at −70 °C. Subsequent column chromatography on silica gel (elution with benzene) gave ethyl 3-methyl-5-phenyl-1,2,4-trioxolane-3-carboxylate (**37a**) (214 mg, 90%) as a mixture of two isomers (2:3): oil; ^1H NMR δ 1.32 (t, J = 7 Hz, 3 H), 1.73 (s, 3 H), 4.28 (q, J = 7 Hz, 2 H), 6.02 (s, CH, major), 6.24 (s, CH, minor), 7.3–7.7 (m, 5 H); ^{13}C NMR δ 13.93 (minor), 13.96 (major), 18.95 (major), 19.36 (minor), 62.06 (major), 62.26 (minor), 104.28 (major), 105.07 (minor), 105.13 (major), 105.16 (minor), 126.95–134.04 (6 C), 167.65 (minor), 168.60 (major). Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.51; H, 5.88. Found: C, 60.56; H, 5.99.

Ethyl 3,3-diphenyl-5-methyl-1,2,4-trioxolane-5-carboxylate (37b): mp 35–36 °C (from hexane); ^1H NMR δ 1.26 (t, J = 7 Hz, 3 H), 1.55 (s, 3 H), 4.23 (q, J = 7 Hz, 2 H), 7.2–7.7 (m, 10 H); ^{13}C NMR δ 13.99, 19.38, 62.10, 105.91, 111.50, 126.39–140.41 (12 C), 168.61. Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.79; H, 5.73. Found: C, 69.33; H, 5.77.

Ethyl 9-methyl-7,8,10-trioxaspiro[5.4]decane-9-carboxylate (37c): oil; ^1H NMR δ 1.32 (t, J = 7 Hz, 3 H), 1.56 (s, 3 H), 1.2–1.9 (m, 10 H), 4.23 (q, J = Hz, 2 H); ^{13}C NMR δ 13.93, 19.25, 23.31, 23.80, 24.62, 32.35, 35.05, 103.87, 111.26, 168.99. Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.39; H, 7.83. Found: C, 57.12; H, 7.95.

Methyl 3,5-diphenyl-1,2,4-trioxolane-3-carboxylate (37d): a mixture of two isomers (2:3); oil; ^1H NMR δ 3.81 (s, CH_3, minor), 3.86 (s, CH_3, major), 6.15 (s, CH, major), 6.36 (s, CH, minor), 7.2–7.9 (m, 10 H). By repeated column chromatography the major isomer could be isolated in a pure state: oil; ^{13}C NMR δ 53.15, 106.08, 106.18, 126.22–131.81 (12 C), 168.68. Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.13; H, 4.90. Found: C, 67.70; H, 4.96.

Methyl 3,3,5-triphenyl-1,2,4-trioxolane-5-carboxylate (37e): mp 106–108 °C (from benzene/hexane); ^1H NMR δ 3.83 (s, 3 H), 7.3–7.7 (15 H). Anal. Calcd for $C_{22}H_{18}O_5$: C, 72.93; H, 4.97. Found: C, 72.95; H, 4.99.

Methyl 3-phenyl-5-heptyl-1,2,4-trioxolane-3-carboxylate (37f): a mixture of two isomers (2:3); oil; ^1H NMR δ 0.8–2.0 (m, 15 H), 3.71 (s, 3 H), 5.24 (t, J = 4.5 Hz, CH, major), 5.45 (t, J = 4.5 Hz, CH, minor), 7.2–7.6 (m, 5 H).

Diethyl 5-phenyl-1,2,4-trioxolane-3-malonate (37g): oil; ^1H NMR δ 1.35 (t, J = 7 Hz, 6 H), 4.32 (q, J = 7 Hz, 4 H), 6.13 (s, 1 H), 7.2–7.8 (m, 5 H). Anal. Calcd for $C_{14}H_{16}O_7$: C, 56.75; H, 5.41. Found: C, 56.80; H, 5.43.

Diethyl 5,5-diphenyl-1,2,4-trioxolane-3-malonate (37h): mp 38–43 °C; ^1H NMR δ 1.18 (t, J = 7 Hz, 6 H), 4.17 (q, J = 7 Hz, 4 H), 7.2–7.8 (m, 10 H); ^{13}C NMR δ 13.84 (2 C), 63.05 (2 C), 101.18, 113.41, 127.71–136.13 (12 C), 163.62 (2 C). Anal. Calcd for $C_{20}H_{20}O_7$: C, 64.51; H, 5.38. Found: C, 64.75; H, 5.30.

Diethyl 7,8,10-trioxaspiro[5.4]decane-9,9-dicarboxylate (37i): oil; ^1H NMR δ 1.32 (t, J = 7 Hz, 6 H), 1.2–2.1 (m, 10 H), 4.25 (q, J = 7 Hz, 4 H).

Registry No. **1a**, 109-53-5; **1b**, 4747-15-3; **1c**, 40237-72-7; **1d**, 19096-89-0; **1e**, 120872-41-5; **4**, 82-86-0; **5**, 81-84-5; **6b**, 100-52-7; **6c**, 119-61-9; **6d**, 108-94-1; **7**, 963-63-3; **9**, 10027-71-1; **12**, 65-85-0; **16**, 505-48-6; **18**, 84-11-7; *trans*-**19**, 136460-07-6; *cis*-**19**, 136460-08-7; **20**, 136460-09-8; **21**, 136460-10-1; **22**, 136460-11-2; **24**, 6050-13-1; **25**, 5682-83-7; **27**, 1011-12-7; **28**, 5679-13-0; **29**, 42063-01-4; **30**, 110-94-1; **31**, 111-16-0; **33**, 136460-21-4; **34**, 617-35-6; **35**, 15206-55-0; **36**, 609-09-6; *trans*-**37a**, 136460-12-3; *cis*-**37a**, 136460-13-4; **37b**, 136460-14-5; **37c**, 136460-15-6; *trans*-**37d**, 136460-16-7; *cis*-**37d**, 136460-17-8; **37e**, 136460-06-5; *trans*-**37f**, 136460-18-9; *cis*-**37f**, 136460-19-0; **37g**, 136460-20-3; **37h**, 136460-22-5; **37i**, 136460-23-6; 3,3,6,6-tetraphenyl-1,2,4,5-tetroxane, 16204-36-7.

Transformation of Neoclerodane Diterpenoids into 19-Norneoclerodane Derivatives

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The neoclerodane diterpenoid eriocephalin (**1**) was transformed into its 19-nor derivatives **3** and **4** by reaction with potassium *tert*-butoxide in THF, whereas with the same treatment compound **6** yielded only the trans-acetylation derivative **7**. These results indicated that 19-acetoxy-4α,18-epoxy-7α-hydroxy-6-oxoneoclerodane derivatives are transformed into the corresponding 19-nor compounds in a retroaldol reaction by loss of the C-19 carbon as formaldehyde followed by opening of the oxirane ring and intramolecular attack by a C-18 alkoxide on the carbonyl C-6 carbon atom, giving the allylic hemiacetal **3**, which is easily dehydrated to the furanic derivative **4**. Compound **4** was transformed into the α,β-unsaturated γ,δ-enol γ-lactone **8** by an oxidation reaction with atmospheric oxygen in chloroform solution. Alternatively, it gave the α,β-unsaturated γ-lactone **11** under acid catalysis. These reactions allowed the partial syntheses of the naturally occurring diterpenoids teuscorolide (**9**) and teucvin (**12**) and are of interest for chemical transformations of substances of this kind.

A large number of neoclerodane and 19-norneoclerodane diterpenoids[2] have been isolated from plants in the last few years.[3] These compounds have attracted interest owing to their biological activities, especially as insect

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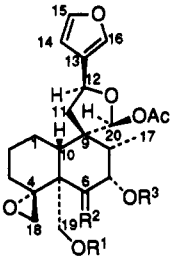
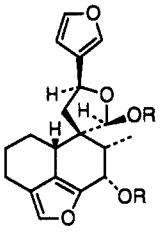
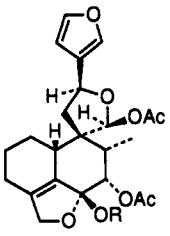
Chart I



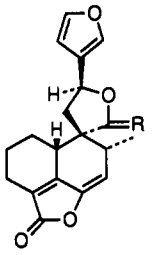
	R^1	R^2	R^3
1	Ac	O	H
6	Ac	αOH,βH	Ac
7	H	αOAc,βH	Ac



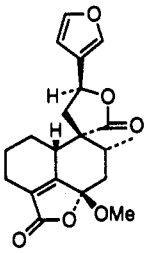
2 R=H
4 R=Ac



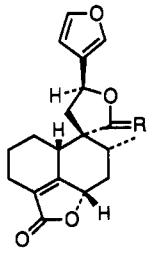
3 R=H
5 R=Me



8 R=αH,βOAc
9 R=O



10



11a R=αH,βOH
11b R=αOH,βH
12 R=O

antifeedants and as antifungal, antitumour, antimicrobial, and moluscicidal agents.[4] The genus *Teucrium* (family Labiatae) is the most abundant natural source of this kind of diterpenoids.[5]

In continuation of our studies on neoclerodane diterpenoids from *Teucrium* species,[5] we were interested in establishing chemical correlations between some of these compounds[6] and also in obtaining synthetic derivatives in order to test their biological activities.[7] In this paper we report some reactions of the diterpenoid eriocephalin[8] (**1**, Chart I), providing data on the mechanism of the transformation of neoclerodane diterpenoids into their 19-nor derivatives. In addition, some interesting and useful reactions of 19-norneoclerodane compounds and partial syntheses of the naturally occurring substances teuscorolide[9] (**9**) and teucvin[6a,10] (**12**) are also reported.

Results and Discussion

It is known that 19-acetoxy- or 19-hydroxy-4α,18-epoxy-6-oxoneoclerodane derivatives, such as eriocephalin[8] (**1**), are easily transformed into the corresponding 19-nor compounds possessing a furan ring, which involves the C-4, C-5, C-6, and C-18 carbon atoms of the neoclerodane skeleton, as in compound **2**. This transformation has been achieved by alkaline treatment[6a,11] and, in the case of the 19-hydroxy derivatives, also by thermal rearrangement[6b] and by slow chromatography through silica gel.[6a,12] In all these cases, the process seems to involve the initial loss of the C-19 carbon as formaldehyde by a retroaldol reaction and the formation of a furan from the β-epoxy ketone by a cyclodehydration reaction,[11,13] but a study of the mechanism of this transformation has not previously been undertaken.

In accordance with previous results[6a,b,11,12] for other neoclerodane derivatives, treatment of eriocephalin[8] (**1**) with an ethanolic solution of potassium hydroxide (see Experimental Section) gave the expected derivative **2** in moderate yield (56%). However, when compound **1** was treated with potassium *tert*-butoxide in dry THF, it was almost quantitatively transformed (96% yield) into a highly unstable compound (**3**), which in turn, under very mild conditions (see Experimental Section), underwent a dehydration reaction yielding compound **4**. Moreover, if the above-mentioned transformation of eriocephalin (**1**)

(1) Present address: Departamento de Química Orgánica, Facultad de Ciencias Químicas, 'Complutense' University, 28040-Madrid, Spain.

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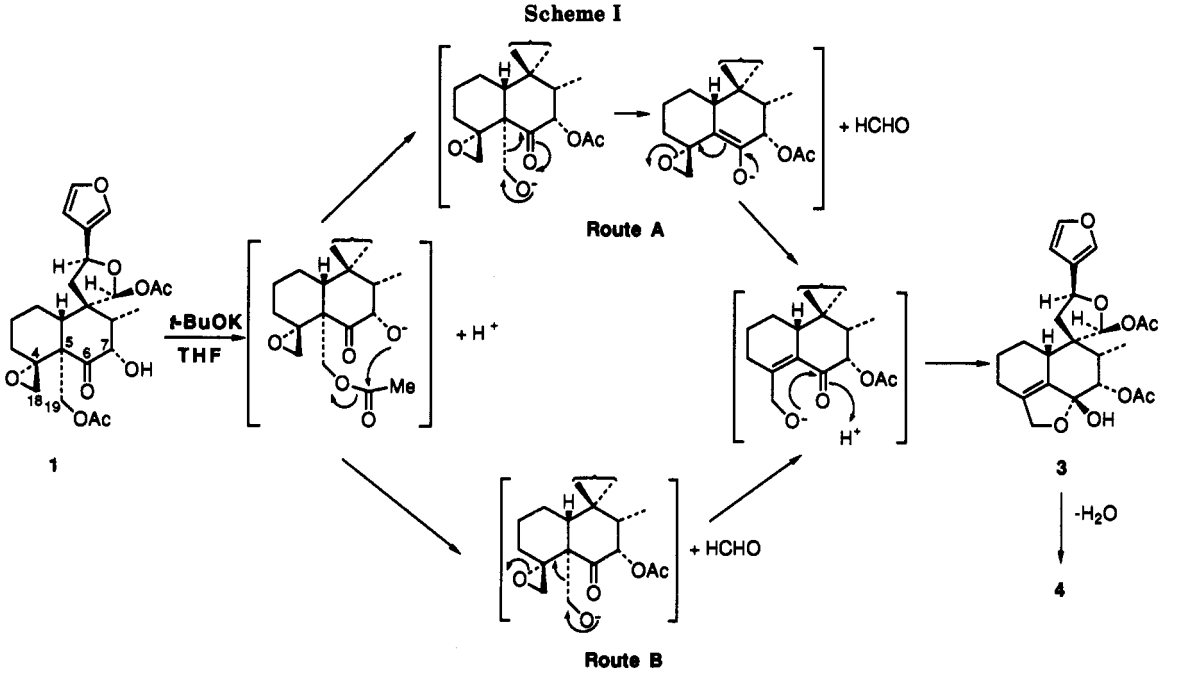
Table I. ^{1}H NMR Data of Compounds 2–5, 7, 8, and 10[a]

H	2	3	4	5	7	8	10	J	2	3	4	5	7	8	10
6β					4.79 dd			6β,7β					4.1		
7α						5.44 d[b]	2.42 t	7α,7β							13.2
7β	4.63 d	5.07 d	5.97 d	5.14 d	5.22 dd		2.19 dd	7α,8β						2.7[b]	13.2
8β	2.34 qd	2.58 qd	2.49 qd	2.49 qd	1.70 qd	2.91 qd	2.14 ddq	7β,8β	3.6	2.2	3.7	2.2	2.8		3.6
10β	2.67 br dd	c	c	2.20[c]	c	c	c	8β,17	7.5	7.4	7.4	7.4	7.1	7.6	6.7
11A	2.09 dd	2.27 dd	2.18 dd	2.20[c]	1.80 dd	2.23 dd	2.52 dd	10β,1α	16.4	c	c	c	c	c	c
11B	2.61 dd	2.55 dd	2.66 dd	2.53 dd	2.32 dd	2.54 dd	2.58 dd	10β,1β	4.9	c	c	c	c	c	c
12	5.19 t	5.26 t	5.27 t	5.22 t	5.12 dd	5.22 t	5.46 t	11A,11B	13.1	12.6	12.9	13.4	13.2	13.4	14.1
14	6.50 dd	6.52 dd	6.41 dd	6.38 dd	6.39 dd	6.39 dd	6.40 dd	11A,12	8.1	8.1	8.1	8.2	10.4	8.1	8.5
15	7.38 t	7.50[c]	7.39 t	7.38 t	7.40[c]	7.40 t	7.46 t	11B,12	8.4	8.1	8.1	8.2	6.7	8.1	8.5
16	7.39 m	7.50[c]	7.36 m	7.35 m	7.40[c]	7.39 m	7.47 m	14,15	1.8	1.8	1.7	1.8	1.7	1.8	1.8
17(3)	1.47 d	1.24 d	1.39 d	1.24 d	1.00 d	1.47 d	1.02 d	14,16	0.9	0.9	0.9	0.8	1.1	0.8	0.9
18A	7.12 br s	4.34 dd	7.09 br s	4.44 dd	2.19 d			15,16	1.8	c	1.7	1.8	c	1.8	1.8
18B		4.54 dd		4.65 dd	2.94 dd			18A,18B		12.8		13.2	3.7		
19A					4.69 dd			18A10β	<0.3	2.1	<0.3	1.2	0		
19B					5.41 d			18B,10β		3.6		3.5	0		
20	5.08 s	6.09 s	6.04 s	6.10 s	5.85 s	5.84 s		18B,3α		0		0	2.9		
OAc(3)		1.97 s	2.01 s	1.97 s	2.18 s	2.01 s		19A,19B					12.8		
		1.88 s	2.01 s	1.97 s	2.09 s			19A,6β					1.0		
					1.92 s										
OH[d]	4.20 br s	5.02 br s			e										
	3.92 br s														
OMe(3)				3.12 s			3.15 s								

[a] Chemical shifts are reported in ppm downfield from internal TMS; J values in Hz. All spectra were recorded in $CDCl_3$ solution, except for 3, which was taken in acetone-d_6. [b] Olefinic C-7 proton. [c] Overlapped signal. [d] Disappeared after addition of D_2O. [e] Not measured.

Scheme I

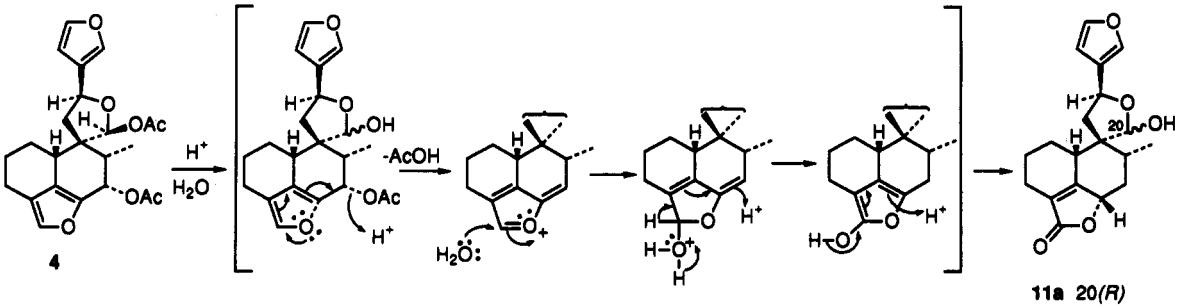


into compound 3 was quenched with methyl iodide instead of a proton source, the stable methyl acetal 5 was obtained in 69% yield and this substance was easily transformed into compound 4 by a thermal 1,4-elimination of methanol.

The structures of compounds 3 and 5 are strongly supported by their ^{1}H and ^{13}C NMR data (see Table I and supplementary material, respectively). In particular, the existence of an allylic C-18, C-6 hemiacetal (3) or methyl acetal (5) moiety is clearly evidenced by the ^{13}C NMR chemical shift of the C-4, C-5, C-6, and C-18 carbon atoms (δ_{C-4} 133.0 s and 128.0 s, δ_{C-5} 137.6 s and 139.7 s, δ_{C-6} 107.1 s and 109.9 s, and δ_{C-18} 75.9 t and 77.5 t, in 3 and 5, respectively) and the C-6β configuration of the methoxyl group of compound 5 is in agreement with NOE experiments because irradiation at δ 3.12 (OMe protons signal) caused NOE enhancement in the signals of the H-7β (δ 5.14, 4% NOE enhancement), H-8β (δ 2.49, 3%), H-10β (δ 2.20, 2%), and H_B-18 (δ 4.65, 5%) protons. In addition, the location in compounds 3–5 of an acetoxyl group at the C-7α position (which must originate by a 1,3-diaxial transacetylation from the C-19 acetoxyl group to the C-7α hydroxyl function of eriocephalin (1)) is evident from the NMR spectroscopic data. In particular, the signal of the H-7β proton appeared downfield shifted in all these compounds (Δδ +0.30 to +1.20) with respect to diterpenoid 1 ($\delta_{H-7\beta}$ 4.77).[8a]

The structure of compound 3 is compatible with the two mechanistic pathways shown in Scheme I. Both mechanisms are initiated by the formation of an alkoxide in the C-7α hydroxyl group of eriocephalin (1) followed by a transacetylation of the C-19 acetyl substituent. The resulting C-19 alkoxide could produce compound 3 by loss of the C-19 alkoxymethylene substituent as formaldehyde in a retroaldol reaction in which the C-6 ketone takes part (route A, Scheme I) or, alternatively, by a fragmentation reaction of the 3,4-epoxy alkoxide[14] (route B, Scheme I)

Scheme II



giving a C-18 alkoxide, which may also be formed from the enolate postulated in route A. Finally, an intramolecular attack by the C-18 allylic alkoxide on the carbonyl C-6 carbon produces compound **3**.

On the other hand, treatment of compound **6** (a synthetic derivative[8b] of eriocephalin (**1**) without the ketone function at the C-6 position) with potassium *tert*-butoxide under the same conditions as for compound **1** (see Experimental Section) yielded almost quantitatively the C-19 to C-6α transacetylation derivative (**7**) as the sole detectable reaction product, thus indicating that route A of Scheme I is probably the mechanism for the transformation of 19-acetoxy-4α,18-epoxy-6-oxoneoclerodane diterpenoids into their corresponding 19-nor derivatives.

We next turned our attention to compound **4** as a suitable derivative for obtaining the naturally occuring diterpenoid teuscorolide[9] (**9**). It is known[6a,11,15] that 19-norneoclerodanes with a furan involving the C-4, C-5, C-6, and C-18 carbons such as in compound **4**, but without any substituent at the C-7 position, undergo an interesting reaction yielding α,β-unsaturated γ-lactones (such as compounds **11a**, **11b**, and **12**) when they are kept in a pure chloroform solution in the presence of atmospheric oxygen for several days (see Experimental Section). Although this reaction was reported a long time ago,[16] its mechanism has remained unknown and only a complicated radical pathway has been suggested for it hitherto.[17] In the case of compound **4**, which possesses an acetoxyl group at the C-7α position, this reaction gave, in low yield (20%), the derivative **8** as the main product. Obviously, the transformation of compound **4** into the α,β-unsaturated γ,δ-enol γ-lactone **8** occurs via oxidation of the furan and additional 1,2-elimination of the C-7α acetoxyl group.

In order to obtain teuscorolide (**9**) from compound **8**, we treated this substance with potassium carbonate in methanol solution and next with the chromium trioxide–pyridine complex (see Experimental Section). After these reactions compound **10** was obtained (77% yield), and it was identical with a substance arising from teuscorolide (**9**) by addition of methanol to the C-6, C-7 double bond of the α,β-unsaturated γ,δ-enol γ-lactone moiety of compound **9** when it was treated with a methanolic solution of potassium carbonate. The C-6β configuration of the methoxyl group of compound **10** was established by NOE experiments, the irradiation at δ 3.15 (methoxyl protons) producing NOE enhancement of the signals of the H-7β (δ 2.19, 2% NOE enhancement), H-8β (δ 2.14, 3%), and Me-17 (δ 1.02, negative NOE enhancement, −2%) protons.

Since several attempts at obtaining teuscorolide (**9**) from compound **10** by a 6,7-elimination of methanol were unsuccessful, we performed the hydrolysis of the acetate at C-20 of compound **8** with sulfuric acid in THF (see Experimental Section). The crude product was then oxidized with chromium trioxide–pyridine, giving a substance identical in all respects (mp, mixed mp, $[\alpha]_D$, IR, UV, ^{1}H NMR, and MS) with natural teuscorolide[9] (**9**).

On the other hand, treatment of compound **4** with sulfuric acid in THF produced the hydrolysis of the C-20 acetate group, with epimerization at this asymmetric center. At the same time, the acid catalyst also caused a rearrangement of the furfuryl alcohol acetate moiety yielding an inseparable mixture[18] of compounds **11a** and **11b**. Scheme II shows the transformation mechanism, which is proposed on the basis of its similarity with the known conversion of furfuryl alcohol into levulinic acid.[19]

Finally, chromium trioxide–pyridine oxidation of the mixture of compounds **11a** and **11b** gave teucvin[6a,10] (**12**), a diterpenoid previously isolated from several *Teucrium* species.[5]

In summary, starting from an easily available natural diterpenoid (**1**),[8a] we have established a likely mechanism for the transformation of neoclerodane diterpenes into their 19-nor derivatives and a versatile route for obtaining a wide range of enantiomerically pure natural and synthetic 19-norneoclerodane compounds, which are interesting on account of their biological activities.[7]

Experimental Section

Melting points were determined in a Kofler apparatus and are uncorrected. ^{1}H NMR spectra were measured at 300 or 200 MHz. The proton NOE measurements were made at 300 MHz by the FT difference method. ^{13}C NMR spectra were performed at 50.3 MHz. Low-resolution mass spectra were obtained at 70 eV (mode EI, solid probe).

Starting material (**1**, eriocephalin) was available from previous studies.[8]

(12*S*,20*R*)-6,18;15,16-Diepoxy-7α-hydroxy-19-norneoclerodane-4(18),5,13(16),14-tetraene 20,12-Hemiacetal[20] (2) from Eriocephalin (1). To an EtOH (2.5 mL) solution of

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(15) Malakov, P. Y.; Papanov, G. Y.; Mollov, N. M. *Tetrahedron Lett.* **1978**, 2025.

(16) Hikino, H.; Hikino, Y.; Yoshioka, I. *Chem. Pharm. Bull.* **1962**, *10*, 641.

(17) Malakov, P. Y. Ph.D. Dissertation, University of Plovdiv, Plovdiv, Bulgaria, 1978.

(18) This mixture was clearly revealed by its ^{1}H NMR spectrum, which showed, among others, two signals for the H-6β (δ 4.85 and 4.70), H-12 (δ 5.20 and 5.09), H-20 (δ 5.28 and 5.02), and Me-17 (δ 0.99 and 0.98) protons.

(19) Bird, C. W.; Cheeseman, G. W. H. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Pergamon Press: Oxford, 1984; Vol. 4, pp 70–71.

(20) In accordance with the convention of Canh, Ingold, and Prelog, a 20(*R*) (or 20(*S*)) carbon atom of a neoclerodane-20,12-hemiacetal must be defined as 20(*S*) (or 20(*R*)) when the hemiacetalic hydroxyl group is acetylated, although the C-20 absolute stereochemistry is the same in both cases.

compound 1 (200 mg) was added 2.5 mL of a 5% (w/v) ethanolic solution of KOH, and the mixture was stirred at rt for 1.5 h under Ar. Then, 10 mL of a saturated solution of NH_4Cl was added, and the reaction mixture was extracted with EtOAc (3 × 5 mL). The organic extract was dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was chromatographed on a silica gel column eluted with *n*-hexane–EtOAc (7:3) yielding 80 mg (56%) of compound **2**: an amorphous solid, mp 115–125 °C; $[\alpha]_D^{22}$ +27.8° (*c* 0.054, $CHCl_3$); IR (KBr) 3400 br (OH), 3140, 1560, 1505, 875 (furan rings) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) see Table I; MS *m/z* (rel intensity) 330 (M^+, 4), 312 (8), 294 (6), 136 (100), 95 (50), 94 (50), 91 (32). Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71. Found: C, 69.12; H, 6.83.

(12*S*,20*S*)-7α-Acetoxy-20-*O*-acetyl-15,16-epoxy-19-norneoclerodane-4,13(16),14-triene 6α,18;20,12-Dihemiacetal[20] (3) and (12*S*,20*S*)-7α-Acetoxy-20-*O*-acetyl-6,18;15,16-diepoxy-19-norneoclerodane-4(18),5,13(16),14-tetraene 20,12-Hemiacetal[20] (4) from Eriocephalin (1). A solution of compound 1 (200 mg, 0.43 mmol) and *t*-BuOK (120 mg, 1.07 mmol) in dry THF (15 mL) was stirred at 0 °C for 20 min under Ar. Then, 8 mL of an aqueous NH_4Cl saturated solution was added to the reaction and the mixture was extracted with EtOAc (3 × 5 mL). The EtOAc extract was dried over Na_2SO_4, filtered, and evaporated to dryness giving a residue (185 mg) that was subjected to column chromatography (silica gel Merck No. 7734, deactivated with 15% (w/v) H_2O, EtOAc–*n*-hexane (1:1) as eluent) yielding compound 3 (179 mg, 96% yield), which was always accompanied by minor quantities (~5–10%, ^1H NMR) of compound 4 (see below). Attempts at obtaining pure 3 by flash chromatography or crystallization were unsuccessful because this substance is extremely unstable, and it was quantitatively transformed into compound 4 by storage, mild acid treatment, slow chromatography through silica gel or alumina, and heating its solutions in acetone or EtOAc or when its $CHCl_3$ solution was left at room temperature for 1 h.

Compound 3 (contaminated with 4) was also obtained by treatment of eriocephalin (1) with *t*-BuOK in *t*-BuOH solution at 30 °C for 15 min. For the ^1H NMR (200 MHz, acetone-d_6) and ^{13}C NMR (50.3 MHz, acetone-d_6) spectra of compound 3, see Table I and supplementary material, respectively.

Compound 4 was obtained from compound 3 as described above or by treating eriocephalin (1, 500 mg, 1.08 mmol) with *t*-BuOK (303 mg, 2.70 mmol) in dry THF (38 mL) solution at 0 °C for 20 min and by drying the EtOAc extract of the reaction with $MgSO_4$ (85% yield). Compound 4 had mp 188–191 °C (EtOAc–*n*-hexane); $[\alpha]_D^{21}$ –187.7° (*c* 0.975, $CHCl_3$); IR (KBr) 3140, 3110, 1600, 1560, 1510, 875, 865 (furan rings), 1740, 1735, 1250, 1220 (OAc) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) see Table I; MS *m/z* (rel intensity) 414 (M^+, 0.8), 354 (38), 201 (89), 150 (100), 95 (21), 91 (23). Anal. Calcd for $C_{23}H_{26}O_7$; C, 66.65; H, 6.32. Found: C, 66.49; H, 6.39.

(12*S*,20*S*)-7α-Acetoxy-20-*O*-acetyl-15,16-epoxy-19-norneoclerodane-4,13(16),14-triene 20,12-Hemiacetal 6α,18-Methyl Acetal (5) from Eriocephalin (1). A cooled (0 °C) solution of compound 1 (200 mg, 0.43 mmol) in dry THF (15 mL) was treated with *t*-BuOK (121 mg, 1.08 mmol) for 5 min with stirring under Ar. Then, 0.1 mL (1.1 mmol) of MeI was added and the reaction mixture was stirred at 0 °C for a further 20 min. Workup in the usual manner (see above) gave a residue (160 mg) that was chromatographed (silica gel column, *n*-hexane–EtOAc (4:1) as eluent) yielding compound 5 (134 mg, 69% yield): mp 145–147 °C dec (EtOAc–*n*-hexane); $[\alpha]_D^{21}$ –56.7° (*c* 0.178, $CHCl_3$); IR (KBr) 3130, 1508, 875 (furan), 1750, 1735, 1250, 1230 (OAc) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) see Table I; MS *m/z* (rel intensity) 446 (M^+, 0.3), 387 (3.5), 283 (49), 95 (28), 91 (34), 43 (100). Anal. Calcd for $C_{24}H_{30}O_8$: C, 64.56; H, 6.77. Found: C, 64.61; H, 6.69.

Thermal Transformation of Compound 5 into Compound 4. Compound 5 (50 mg) in a round-bottomed flask, without any solvent, was heated for 5 min under Ar in a silicone bath preheated at 150 °C. The reaction mixture was allowed to cool to rt, and the solid residue was crystallized from EtOAc–*n*-hexane giving 40 mg of compound 4 (86% yield).

(12*S*,20*S*)-6α,7α-Diacetoxy-20-*O*-acetyl-4α,18;15,16-diepoxy-19-hydroxyneoclerodane-13(16),14-diene 20,12-Hemiacetal (7) from (12*S*,20*S*)-7α,19-Diacetoxy-20-*O*-acetyl-4α,18;15,16-diepoxy-6α-hydroxyneoclerodane-13(16),14-diene 20,12-Hemiacetal (6). Treatment of compound 6[8b] (40 mg) with *t*-BuOK as described above for eriocephalin (1) yielded the transacetylation product 7 (36 mg, 90% yield): thick oil, $[\alpha]_D^{20}$ –10.0° (*c* 0.219, $CHCl_3$); IR (NaCl) 3440 (OH), 3140, 3125, 1505, 880 (furan), 1730 br, 1250 br (OAc) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) see Table I; MS *m/z* (rel intensity) 506 (M^+, 0.2), 446 (3), 381 (32), 95 (34), 94 (41), 43 (100). Anal. Calcd for $C_{26}H_{34}O_{10}$: C, 61.65; H, 6.77. Found: C, 61.36; H, 6.41.

(12*S*,20*S*)-20-*O*-Acetyl-15,16-epoxy-19-norneoclerodane-4,6,13(16),14-tetraen-18,6-olide 20,12-Hemiacetal (8) from Compound 4. A solution of compound 4 (400 mg) in pure $CHCl_3$ (30 mL, without EtOH as stabilizer) was allowed to stand at rt until disappearance (4 days) of the starting material (TLC). The solvent was evaporated and the residue chromatographed (silica gel column, *n*-hexane–EtOAc (4:1) as eluent) giving compound 8 (72 mg, 20% yield) as an amorphous solid: mp 75–85 °C; $[\alpha]_D^{22}$ –97.7° (*c* 0.130, $CHCl_3$); IR (KBr) 3140, 1505, 875 (furan), 1770, 1660 (α,β-unsaturated enol γ-lactone), 1740, 1230 (OAc) cm^{-1}; UV (MeOH) λ_{max} 279 nm (log ε 4.08); ^1H NMR (200 MHz, $CDCl_3$) see Table I; MS *m/z* (rel intensity) 370 (M^+, 1), 310 (54), 176 (87), 95 (48), 91 (45), 60 (100). Anal. Calcd for $C_{21}H_{22}O_6$: C, 68.09; H, 5.99. Found: C, 68.18; H, 5.78.

(12*S*)-15,16-Epoxy-6β-methoxy-19-norneoclerodane-4,13(16),14-triene-18,6α;20,12-diolide (10) from Compound 8. To a solution of compound 8 (40 mg, 0.11 mmol) in MeOH (8 mL) was added K_2CO_3 (60 mg, 0.43 mmol), the reaction mixture was stirred at rt for 3 h, poured into water (10 mL), extracted with CH_2Cl_2 (3 × 6 mL), and the extract was evaporated to dryness. The residue (35 mg), without characterization, was dissolved in pyridine (0.5 mL) and oxidized with the CrO_3–pyridine complex (50 mg of CrO_3 in 0.5 mL of pyridine) for 4 h. The reaction mixture was diluted with water (5 mL) and extracted with Et_2O (6 × 5 mL). Workup in the usual manner gave a residue (32 mg), which was purified by column chromatography (silica gel, *n*-hexane–EtOAc (2:1) as eluent) yielding 30 mg (77%) of compound 10: mp 196–198 °C (EtOAc–*n*-hexane); $[\alpha]_D^{23}$ +213.0° (*c* 0.338, $CHCl_3$); IR (KBr) 3160, 3135, 1510, 880 (furan), 1760 br (γ-lactones) cm^{-1}; UV (MeOH) λ_{max} 221 nm (log ε 4.11); ^1H NMR (300 MHz, $CDCl_3$) see Table I; MS *m/z* (rel intensity) 358 (M^+, 8), 330 (6), 298 (100), 95 (22), 91 (8). Anal. Calcd for $C_{20}H_{22}O_6$; C, 67.02; H, 6.19. Found: C, 67.18; H, 6.24.

Compound 10 from (12*S*)-15,16-Epoxy-19-norneoclerodane-4,6,13(16),14-tetraene-18,6;20,12-diolide (9, Teuscorolide[9]). A solution of teuscorolide[9] (9, 270 mg, 0.83 mmol) in MeOH (50 mL) was treated with K_2CO_3 (460 mg, 3.33 mmol) at rt for 2 h with stirring. The reaction mixture was then diluted with water (50 mL) and extracted with $CHCl_3$ (3 × 30 mL). Drying and removal of the solvent gave a crude product of reaction that was chromatographed on a silica gel column (*n*-hexane–EtOAc (2:1) as eluent) yielding 250 mg of compound 10 (84%).

Teuscorolide[9] (9) from Compound 8. A solution of compound 8 (30 mg, 0.08 mmol) in THF (3 mL) was dropwise acidified with 1 N H_2SO_4 aqueous solution until pH ~2 with stirring at rt. After a further 30 min of stirring, the reaction was poured into water (10 mL) and extracted with EtOAc (4 × 5 mL) and the organic extract successively washed with a saturated solution of $NaHCO_3$ and brine. After drying and removal of the solvent, the residue (30 mg), without further characterization, was oxidized with the CrO_3–pyridine complex (25 mg of CrO_3 in 0.25 mL of pyridine) in pyridine (0.25 mL) solution at rt for 2 h. Workup in the usual way, followed by chromatographic purification (silica gel column, *n*-hexane–EtOAc (2:1) as eluent) gave a substance (21 mg, 80% yield, mp 198–200 °C (Me_2CO–*n*-hexane); $[\alpha]_D^{21}$ +14.2° (*c* 0.639, $CHCl_3$)) identical in all respects (mp, $[\alpha]_D$, IR, UV, ^1H NMR, MS) with natural[9a,e] and synthetic[9b-d] teuscorolide [9, lit.[9d] mp 198–200 °C; $[\alpha]_D^{20}$ +13.5° (*c* 0.31, $CHCl_3$), +18° (*c* 3.4, $CHCl_3$)). Direct comparison (mmp, TLC) with an authentic sample[9a,e] proved the identity of the products.

(12*S*,20*R*)- and (12*S*,20*S*)-15,16-Epoxy-19-norneoclerodane-4,13(16),14-trien-18,6α-olide 20,12-Hemiacetal (11a and 11b) from Compound 4. A stirred solution of compound 4 (42 mg, 0.10 mmol) in THF (9 mL) was dropwise acidified with 1 N H_2SO_4 until pH ~2 at rt. After a further 3 h of stirring, the reaction was worked up as usual to provide a crude product (26 mg), the ^1H NMR spectrum of which[18] showed that it was a mixture of the C-20 epimeric products 11a and 11b. Attempts

at isolating these compounds were unsuccessful. Without further characterization, this mixture was used in the following step.

(12*S*)-15,16-Epoxy-19-norneoclerodane-4,13(16),14-triene-18,6α;20,12-diolide (12, Teucvin[6a,10]) from Compounds 11a and 11b. The mixture of compounds **11a** and **11b** (26 mg) was oxidized with the CrO_3–pyridine complex (50 mg of CrO_3 in 0.5 mL of pyridine) in pyridine (0.5 mL) solution at rt for 2 h. The reaction was worked up as usual to provide a crude product that was purified by chromatography (silica gel column, $CHCl_3$–MeOH (19:1) as eluent) yielding 16 mg of a substance (48% yield from **4**, mp 206–208 °C (EtOAc–*n*-hexane); $[\alpha]_D^{21}$ +185.3° (*c* 0.413, $CHCl_3$)) identical in all respects (mp, $[\alpha]_D$, IR, ^1H NMR, MS) with teucvin (**12**, lit.[6a,10] mp 205–208 °C; $[\alpha]_D^{28}$ +186.1° (*c* 0.59, $CHCl_3$)). Comparison (mmp, TLC) with an authentic sample[6a] proved the identity of the products.

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Supplementary Material Available: Table II containing ^{13}C NMR spectra (50.3 MHz) of **2–5**, **8**, and **10** (1 page). Ordering information is given on any current masthead page.

The Furan Approach to Oxygenated Natural Products. Total Synthesis of (+)-KDO

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A de novo asymmetric synthesis of the higher monosaccharide 3-deoxy-D-*manno*-2-octulosonic acid, (+)-KDO (**1**), was completed in 12 steps starting from furan and isopropylidene-D-glyceraldehyde. The synthesis commenced with the conversion of furan (**4**) into the protected furfuryl carbinol **5** by the highly stereoselective addition of 2-lithiofuran to isopropylidene-D-glyceraldehyde and subsequent trapping of the intermediate alkoxide. Metalation of **5** followed by alkylation with benzyl chloromethyl ether and hydroxyl deprotection then provided **9** in a single operation. The key transformation of the synthesis entailed sequential oxidative processing of **9** with *t*-BuOOH in the presence of a catalytic amount of $VO(acac)_2$ and O-methylation of the intermediate hemiacetal moiety to furnish the α-methyl glycoside **12** as the major product. Stereoselective 1,2-reduction of **12** using K-Selectride (Aldrich) gave the allylic alcohol **15**, which was elaborated to **20** by electrophile-induced cyclization of the allylic carbamate **19**. Refunctionalization of **20** proceeded in a straightforward fashion by a process involving reductive removal of iodide at C(3) and the benzyl protecting group at C(1) to furnish **23**. Oxidation of the intermediate primary alcohol moiety at C(1) of **23** and deprotection of the remaining hydroxyl functions delivered (+)-KDO (**1**).

Introduction

3-Deoxy-D-*manno*-2-octulosonic acid, (+)-KDO (**1**),[2] is a higher monosaccharide that forms a vital and unique link between the hydrophobic lipid A and the hydrophilic polysaccharide subunits in the outer membrane lipopolysaccharides (LPS) of Gram-negative bacteria.[3] The rate-limiting enzyme for the incorporation of KDO into these LPS is CMP-KDO synthetase (3-deoxy-D-*manno*-octulosonate cytidylyl transferase),[4] and the preparation of analogues of **1** as potential inhibitors of this enzyme emerged as an attractive strategy for the discovery of novel antibiotics.[5] These investigations lead to the development of several effective antibacterial agents derived from 2-deoxy-KDO that specifically inhibit LPS biosynthesis.

The biological importance of (+)-KDO (**1**) has also served as the impetus for a number of efforts directed toward its total synthesis.[6] Inasmuch as (+)-KDO is a higher monosaccharide, it follows that simple carbohydrates, which could provide all of the requisite stereogenic centers present in **1**, would be attractive starting materials. Indeed, with only two exceptions,[6c,l] the common strategic device employed in previous approaches to **1** has involved extension of the carbohydrate backbone of D-mannose or D-arabinose by two or three carbon atoms, respectively. A number of useful chemical and enzymatic methods were developed and implemented to effect this key construction. It was against this backdrop that we were attracted to the challenge of developing a concise and efficient strategy for

(1) Recipient of a National Research Service Award from the National Institutes of Health.

(2) For a review, see: Unger, F. M. *Adv. in Carbohydr. Chem. Biochem.* **1981**, *38*, 323.

(3) For a review of the biosynthesis of LPS, see: Anderson, L., Unger, F. M., Eds. *Bacterial Lipopolysaccharides: Structure, Synthesis, and Biological Activities*; ACS Symposium Series 231; American Chemical Society: Washington, DC, 1983.

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