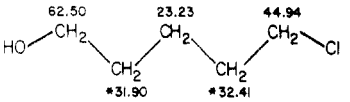
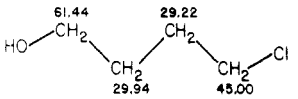
solvent was removed (rotary evaporator) and the aqueous solution was extracted with benzene (4 × 150 mL). The benzene solution was concentrated (rotary evaporator) to afford an oil which was distilled under reduced pressure to give chlorohydrin 14 (36.5 g, 57%), bp 56–57 °C (0.7 torr) [lit.[32] bp 57 °C (0.7 torr)]. The ^{13}C NMR chemical shift assignments in $CDCl_3$ are shown below. (Carbons with the asterisk may be interchangeable.)

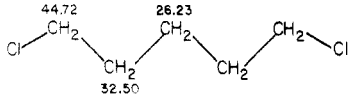


4-Chloro-1-butanol. Tetrahydrofuran (114 g, 1.58 mol) was heated to its boiling point and a slow stream of hydrochloric acid gas was bubbled into the liquid. After 8 h, the internal temperature of the reaction mixture had reached 100 °C and the reaction mixture was allowed to cool. Excess THF was removed (rotary evaporator) and the residue was distilled under reduced pressure to give the chlorohydrin (88 g, 45%): bp 65–76 °C (7 torr) [lit.[33] bp 65–75 °C (7 torr)]; ^1H NMR ($CDCl_3$) δ 1.48–2.02 (m, 4 H, CH_2), 3.20–3.82 (m, 4 H, CH_2Cl and CH_2OH), and 3.90 (s, 1 H, OH). The ^{13}C NMR chemical shift assignments in $CDCl_3$ are shown below.



1,3-Dichloropropane. A mixture of 1,3-propanediol (67 g, 0.88 mol, 63 mL) and concentrated hydrochloric acid (685 mL) was heated at 80 °C for 48 h. The resulting mixture was extracted with toluene (4 × 250 mL) and the resulting organic solution was dried (anhydrous potassium carbonate). Removal of the toluene solvent (rotary evaporator) gave an oily residue which was distilled under reduced pressure to afford 1,3-dichloropropane (9.6 g, 10%): bp 120–121 °C (760 torr) [lit.[34] bp 120.3–120.5 °C (760 torr)]; ^{13}C NMR ($CDCl_3$) δ 35.07 (CH_2), 41.43 (CH_2Cl).

1,5-Dichloropentane. A mixture of 1,5-pentanediol (92 g, 0.89 mol, 93 mL) and concentrated hydrochloric acid (685 mL) was heated at 80 °C for 48 h. The resulting mixture was extracted with toluene (4 × 250 mL) and the resulting organic solution was dried (anhydrous potassium carbonate). Removal of the toluene solvent (rotary evaporator) gave an oily substance which was distilled under reduced pressure to give 1,5-dichloropentane (83.2 g, 59%), bp 66–69 °C (11 torr) [lit.[34] bp 64–66 °C (10 torr)]. The ^{13}C NMR chemical shift assignments in $CDCl_3$ are shown below.



Acknowledgement is made to the National Science Foundation (CHE 78-05921) and Research Corporation for support of this research. We are grateful to Mr. Philip Robinson for preparing 2,5-dihydrofuran. We thank Dr. David L. Harris for recording some of the ^1H and ^{13}C NMR spectra related to this work. Purchase of the Varian Model XL-100-12 NMR spectrometer was made possible by NSF Instrument Grants GU-2059, 2059-Amendment I, and GP-376062 and by NIH Grant 5S05RR07072.

Registry No. 1, 1460-57-7; 2, 6628-80-4; 3, 17002-09-4; 4, 286-20-4; 5, 504-63-2; 7, 110-63-4; 8, 6117-80-2; 9, 15753-50-1; 10, 109-99-9; 11, 1708-29-8; 12, 13149-01-4; 13, 111-29-5; 14, 5259-98-3; 15, 629-11-8; 16, 51097-04-2; 17, 49852-39-3; TPP, 603-35-0; CCl_4, 56-23-5; cyclohexene, 110-83-8; diethyl *cis*-hexahydrophthalate, 17351-07-4; 5-chloro-1-pentylacetate, 20395-28-2; 4-chloro-1-butanol, 928-51-8; 1,3-dichloropropane, 142-28-9; 1,5-dichloropentane, 628-76-2; 6-chlorohexanol, 2009-83-8; 1,6-dichlorohexane, 2163-00-0.

(32) Ames, D. E.; Islip, P. J. *J. Chem. Soc.* **1963**, 4363.
(33) Starr, D.; Hixon, R. M. "Organic Syntheses"; Wiley: New York, 1943; Collect. Vol. 2, p 571.
(34) Huntress, E. H. "Organic Chlorine Compounds"; Wiley: New York, 1948.

New Clerodane Diterpenoid from *Teucrium polium* subsp. *aureum*. X-ray Structure Determination

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Continuing our studies on diterpenic compounds from the *Teucrium* species (family Labiatae),[2,3] we have now investigated *T. polium* subsp. *aureum* (Schreber) Arcangeli collected in Western Sicily (Italy) and in Southern Spain. In the case of the Sicilian sample only previously known diterpenoids (gnaphalidin[4] and teucrin P_1[5,6]) were isolated, whereas from the Spanish sample we have extracted 19-acetylgnaphalin[4] and a new product, auropolin, whose structure was established as follows.

Auropolin (1) was isolated as a syrup, and its ^1H NMR spectrum showed signals for a secondary methyl group at δ 1.19 (d, J = 7 Hz), a β-substituted furan ring (two α-furan protons at δ 7.47 and 7.44 and one β-furan proton at δ 6.45), and two acetates (δ 2.10 and 2.06), one of which was placed on a methylene group attached to a fully substituted carbon atom (a two-proton singlet at δ 4.99) and the other one on a secondary carbon atom probably placed between the furan ring and a methylene group (geminal proton as a doublet of doublets at δ 5.90, J_1 = 7.5, J_2 = 5 Hz). In addition, the ^1H NMR spectrum of auropolin (1) showed a one-proton singlet at δ 5.30, which was assigned to an hemiacetalic function placed on a carbon atom without vicinal protons. The closure of this hemiacetal group was revealed by a one-proton singlet at δ 4.13 ($W_{1/2}$ = 1 Hz) which may be attached to a secondary carbon atom placed between fully substituted carbon atoms or, alternatively, by the fact that its dihedral angle with a vicinal proton gave a J value of ~0 Hz. Finally, two one-proton signals at δ 3.05 (dd, J_{gem} = 5.5 Hz, J(long range) = 1.5 Hz) and 2.33 (d, J_{gem} = 5.5 Hz) were assigned to an α,α-disubstituted oxirane ring.[2]

In accord with all the above assignments, Ac_2O–pyridine treatment of auropolin (1) gave a crystalline derivative (2, $C_{26}H_{32}O_{10}$), the ^1H NMR spectrum of which showed the hemiacetalic proton paramagnetically shifted (δ 6.15). CrO_3–pyridine treatment of the natural substance (1) gave a compound (3, $C_{24}H_{28}O_9$) which possessed a γ-lactone group (ν_{CO} 1785 cm^{-1}) instead of the hemiacetalic function found in 1, since the ^1H NMR spectrum of this derivative (3) lacked the signal assigned to the hemiacetalic proton, and the signal attributed to the closure of the hemiacetal

(1) (a) Instituto "Rocasolano", CSIC. (b) Instituto di Chimica Organica, Università di Palermo. (c) Instituto de Química Orgánica, CSIC.
(2) Fayos, J.; Martínez-Ripoll, M.; Paternostro, M.; Piozzi, F.; Rodríguez, B.; Savona, G. *J. Org. Chem.* **1979**, *44*, 4992.
(3) Savona, G.; Paternostro, M.; Piozzi, F.; Rodríguez, B. *Heterocycles* **1980**, *14*, 193.
(4) Savona, G.; Paternostro, M.; Piozzi, F.; Rodríguez, B. *Tetrahedron Lett.* **1979**, 379.
(5) Popa, D. P.; Tkhuk An', F.; Salei, L. A. *Khim. Prir. Soedin.* **1977**, *13*, 49.
(6) Martínez-Ripoll, M.; Fayos, J.; Rodríguez, B.; García-Alvarez, M. C.; Savona, G.; Piozzi, F.; Paternostro, M.; Hanson, J. R. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1186.

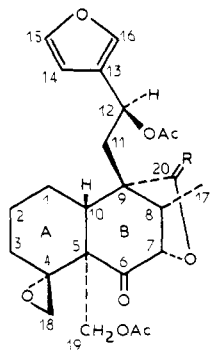
0022-3263/81/1946-3364$01.25/0

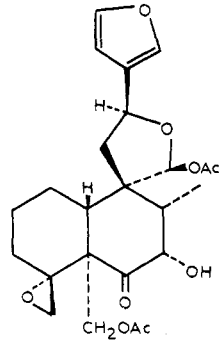
Table I. ^{13}C Chemical Shifts of 2-4[a]

carbon no.	2	3	4[b]
1	21.1 t	21.5 t	22.6 t
2	24.6 t	24.2 t	25.7 t
3	31.4 t[c]	31.6 t[c]	30.4 t
4	62.4 s	62.1 s	60.8 s
5	52.9 s[d]	52.8 s	53.6 s[c]
6	202.6 s	199.4 s	206.7 s
7	91.1 d	87.3 d	74.6 d[d]
8	46.5 d	47.4 d	43.0 d
9	53.2 s[d]	50.4 s	53.2 s[c]
10	51.1 d	50.4 d	51.2 d
11	31.1 t[c]	32.1 t[c]	49.6 t
12	65.6 d	64.9 d	73.2 d[d]
13	125.2 s	124.7 s	127.6 s
14	108.4 d	108.4 d	108.5 d
15	143.7 d	143.8 d	143.4 d
16	139.9 d	140.1 d	139.3 d
17	14.8 q	14.6 q	10.6 q
18	48.8 t	49.5 t	51.9 t
19	62.4 t	61.1 t	62.5 t
20	97.7 d	176.4 s	98.8 d
OCOMe	170.5 s	170.0 s	170.1 s
	169.7 s	169.7 s	169.3 s
	169.2 s		
OCOMe	21.5 q	21.5 q	21.4 q
	21.1 q	20.9 q	20.9 q
	21.1 q		

[a] In parts per million relative to Me_4Si. [b] Taken from ref 2. [c,d] These assignments may be reversed, but those given here are considered to be the most likely.

group in auropolin (1) was now shifted to δ 4.31 and appeared also as a singlet.





1, R = H, OH

2, R = H, OAc

3, R = O

4

In addition the ^{13}C NMR spectra of compounds 2 and 3 (Table I) were in agreement with all the above deductions and also revealed the presence of a keto group in these substances (singlets at 202.6 ppm in 2 and at 199.4 ppm in 3).

All the above data may be accommodated in structures as 1–3 on the basis of the following reasons.

The chemical shifts and coupling constants shown by the C-12 proton in compounds 1 (δ 5.90, J_1 = 7.5, J_2 = 5 Hz), 2 (δ 5.88, J_1 = 7.5, J_2 = 5 Hz), and 3 (δ 5.83, J_1 = 9, J_2 = 3.8 Hz) are almost identical with those observed for C-12 acetoxy derivatives such as plaunol E (δ 5.95, J_1 = 10, J_2 = 2 Hz)[7] but very different from those found in eriocephalin (4; δ 5.20, $J_1 = J_2$ = 8 Hz);[2] thus the C-12 hydroxyl group of auropolin (1) is acetylated and closure of the C-20 hemiacetalic function must be with the C-1 or C-7 atom, as the oxidation of this function gave a γ-lactone (3).

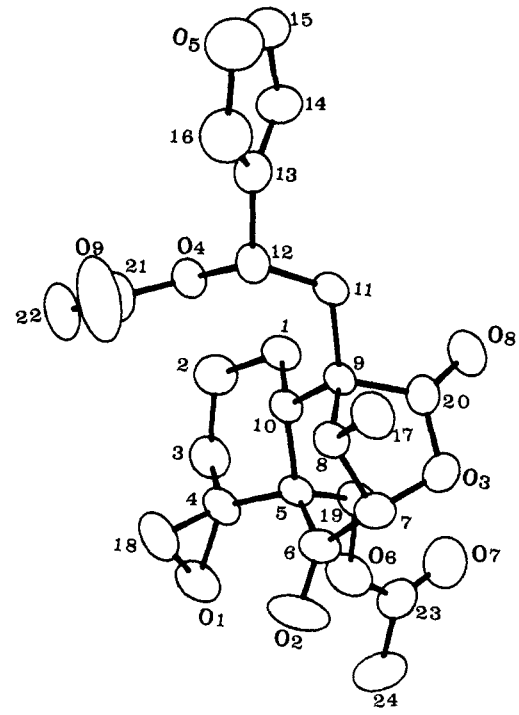


Figure 1. X-ray molecular model of 3.

The ^1H NMR spectra of compounds 1–3 showed a typical pattern for an α,α-disubstituted oxirane ring (see above and Experimental Section) identical with those found in eriocephalin (4)[2] and related diterpenoids,[4] in which the great difference in the chemical shifts of the C-18 protons is due to the presence of a keto group on C-6; thus the keto group of auropolin and its derivatives must also be placed at C-6 and the hemiacetal group in compounds 1 and 2, and the γ-lactone in the derivative 3, must be closed to the C-7 carbon atom. This conclusion was also supported by the ^{13}C NMR spectra of compounds 2 and 3 (Table I), in which the downfield resonance of the C-7 carbon atom (91.1 ppm in 2 and 87.3 ppm in 3) is only compatible with these structures.

As the C-20 → C-7 hemiacetal or γ-lactone groups of these compounds (1–3) must be in a diaxial configuration, the C-17 methyl group must be equatorial, because the C-7 proton signal appeared in the ^1H NMR spectra as a clear singlet ($J \simeq 0$ Hz), which requires that the 7β equatorial proton–8β axial proton dihedral angle be close to 90°. An identical behavior between the same protons has been found in the diterpenoid isodiasin.[8]

Finally, the presence in auropolin (1) and its derivatives (2 and 3) of an acetylated hydroxy methylene group attached to the C-5 position of an A/B ring *trans*-clerodane skeleton was established by comparing the ^1H and ^{13}C NMR data of these compounds with those of eriocephalin (4).[2] The small differences observed in the δ_C of some of the carbon atoms (C-1, C-2, C-3, C-4, C-5, C-6, C-8, C-17, and C-18) of compounds 2 and 4 (see Table I) are due to the fact that in eriocephalin (4) ring B presents a distorted boat conformation,[2] whereas in compound 3 (and very probably in 1 and 2) ring B shows a deformed chair conformation (see below). This conformational difference was also revealed by the Cotton effects of 2 ($\Delta\epsilon_{316}$ = +0.80) and

(7) Kitazawa, E.; Sato, A.; Takahashi, S.; Kuwano, H.; Ogiso, A. *Chem. Pharm. Bull. (Tokyo)* **1980**, *28*, 227.

(8) Alvarenga, M. A. de; Gottlieb, H. E.; Gottlieb, O. R.; Magalhaes, M. T.; Da Silva, V. O. *Phytochemistry* **1978**, *17*, 1773.

eriocephalin (4, $\Delta\epsilon_{294}$ = +2.53).[2]

As the absolute configuration of clerodin-like diterpenoids has been recently reversed,[9] a single-crystal X-ray determination was undertaken in order to establish the structure and absolute configuration of the derivative 3, and thus of auropolin (1), except for its C-20 center. Figure 1 shows the absolute configuration of the final X-ray model of the derivative 3, confirming all the above assignments.

The six-membered rings A and B are deformed chair conformations, the A/B junction being e-e trans. The sum of the ring torsional angles around the junction is 101.3°; this is a very small value compared with that of 113.1°[10] found for some e-e trans-decalins with the same degree of substitution at the bridgehead atoms. This could be due to bulky α-axial substituents in ring B. The conformations of rings A and B are described by Cremer's[11] parameters, θ, ϕ and Q, where θ = 0° for the chair conformation and θ = 90° for the boat-skew conformation, ϕ is the pseudorotation angle, and Q is the total puckering amplitude. The θ, ϕ, and Q values found in 3 are 17.6°, 258.6°, and 0.62 Å for ring A, and 29.6°, 173.7°, and 0.67 Å for ring B. The intraannular lactonic bridge between C-20 and C-7 forces ring B to adopt a very deformed chair conformation, transmitting some deformation to ring A. The significant axial interactions in rings A and B are as follows: H-19(2)–C-20 = 2.59 Å, H-19(2)–O-3 = 2.42 Å, H-19(1)–H-3(axial) = 2.25 Å; H-8–H-10 = 2.29 Å, H-10–H-2(axial) = 2.71 Å.

The lactone ring has an envelope conformation, C-8 being at the flap, 0.683 Å out of the plane. The C-12 stereochemistry is *S*, as in all the diterpenoids from *Teucrium* species.[12] Both acetyl groups show the usual CHOC=O cis conformation. All bond distances and angles are of the usual magnitudes. There are no intermolecular contacts among nonhydrogen atoms less than 3.2 Å. (For details on the X-ray structure determination see Experimental Section.)

The H-7–H-8 dihedral angle in 3 is 77.1(4)°, for which the Karplus equation in its original form[13] gave a *J* value of approximately 0 Hz, in complete agreement with all the above ^{1}H NMR observations.

Therefore, in accordance with the terminology suggested by Rogers et al.,[9,14] auropolin (1) has the absolute configuration of neoclerodane. It and the two diterpenoids isolated from *Teucrium fruticans*[15] are the only neoclerodane diterpenoids from *Teucrium* species lacking the usual C-20 → C-12 hemiacetalic or lactonic bridge.

Experimental Section

Melting points were determined in a Kofler apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 141 polarimeter with a 1-dm cell. Elemental analyses were carried out in Madrid[1c] with the help of a Perkin-Elmer 240 analyzer. IR spectra were determined on a Perkin-Elmer 257 spectrometer. ^{1}H and ^{13}C NMR spectra were measured at 90 or 360, and 25.2 MHz, respectively, in $CDCl_3$ solutions with Me_4Si as internal standard. Assignments of ^{13}C chemical shifts were made with the aid of off-resonance and noise-decoupled ^{13}C NMR spectra. Mass spectra were obtained on a JEOL MS-01SG-2 instrument.

Isolation of Auropolin (1). Dried and finely powdered *T. polium* subsp. *aureum* aerial parts (1.2 kg), collected at Sierra de Cázulas (Granada, Spain), were extracted with acetone (10 L) at room temperature for 1 week. Filtration and evaporation of the solvent yielded a gum (23 g) which was subjected to dry-column chromatography over silica gel (500 g, Merck No. 7734, deactivated with 15% water). Elution with petroleum ether–EtOAc (1:1) gave a mixture (1.2 g) of two compounds. This mixture was subjected to further column chromatography on silica gel, yielding impure auropolin (1, an oil, 170 mg) and 19-acetylgnaphalin[4] (800 mg).

Aerial parts of *T. polium* subsp. *aureum* (1.1 kg), collected in Western Sicily (Italy), were treated as above, yielding gnaphalidin[4] (130 mg) and teucrin P_1[5,6] (700 mg).

The previously known compounds were identified by conventional methods and by comparison with pure specimens.

For the ^{1}H NMR spectrum of auropolin (1, 90 MHz) see the text.

Compound 2. A solution of 70 mg of crude auropolin in 2 mL of pyridine and 0.5 mL of acetic anhydride was allowed to stand overnight at room temperature. The reaction mixture was poured into ice–water and extracted with EtOAc. The EtOAc layer was washed with water, dried, and evaporated. The crude product was purified by column chromatography on silica gel. Elution with petroleum ether–EtOAc (2:3) gave 45 mg of 2: mp 186 °C (from EtOAc–*n*-hexane); $[\alpha]^{19}_D$ +63.6° (*c* 0.225, $CHCl_3$); IR (Nujol) 3145, 3120, 1735, 1505, 1265, 1250, 1235, 1160, 1045, 1025, 1005, 985, 875, 820 cm^{-1}; CD (EtOH, *c* 0.88) $\Delta\epsilon_{352}$ = 0, $\Delta\epsilon_{316}$ = +0.80, $\Delta\epsilon_{257}$ = 0; ^{1}H NMR (90 MHz) δ 7.45 (2 H, m, $W_{1/2}$ = 5 Hz, H-15 and H-16), 6.46 (1 H, m, $W_{1/2}$ = 4 Hz, H-14), 6.15 (1 H, s, H-20), 5.88 (1 H, dd, J_1 = 7.5, J_2 = 5 Hz, H-12), 5.26 and 4.86 (AB system, *J* = 12 Hz, 2H-19), 4.18 (1 H, s, $J_{7,8} \simeq$ 0 Hz, H-7), 3.05 (1 H, dd, J_{gem} = 5.5 Hz, *J*(long range) = 1.5 Hz, H-18), 2.35 (1 H, d, J_{gem} = 5.5 Hz, H′-18), 2.11 (6 H,s, 2 OAc), 2.05 (3 H, s, OAc), 1.16 (3 H, d, *J* = 7 Hz, 3H-17); ^{13}C NMR, see Table I; mass spectrum (75 eV, direct inlet), *m/z* (relative intensity) 504 (M^+, 1), 444 (4), 431 (26), 403 (2), 402 (2), 387 (2), 384 (2), 371 (3), 354 (2), 343 (3), 311 (6), 307 (4), 283 (11), 266 (8), 238 (6), 233 (10), 218 (20), 203 (20), 191 (32), 190 (34), 175 (50), 173 (43), 163 (26), 149 (34), 145 (22), 137 (28), 121 (20), 105 (22), 97 (40), 95 (41), 91 (38), 81 (48), 79 (30), 77 (28), 69 (24), 55 (28), 43 (100, base peak). Anal. Calcd for $C_{26}H_{32}O_{10}$: C, 61.89; H, 6.39. Found: C, 62.01; H, 6.48.

Compound 3. Auropolin (1, 80 mg) was added to a solution of CrO_3 (100 mg) in pyridine (5 mL) and the mixture was stirred overnight at room temperature. Dilution with water and extraction with Et_2O yielded crude 3, which was purified by silica gel column chromatography, eluting with petroleum ether–EtOAc (1:1) to yield 50 mg of pure 3: mp 198–200 °C (EtOAc–*n*-hexane); $[\alpha]^{19}_D$ +38.4° (*c* 0.185, $CHCl_3$); IR (KBr) 3140, 3110, 2995, 2950, 2895, 2865, 1785, 1735, 1505, 1445, 1375, 1260, 1230, 1160, 1090, 1045, 1020, 990, 880, 820 cm^{-1}; ^{1}H NMR (360 MHz) δ 7.46 (1 H, m, $W_{1/2}$ = 3 Hz, H-15 or H-16), 7.42 (1 H, m, $W_{1/2}$ = 4 Hz, H-16 or H-15), 6.43 (1 H, m, $W_{1/2}$ = 3.5 Hz, H-14), 5.83 (1 H, dd, part X of an ABX system, J_{XB} = 9, J_{XA} = 3.75 Hz, H-12), 5.08 and 4.54 (AB system, *J* = 12.5 Hz, 2H-19), 4.31 (1 H, s, $W_{1/2}$ = 1 Hz, $J_{7,8} \simeq$ 0 Hz, H-7), 3.26 (1 H, dd, J_{gem} = 5.5, *J*(long range) = 2 Hz, H-18), 2.74 (1 H, dd, B part of ABX system, $J_{BA(gem)}$ = 16.5, J_{BX} = 9 Hz, H-11), 2.42 (1 H, d, J_{gem} = 5.5 Hz, H′-18), 2.39 (1 H, q, *J* = 7 Hz, H-8), 2.10 (1 H, dd, $J_{ae'}$ = 12, $J_{ae'}$ = 2 Hz, H-10), 2.07 and 2.06 (3 H each, 2 s, 2 OAc), 1.94 (1 H, dd, A part of ABX system, J_{AB} = 16.5, J_{AX} = 3.75 Hz, H′-11), 1.10 (3 H, d, *J* = 7 Hz, 3H-17); ^{13}C NMR, see Table I; mass spectrum (75 eV, direct inlet), *m/z* (relative intensity) 460 (M^+, 1), 417 (3), 387 (1.2), 329 (3), 303 (19), 299 (2), 271 (6), 259 (3), 243 (5), 239 (4), 215 (51), 211 (7), 183 (10), 159 (30), 155 (39), 133 (85), 131 (78), 127 (100, base peak), 97 (19), 95 (18), 85 (22), 81 (31), 75 (86), 71 (24), 59 (68), 53 (35), 43 (20). Anal. Calcd for $C_{24}H_{28}O_9$: C, 62.60; H, 6.13. Found: C, 62.51; H, 6.26.

X-ray Structure Determination of 3. $C_{24}H_{28}O_9$ crystalizes in the space group $P2_12_12_1$ and *Z* = 4 with *a* = 28.403 (2), *b* = 9.1958 (3), and *c* = 8.7671 (3) Å. The molecular weight is 460.48 and the calculated density is 1.336 g·cm^{-3}. A single crystal of 0.14 × 0.11 × 0.16 mm was used to measure the intensities of 2223

(9) Rogers, D.; Unal, G. G.; Williams, D. J.; Ley, S. V.; Sim, G. A.; Joshi, B. S.; Ravindranath, K. R. *J. Chem. Soc., Chem. Commun.* **1979**, 97.
(10) Geise, H. J.; Altona, C.; Romers, G. *Tetrahedron* **1966**, *23*, 439.
(11) Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1354.
(12) Piozzi, F. *Heterocycles* **1981**, *15*, 1489.
(13) Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870.
(14) There is a risk of confusion in this new nomenclature,[9] since the neoclerodanes are related biogenetically to *ent*-labdanes in which C-20 is an α-substituent, while the *ent*-neoclerodanes are related biogenetically to the *normal* labdanes in which C-20 is a β-substituent.
(15) Savona, G.; Passannanti, S.; Paternostro, M.; Piozzi, F.; Hanson, J. R.; Hitchcock, P. B.; Sieverns, M. *J. Chem. Soc., Perkin Trans. 1* **1978**, 356.

independent Friedel pairs, alternately collected in the range $2° < \theta < 65°$ on a computer-controlled four-circle diffractometer. Some experimental details are the following: $\omega/2\theta$ scan mode; 1.40° scan width; 0.035° sg^{-1} scan speed with the same measurement time for both backgrounds as for the peak. Graphite-monochromated Cu Kα radiation (1.5418 Å) was used. No crystal decomposition was observed during the data collection process. After the usual correction for Lorentz and polarization effects, 1742 Friedel pairs were considered as observed according to the criterion $I > 2\sigma(I)$ and were used in the least-squares refinement.[16] No absorption correction was applied. The atomic scattering factors and the anomalous dispersion corrections were taken from the literature.[17] The structure was solved by direct methods.[18] The hydrogen atoms were placed at their expected positions, but they were checked in a Fourier difference map and included as fixed contributors in the refinement. For the last refinement Δ^2F was weighted with $w = w_1w_2$, where $w_1 = 1/(a + b|F_o|)^2$ and $w_2 = 1/(c + d(\sin\theta)/\lambda)$ with coefficients calculated in order to prevent bias in $w\Delta^2F$ vs. $|F_o|$ and $|(\sin\theta)/\lambda|$.[19] Several cycles of weighted anisotropic refinement including both hkl and $\bar{h}\bar{k}\bar{l}$ gave for the right enantiomer the following unweighted and weighted discrepancy indices: $R = 0.056$ and $R_w = 0.064$. The absolute configuration was confirmed by comparing the 72 more relevant Bijvoet pairs, giving the following discrepancy indices:[20] average Bijvoet difference $R_1 = \sum||F_o(+h) - F_o(-h)] - [F_c(+h) - F_c(-h)||/N = 0.603$ (0.666 for the reversal enantiomorph), average Bijvoet ratio $R_2 = \sum|R_o - R_c|/N = 0.072$ (0.076), and $R_3 = \sum|\Delta I_o - \Delta I_c|/\sum|\Delta I_o| = 0.901$ (1.113 for the reversal enantiomorph), with $N = 72$, $R_o = \Delta I_o/\langle F^2_o\rangle$, $R_c = \Delta I_c/\langle F^2_o\rangle$, $\Delta I_o = F^2_o(+h) - F^2_o(-h)$, and $\Delta I_c = F^2_c(+h) - F^2_c(-h)$.

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Supplementary Material Available: A list of bond distances, bond angles, deviations of atoms from the ring planes, and torsion angles (6 pages). Ordering information is given on any current masthead page.

(16) Stewart, J. M.; Kundell, F. A.; Baldwin, J. C. "The X-Ray 70 System"; Computer Science Center, University of Maryland; College Park, MD, 1970.
(17) "International Tables for X-Ray Crystallography"; Kynoch Press: Birmingham, 1974; Vol. IV.
(18) Main, P.; Lessinger, L.; Woolfson, M. M.; Germain, G.; Declercq, J. P. "MULTAN"; Physics Department, University of York: England, 1977.
(19) Martínez-Ripoll, M.; Cano, F. H. "PESOS"; Instituto "Rocasolano", CSIC: Serrano 119, Madrid-6, Spain, 1975.
(20) Martínez-Ripoll, M.; Fayos, J. "CONFAB"; Instituto "Rocasolano", CSIC: Serrano 119, Madrid-6, Spain, 1977.

Reduction of Aldehydes and Ketones Using Sodium Formate in 1-Methyl-2-pyrrolidinone

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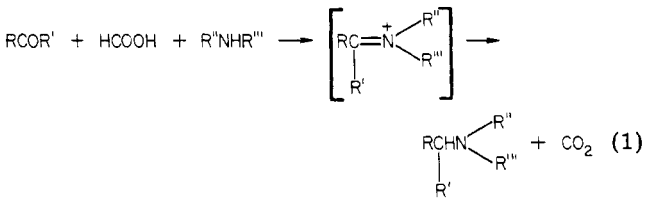
Recently Heck and co-workers have reported[1] the reduction of alkynes, aromatic halides, conjugated dienes, and several other types of functionalized organic compounds using triethylammonium formate in the presence of a palladium catalyst. Prior to initiation of their studies, it was well-known that ammonium formate by itself was capable of reducing iminium salts to amines (the Leuckart reaction[2]). Subsequently Wallach[3] demonstrated that better results could be obtained in the latter reaction by using a mixture of ammonia or a substituted amine with formic acid (eq 1).



(1)

Although there is a legion of methods available for effecting the reduction of a carbonyl moiety to the corresponding alcohol,[4] formic acid (or formate salts) has not been utilized for this transformation. In a study involving the preparation of tertiary *N,N*-dimethylamines by the Leuckart reaction, Bach reported[5] that treatment of cyclooctanone with formic acid and *N,N*-dimethylformamide in an autoclave at 190 °C afforded, in addition to the expected tertiary amine, cyclooctanol as a byproduct in 10% yield. Intrigued by this report, we decided to investigate the potential use of formic acid in the reduction of aldehydes and ketones.

Results of our initial experiments using 4-phenyl-2-butanone as a representative substrate were discouraging. Treatment of this ketone with formic acid (2 molar equiv) in 1-methyl-2-pyrrolidinone at reflux afforded only a trace (<3%) of any reduction product after 18 h. In order to enhance the ability of formic acid to function as a hydride donor, triethylammonium formate was prepared[6] in situ by addition of a molar excess of triethylamine to the same reaction mixture. However, after 20 h at reflux, isolation of the reaction product and subsequent NMR and VPC analysis showed the presence of only 4% 4-phenyl-2-butanol, the rest of the material being starting ketone.

In view of the above results, we were pleasantly surprised by the fact that treatment of 4-phenyl-2-butanone with sodium formate (2.5 molar equiv) in 1-methyl-2-pyrrolidinone[7] containing 1 molar equiv of potassium phosphate monobasic as a buffer[8] afforded, after 20 h at reflux, 4-phenyl-2-butanol in 40% yield, contaminated only by the starting ketone. A similar experiment conducted

(1) Weir, J. R.; Patel, B. A.; Heck, R. F. *J. Org. Chem.* **1980**, *45*, 4926 and references therein.
(2) Leuckart, R. *Chem. Ber.* **1885**, *18*, 2341. Leuckart, R.; Bach, E. *Ibid.* **1886**, *19*, 2128. For a review of the Leuckart reaction, see: Moore, M. L. *Org. React.* **1949**, *5*, 301.
(3) Wallach, O. *Justus Liebigs Ann. Chem.* **1905**, *343*, 54.
(4) March, J. "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure", 2nd ed.; McGraw-Hill: New York, 1977; pp 829-834.
(5) Bach, R. D. *J. Org. Chem.* **1968**, *33*, 1647.
(6) This experiment was run by refluxing a mixture of 3 mmol of 4-phenyl-2-butanone, 0.25 mL (6.64 mmol) of 98% formic acid, 1.2 mL (8.6 mmol) of triethylamine, and 4 mL of 1-methyl-2-pyrrolidinone for 20 h.
(7) Although use of other dipolar aprotic solvents that enhance the nucleophilicity of formate anion might be possible for this reaction, a mixture of 3:1 (v/v) *N,N*-dimethylformamide–hexamethylphosphoramide was clearly inferior and led (especially for the less easily reduced ketones) to a substantial amount of amine byproduct. Presumably a transformation similar to that reported by Bach[5] had occurred in the reaction mixture.
(8) No systematic study of the advantage of this or other buffers was attempted. However, replacement of monobasic potassium phosphate by an equivalent amount of boric acid led to poorer results (as evidenced by a significant increase in the formation of unidentified byproducts) in an experiment involving reduction of *p*-tolualdehyde.

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