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A FACILE ROUTE TO IODOHYDRINS AND EPOXIDES BY OXIDATION OF OLEFIN-IODINE COMPLEXES WITH PYRIDINIUM DICHROMATE

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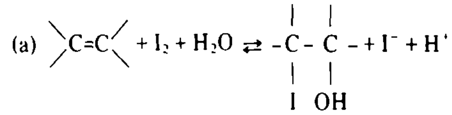
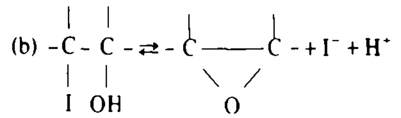
Abstract—Trisubstituted olefins, activated with I_2, are changed into iodohydrins and epoxides by pyridinium dichromate. The conversion shows to proceed in regiospecific and stereospecific manner. Moreover some naturally occurring polyenes, submitted to similar treatment, afford selectively only terminal iodohydrins. These latter are converted into the corresponding epoxides through a new and convenient alumina supported reaction.

Although the preparation of bromohydrins and chlorohydrins from reaction of dilute *aqueous* solutions of halogens with alkenes is a well-known preparative and industrial process, the formation of iodohydrins, under the same conditions, is preparatively unsatisfactory because of the reversibility of the reactions (a) and (b).

(a) 

$$>C=C< + I_2 + H_2O \rightleftarrows -\underset{I}{\underset{|}{\overset{|}{C}}}-\underset{OH}{\underset{|}{\overset{|}{C}}}- + I^- + H^+$$

(b) 

$$-\underset{I}{\underset{|}{\overset{|}{C}}}-\underset{OH}{\underset{|}{\overset{|}{C}}}- \rightleftarrows -\underset{\diagdown\ O\ \diagup}{\overset{|}{C}—\overset{|}{C}}- + I^- + H^+$$

On the contrary, this procedure represents a useful route both to iodohydrins and epoxides if the iodination is carried out in presence of reagents operating as scavengers of iodide ions, such as mercuric oxide, silver oxide or salts, oxidizing agents (iodic acid or oxygen and sodium nitrite).[1]

In the course of recent investigations on the reactivity of pyridinium dichromate (PDC), a reagent originally introduced for the oxidation of alcohols to carbonyl compounds,[2] we have pointed out its nucleophilic properties towards some unsaturated systems, activated with iodine.[3,4]

Now, we wish to report the easy conversion of trisubstituted olefins into iodohydrins and epoxides through a new original *dry* procedure, involving the exploitation of PDC both as nucleophilic and iodide removing agent.

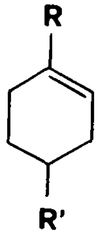
Usually, equimolar amounts of the starting materials and iodine, in anhydrous CH_2Cl_2, were reacted with an excess of PDC. This treatment turned rapidly (~3hr) the conformationally mobile olefins **1a–c** into the *trans*-iodohydrins **2a–c**, whose stereochemistry was assigned on the ground of ^{1}H-NMR data (Experimental). The different conformations assumed by **2a–b** (*trans*-diequatorial) and **2c** (*trans*-diaxial) could be attributed to the greater preference of the phenyl group for the equatorial position than do alkyl groups.[5]

More prolonged reaction times (~16 hr) led to epoxides **3a–b** in good yields, while **3c**, whose formation was clearly monitored by comparison with an authentic sample on TLC, could not be isolated because of its instability under the usual reaction conditions.

When the conformationally rigid olefins **1d–e** and **4** were submitted to the reaction with iodine and PDC, the isolation of appreciable amounts of iodohydrins was generally prevented from their fast conversion into the epoxides **3d–e** and **5**.

Iodohydrin **2e** could be isolated only in rather low yield (10%) and it showed a *trans*-diaxial relationship between -OH and -I groups. Furthermore, the stereochemistry of the oxirane ring in **3d–e** and **5** was unambigously assigned on the ground of physical and spectroscopic data; for ex., **5**: m.p. 132–34° (reported 132–33°).[6] ^{1}H-NMR (CCl_4, δ): 2.81 (d, 1H, 2-$\underline{H}$; J = 6 Hz).

The above reported results pointed out that the con-



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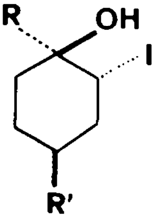

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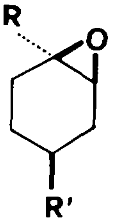
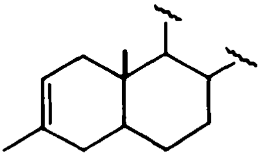


3

a:	R'= H	R= C_5H_{11}
b:	R'= H	R= $C_{10}H_{21}$
c:	R'= H	R= Ph
d:	R'= t–Bu	R= C_9H_{19}
e:	R'= t–Bu	R= Ph



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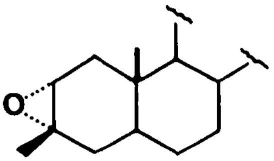

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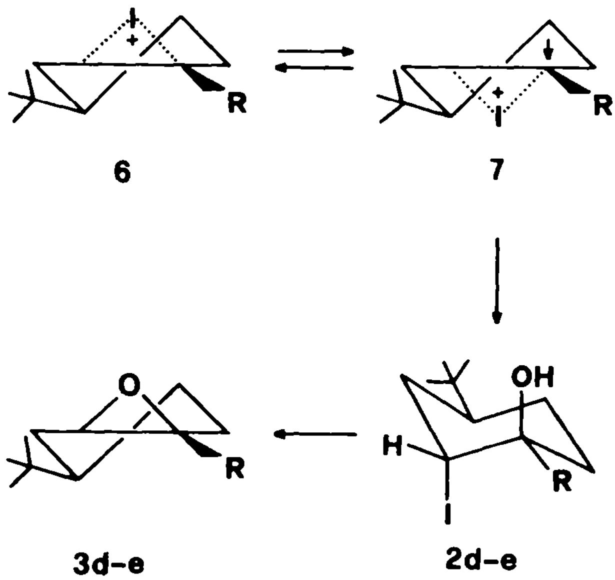


Scheme 1.

version both to iodohydrins and epoxides occurred in regiospecific and stereospecific manner. The regiospecificity could be easily explained assuming, in the first step of the process, the formation of an iodonium ion, which underwent the preferential nucleophilic attack of dichromate anion on the tertiary C atom rather than on the secondary one.

In the case of rigid olefins (as summarized in Scheme 1), the existence of an equilibrium between two iodonium ions, of type **6** and **7**, could not be excluded; however, only the antiperiplanar opening of the 3-membered ring, caused by the *axial* attack of the dichromate anion on the tertiary C atom, could lead to the *trans*-diaxial iodohydrin **2e**.

Furthermore, just because of the extremely favourable steric disposition of I and OH groups, **2d–e** changed so rapidly into the epoxides **3d–e**, that their isolation could not be generally achieved in efficient manner.

The application of this methodology to the linear olefins **8** and **9** emphasized the regiospecific behaviour of PDC again, although some differences of reactivity could be observed.

In fact, α-iodoketone **10** was isolated in rather low yield (25%), as only identifiable product, while most of the starting material (55%) was recovered unchanged. Furthermore, the expected conversion of iodohydrin **11** (isolated in 65% yield) into epoxide **12** took place in unsatisfactory way also after very prolonged reaction times. On the contrary, we have found that the same conversion could be achieved through a new and efficient synthetic procedure, involving an alumina supported process. In fact, the simple adsorption of **11** on neutral Al_2O_3 afforded rapidly **12** in appreciable yield (70%).

At last, we examined the reactivity of PDC/I_2 system towards some naturally occurring polyenes, like **13**, **14**, **15** and **16**.

It must be noted that different procedures had to be introduced in order to limit as much as possible iodine induced processes of intramolecular cyclisation.[7]

In all cases we observed a selective attack on the

Table 1.

Compound	Product	Reaction time (hr)	Yield (%)^a
13 (E,Z)-geranyl-acetate	17 6,7-epoxide	20	65
14 (±)-linalyl-THP	18 6,7-epoxide	20	48^b
15 farnesyl-acetate^c	19 10,11-epoxide	20	46^b
16 (±)-*cis*-nerolidyl-THP	20 10,11-epoxide	20	30^b

a) All yields refer to isolated, chromatographically pure products and are based upon the starting polyenes 13–16.

b) About 10–15% of 14 and 15, and about 30% of 16 were recovered.

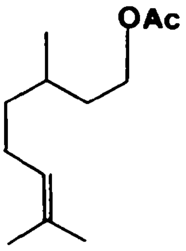
c) This was obtained from Fluka AG, as a mixture of 65% (E,E)- and 35% (Z,E)-isomers.

$C_8H_{17}CH{=}CH_2$

8

$C_8H_{17}COCH_2I$

10



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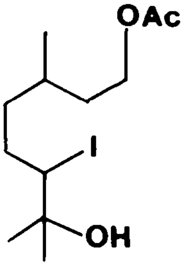
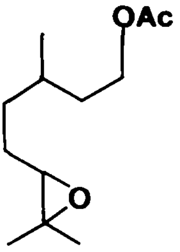


11



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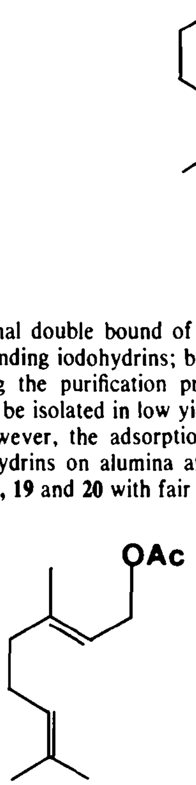
terminal double bound of polyenes, leading to the corresponding iodohydrins; but, because of their instability during the purification procedure, only iodohydrin **21** could be isolated in low yield (37%).

However, the adsorption of the crude, just isolated iodohydrins on alumina afforded the terminal epoxides **17, 18, 19** and **20** with fair yields.



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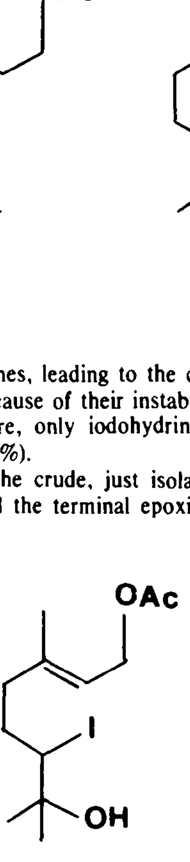

21

In conclusion, while the other available routes are only partially successful[8] or lead to mixtures of different epoxides,[9] on the contrary, PDC/I_2 treatment, combined with the alumina supported process, allows an efficient and completely selective epoxidation at all the polyenes **13, 14, 15** and **16**.

EXPERIMENTAL

^{1}H-NMR spectra were recorded on a Varian EM-360 spectrometer, usually in CCl_4 soln, and shifts are reported in ppm (δ) relative to Me_4S. IR spectra were recorded on a Perkin-Elmer 257 spectrometer, in 1% CCl_4 solution, and are given in cm^{-1}. Mass spectral data were obtained with an AEI-MS 12 spectrometer (70 eV). M.ps were determined on a Kofler block and are uncorrected.

Procedure A (for olefins **1a–e, 4, 8** and **9**). I_2 (1.5 mmol) and 4Å molecular sieves (1g) were added to a well stirred soln of olefin (1.5 mmol) in dry CH_2Cl_2 (30 ml) at room temp under N_2. After 30 min, PDC (3.7 mmol) was added and the mixture stirred for several hr. The best yields in iodohydrins and epoxides were obtained respectively after 3 and 16 hr. The crude products, isolated after the usual work-up,[2] were purified by column chromatography on silica gel eluting with n-hexane/diethyl ether mixtures.

Procedure B (for polyenes **13** and **14**). I_2 (1.5 mmol), PDC (3.7 mmol), 4Å molecular sieves (1g) in dry CH_2Cl_2 (30 ml) were stirred for 30 min under N_2 at room temp. Then the starting material (1.5 mmol) in CH_2Cl_2 (5 ml) was rapidly added. The mixture was stirred for 20 hr.

Procedure C (for polyenes **15** and **16**). I_2 (1.5 mmol) was slowly added under stirring to a mixture of PDC (3.7 mmol), polyene (1.5 mmol), 4Å molecular sieves (1g) in dry CH_2Cl_2 (30 ml). The reaction was prolonged for 20 hr.

The crude products coming both from procedures B and C were submitted directly to chromatography on Al_2O_3 B III. The elution with n-hexane/diethyl ether yielded to pure epoxides **17, 18, 19** and **20**.

1-*n-Pentyl*-trans-2-*iodo-cyclohexane*-1-*ol*. Compound **2a**, $C_{11}H_{21}IO$, oil, yield 48%. IR: 3570, 3520, 1455, 1380, 1332, 1180, 940. ^{1}H-NMR: 4.30 (dd, 1 H, C$\underline{H}$-I; $J_1 = 8$ Hz, $J_2 = 4$ Hz; $W_{1/2} = 14$ Hz), 1.50 (s, 1 H, -O$\underline{H}$; the signal disappeared after shaking with D_2O). Mass spectrum, *m/e* 296 (M^+).

1-*n-Decyl*-trans-2-*iodo-cyclohexane*-1-*ol*. Compound **2b**, $C_{16}H_{31}IO$, oil, yield 52%. IR: 3575, 3525, 1461, 1385, 1355, 1335, 1195, 955. ^{1}H-NMR: 4.47 (dd, 1 H, C$\underline{H}$-I; $J_1 = 9$ Hz, $J_2 = 4$ Hz; $W_{1/2} = 16$ Hz), 1.51 (s, 1 H, -O$\underline{H}$; the signal disappeared after shaking with D_2O). Mass spectrum, *m/e* 366 (M^+).

1-*Phenyl*-trans-2-*iodo-cyclohexane*-1-*ol*. Compound **2c**, $C_{12}H_{15}IO$, oil, yield 60%. IR: 3560, 3520, 1440, 1160, 960, 700. ^{1}H-NMR: 7.20 (m, 5 H, aromatic protons), 4.54 (m, 1 H, C$\underline{H}$-I; $W_{1/2} = 6$ Hz), 1.78 (s, 1 H, -O$\underline{H}$; the signal disappeared after shaking with D_2O). Mass spectrum, *m/e* 302 (M^+).

trans-2-*Iodo*-1-*phenyl*-cis-4-*t-butylcyclohexane*-1-*ol*. Compound **2e**, $C_{16}H_{23}IO$, oil, yield 10%. IR: 3570, 3520, 1445, 1158, 980. ^{1}H-NMR: 7.22 (m, 5 H, aromatic protons), 4.60 (m, 1 H, C$\underline{H}$-I; $W_{1/2} = 7$ Hz), 1.65 (m, 1 H, -O$\underline{H}$; the signal disappeared after shaking with D_2O). Mass spectrum, *m/e* 358 (M^+).

1-*n-Pentyl*-1, 2-*epoxycyclohexane*. Compound **3a**, $C_{11}H_{20}O$, oil, yield 50%. IR: 2910, 2840, 1465, 1385, 865. ^{1}H-NMR: 2.75 (m, 1 H, 2-$\underline{H}$). Mass spectrum, *m/e* 168 (M^+). (Found: C 78.40; H 12.09. Calc for $C_{11}H_{20}O$: C 78.51; H 11.98%.)

1-*n-Decyl*-1, 2-*epoxycyclohexane*. Compound **3b**, $C_{16}H_{30}O$, oil, yield 50%. IR: 2903, 2838, 1465, 1382, 1125. ^{1}H-NMR: 2.86 (m, 1 H, 2-$\underline{H}$). Mass spectrum, *m/e* 238 (M^+). (Found: C 80.80; H 12.75. Calc for $C_{16}H_{30}O$: C 80.61; H 12.68%.)

1-*n-Nonyl*-cis-4-*t-butyl*-1, 2-*epoxycyclohexane*. Compound **3d**, $C_{19}H_{36}O$, very dense oil, yield 86%. IR: 2900, 2835, 1470, 1435, 1397, 1370. ^{1}H-NMR: 2.85 (d, 1 H, 2-$\underline{H}$; J = 6 Hz), 0.85 (s, 9 H, -C-(C$\underline{H}_3$)$_3$). Mass spectrum, *m/e* 280 (M^+). (Found C 81.50; H 13.03. Calc for $C_{19}H_{36}O$: C 81.36; H 12.94%.)

1-*Phenyl*-cis-4-*t-butyl*-1,2-*epoxycyclohexane*. Compound **3e**, $C_{16}H_{22}O$, blades from EtOH, m.p. 67–69° (reported 67–68°)[10], yield 51%. IR: 3040, 3008, 1455, 1370, 1260, 700. ^{1}H-NMR: 2.93 (d, 1 H, 2-$\underline{H}$; J = 6 Hz), 0.90 (s, 9 H, -C-(C$\underline{H}_3$)$_3$). Mass spectrum, *m/e* 230 (M^+). (Found C 83.61; H 9.55. Calc for $C_{16}H_{22}O$: C 83.43; H 9.63%.)

3β-Methyl-2α,3α-epoxycholestane. Compound **5**, $C_{28}H_{48}O$, needles from EtOH, m.p. 132–34°; yield 60%. IR: 2910, 2850, 1471, 1452, 1385, ^{1}H-NMR: (Introduction). Mass spectrum, *m/e* 400 (M$^+$). (Found C 84.02; H 12.21. Calc for $C_{28}H_{48}O$: C 83.93; H 12.07%.)

1-Iodo-decan-2-one. Compound **10**, $C_{10}H_{19}IO$, oil, yield 25%. IR: 1710. ^{1}H-NMR: 3.68 (s, 2 H, $-C\underline{H}_2I$), 2.62 (t, 2 H, $-C\underline{H}_2-\overset{|}{C}O$). Mass spectrum, *m/e* 282 (M$^+$).

6-Iodo-7-hydroxy-3,7-dimethyl-octan-1-ol acetate. Compound **11**, $C_{12}H_{23}IO$, oil, yield 65%. IR: 3460, 1734, 1460, 1385, 1369, 1240. ^{1}H-NMR: 4.10 (m, 3 H, overlapping of $-\overset{|}{C}\underline{H}-I$ and $-C\underline{H}_2-OAc$), 2.13 (s, 1 H, $-O\underline{H}$; it disappeared after shaking with D_2O). 2.00 (s, 3 H, $-O\overset{|}{C}OC\underline{H}_3$) 1.35 (s, 6 H, $-\overset{|}{C}(C\underline{H}_3)_2$). Mass spectrum, *m/e* 342 (M$^+$).

6,7-Epoxy-3,7-dimethyl-octan-1-ol acetate Compound **12**, $C_{12}H_{22}O_3$, oil, yield 70%. IR: 1732, 1460, 1380, 1369, 1240. ^{1}H-NMR: 4.11 (t, 2 H, $-C\underline{H}_2OAc$; J = 7 Hz), 2.50 (m, 1 H, epoxydic proton), 2.00 (s, 3 H, $-OCOC\underline{H}_3$), 1.20 (s, 6 H, $-\overset{|}{C}(C\underline{H}_3)_2$). Mass spectrum, *m/e* 214 (M$^+$). (Found C 67.31; H 10.42. Calc for $C_{12}H_{22}O_3$: C 67.26; H 10.35%.)

10,11-Epoxy-3,7,11-trimethyl-2,6-dodecadien-1-ol acetate. Compound **19**, $C_{17}H_{24}O_3$, oil, yield 46%. IR: 1740, 1670, 1382, 1370, 1230. ^{1}H-NMR: 5.32 (t, 1 H, $=\overset{|}{C}-\underline{H}$; J = 6 Hz), 5.02 (m, 1 H, $=\overset{|}{C}-\underline{H}$), 4.50 (d, 2 H, $-C\underline{H}_2OAc$; J = 6 Hz), 2.50 (t, 1 H, epoxydic proton: J = 5.5 Hz). Mass spectrum, *m/e* 276 (M$^+$). (Found: C 74.01; H 8.80. Calc for $C_{17}H_{24}O_3$: C 73.88; H 8.75%.)

10,11-Epoxy-3,7,11-trimethyl-1,6-dodecadien-3-ol tetra hydropyranyl ether. Compound **20**, $C_{20}H_{34}O_3$, oil, yield 30%. IR: 3030, 1640, 1460, 1388, 1120, 1030. ^{1}H-NMR: 5.82 (complex m, 1 H, $CH_2=C\underline{H}-$), 5.30–5.00 (m, 4 H, olefinic protons), 2.58 (t, 1 H, epoxydic proton; J = 6 Hz). Mass spectrum, *m/e* 322 (M$^+$). (Found C 74.31; H 10.71. Calc for $C_{20}H_{34}O_3$: C 74.49; H 10.63%.)

6-Iodo-7-hydroxy-3,7-dimethyl-2-octen-1-ol acetate. Compound **21**, $C_{12}H_{21}IO_3$, yield 37%. IR: 3500, 1740, 1670, 1390, 1370, 1230. ^{1}H-NMR: 5.35 (t, 1 H, $=\overset{|}{C}-\underline{H}$; J = 9 Hz), 4.50 (d, 2 H, $-C\underline{H}_2OAc$; J = 9 Hz), 3.92 (m, 1 H, $-C\underline{H}-I$), 1.95 (s, 3 H, $-OCOC\underline{H}_3$), 1.72 (s, 3 H, $=\overset{|}{C}-C\underline{H}_3$), 1.38 (s, 6 H, $-\overset{|}{C}(C\underline{H}_3)_2$). Mass spectrum, *m/e* 340 (M$^+$).

6,7-Epoxy-3, 7-dimethyl-2-octen-1-ol acetate. Compound **17**, $C_{12}H_{20}O_3$, oil, yield 65%. IR: 1740, 1670, 1390, 1370, 1235. ^{1}H-NMR: 5.35 (t, 1 H, $=\overset{|}{C}-\underline{H}$; J = 9 Hz), 4.50 (d, 2 H, $-CH_2OAc$; J = 9 Hz), 2.50 (t, 1 H, epoxydic proton; J = 7 Hz), 1.95 (s, 3 H, $-OCOC\underline{H}_3$), 1.72 (s, 3 H, $=\overset{|}{C}-C\underline{H}_3$), 1.22 (S, 6 H, $-\overset{|}{C}(C\underline{H}_3)_2$). Mass spectrum, *m/e* 212 (M$^+$). (Found C 68.00; H 9.43. Calc for $C_{12}H_{20}O_3$: C 67.89; H 9.50%.)

6,7-Epoxy-3,7-dimethyl-1-octen-3-ol tetrahydropyranyl ether. Compound **18**, $C_{15}H_{26}O_3$, oil, yield 48%. IR: 1645, 1460, 1450, 1382, 1330, 992. ^{1}H-NMP.: 5.82 (m, 1 H, $=\overset{|}{C}-\underline{H}$), 5.12 (m, 2 H, $=C\underline{H}_2$), 2.52 (t, 1 H, epoxydic proton; J = 7 HZ), 1.30 (s, 6 H, $-\overset{|}{C}(C\underline{H}_3)_2$). Mass spectrum, *m/e* 254 (M$^+$). (Found C 70.69; H 10.24. Calc for $C_{15}H_{26}O_3$: C 70.83; H 10.30%).

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