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Triphenylphosphine-Induced Ring Contraction of 1,2-Dioxines

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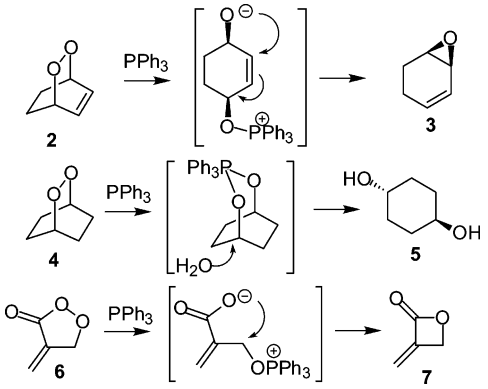
Abstract: Triphenylphosphine inserts into the peroxide bond of 1,2-dioxines, initiating ring contraction with loss of triphenylphosphine oxide. This process yields dihydrofuran oxides in 54−97% yield from oxirenyl[2,3-*c*][1,2]dioxines and dihydrofurans from 3,6-dihydro-1,2-dioxines with inversion of stereochemistry at either the 2 or 5 position in the furan product.

1,2-Dioxines (endoperoxides) **1** are an important class of compounds as they are easily prepared from 1,3-dienes and synthetically useful for the introduction of 1,4-oxygen functionality into organic molecules.[1−3] The weakness of the endocyclic peroxide bond means that a large array of reagents may be used to transform 1,2-dioxines into interesting molecules. One of these, trivalent phosphorus inserts into the peroxide bond yielding reactive phosphorane intermediates which undergo nucleophilic substitution or elimination reactions, Scheme 1.[4−7]

Bicyclic endoperoxides containing a double bond such as **2** are reduced by trivalent phosphorus compounds to allylic epoxides **3** with concomitant phosphorus oxide formation.[8−10] Fully saturated bicyclic endoperoxides **4** yield trans 1,4-diols **5** by hydrolysis of the phosphorus-containing intermediates.[6] Both of these processes occur because of the inability of the intermediate ionic species to undergo intramolecular nucleophilic displacement at the $C-O-P^+R_3$ center because of the barriers to rotation in the cyclic system.

When monocyclic peroxy lactones **6** are treated with triphenylphosphine, ring-contraction to give **7** results from nucleophilic attack at the $C-O-P^+R_3$ center, indicating that when rotation is possible, ring contraction is a favorable process, Scheme 1.[11−14] Ring-contraction is also seen in 1,2-dioxetanes yielding epoxides when treated

SCHEME 1



with phosphines or dialkylsulfides.[15−17] We have recently reported the synthesis of a range of monocyclic 1,2-dioxines **8** where the double bond has been epoxidized and we hypothesized that these substrates would be ideal candidates for ring contraction due to the freedom of rotation that would result in the intermediate ions.[18] Furthermore, the product epoxytetrahydrofuran ring structure **9** finds extensive use in organic synthesis and is found in natural products and is therefore an important target.[19−22]

Both trialkylphosphines and trialkyl phosphites are effective reducing agents for peroxide bonds and so both were used in the reactions of 1,2-dioxines **8**. The results from the reactions of 1,2-dioxines **8a**−**g** with trivalent phosphorus reagents are summarized in Table 1 and Scheme 2.

When **8a** was allowed to react with triphenylphosphine at 25 °C a mixture of products both from ring contraction (**9a**, 12%) and hydrolysis (**10**, 54%) were isolated. The *meso* stereochemistry of **10** indicated that hydrolysis of the intermediates occurred at the phosphorus center rather than the carbon center. Monitoring the reaction by ^1H and ^{31}P NMR showed no phosphorus-containing intermediates. When the mixture of **8a** and triphenylphosphine was heated to reflux in $CDCl_3$, the ring-contracted product **9a** was isolated in 81% yield. In contrast, no reaction was seen between dioxine **8a** and triethyl phosphite at room temperature. When the mixture was heated to reflux for 7 days, full conversion to the ring contracted furan **9a** occurred resulting in an 84% isolated yield, entry 3. The reaction of dicyclohexyl dioxine **8b** and triphenylphosphine only gave a moderate yield of ring-contracted dihydrofuran oxide when heated

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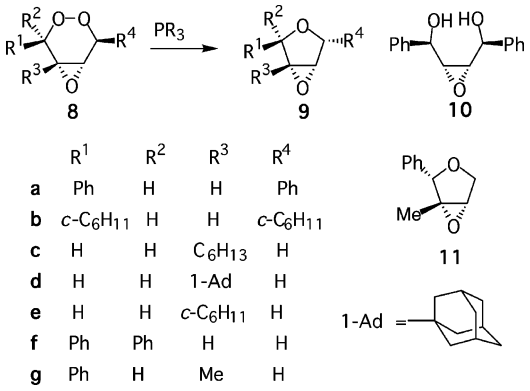
SCHEME 2



	R^1	R^2	R^3	R^4
a	Ph	H	H	Ph
b	*c*-C_6H_{11}	H	H	*c*-C_6H_{11}
c	H	H	C_6H_{13}	H
d	H	H	1-Ad	H
e	H	H	*c*-C_6H_{11}	H
f	Ph	Ph	H	H
g	Ph	H	Me	H

TABLE 1. Ring Contraction of Epoxy-1,2-dioxines 8

entry[a]	1,2-dioxine	PR_3	T, °C (time, h)	yield[b] (%) of **9**
1	**8a**	PPh_3	25 (72)	12
2	**8a**	PPh_3	60 (16)	81
3	**8a**	$P(OEt)_3$	60 (168)	84
4	**8b**	PPh_3	60 (72)	54
5	**8c**	PPh_3	60 (5)	83
6	**8d**	PPh_3	60 (5)	91
7	**8e**	PPh_3	60 (5)	97
8	**8f**	PPh_3	60 (16)	67
9[d]	**8g**	PPh_3	60 (3)	85

[a] Reactions were performed on a scale of 10−300 mg in $CHCl_3$ or $CDCl_3$. [b] Isolated yield by column chromatography. [c] Florisil used as chromatographic stationary phase. [d] Reaction yielded **11** not **9g**.

to 60 °C, entry 4. The dihydrofuran oxide was the sole product from the reaction by ^{1}H NMR but appeared to decompose during isolation. Application of the ring-contraction methodology to 4-substituted 1,2-dioxines **8c**−**e** gave solely ring contraction products in excellent yield, entries 5−7. Comparison of the ^{13}C spectra of these epoxides with that reported for similar analogues confirmed the identity of the epoxides.[23] Methyl substituted 1,2-dioxine **8g** gave a ring-contracted product with inverted stereochemistry at the phenyl center. Definitive assignment of the known product **11** using 2D ROESY NMR was not possible and so **11** was assigned on the basis of the previously reported stereochemistry.

In a recent report by Montaudon et al., a low yield (15%) of dihydrofuran was found in the triphenylphosphine mediated reduction of a 3,6-dihydro-1,2-dioxine.[24] The success we had seen in the ring contractions for the epoxides **8** caused us to examine the ring-contraction of monocyclic 3,6-dihydro-1,2-dioxines that still contained a double bond. The 3,6-dihdro-1,2-dioxines **1** can undergo competing elimination reactions and so could have potentially yielded a mixture of allylic epoxide and ring-contracted compounds. We found that when treated with 1.5 equiv of triphenylphosphine at 60 °C in $CHCl_3$, **1a**−**c** afforded the oxygen sensitive ring-contracted dihydrofurans **12a**−**c** as the major products, Table 2 and Scheme 3. Both 3- and 2-substituted dihydrofurans were prepared by this method in moderate yield.

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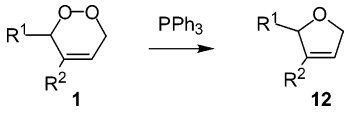
SCHEME 3



a R^1 = *c*-C_6H_{11}, R^2 = H
b R^1 = H, R^2 = 1-Ad
c R^1 = H, R^2 = *c*-C_6H_{11}

TABLE 2. Ring Contraction of 3,6-Dihydro-1,2-dioxines 1 with PPh_3

entry[a]	1,2-dioxine	yield[b] (%) of **12**
1	**1a**	63
2	**1b**	60
3	**1c**	35

[a] Reaction performed on 100−300 mg of **1** with 1.5 equiv of PPh_3 in $CHCl_3$ at 60 °C for 3 h. [b] Isolated yield by flash chromatography.

Once the dihydrofurans **12b**,**c** had been prepared, it was possible to convert them to the dihydrofuran oxides **9d**,**e** to confirm the structural identity of both compounds. Thus, epoxidation of **12a**,**b** with *m*-CPBA gave the dihydrofuran oxides **9d**,**e** in quantitative yield by ^{1}H NMR supporting the assigned structures for both compounds. It appears that increased temperature is necessary to ensure that ring-contraction is the dominant mode of reaction between 1,2-dioxines and triphenylphosphine. The elevated temperature promoted the intramolecular reaction at the expense of the intermolecular hydrolysis giving cleaner reactions.

Due to the ready accessibility of the parent 1,2-dioxines **1** and the near quantitative yield for the epoxidation of the 1,2-dioxines, this procedure represents an efficient synthesis of 3-substituted dihydrofuran oxides. Furthermore, the reaction of phosphines with monocyclic 3,6-dihydro-1,2-dioxines is a useful method for the synthesis of substituted 2,5-dihydrofurans. An examination of the full scope of the ring contraction of monocyclic endoperoxides is underway and may facilitate the use of the ring contraction in targeted structure synthesis.

Experimental Section

General Procedure for the Ring-Contraction of Epoxy-1,2-dioxines 8a−g. To a stirred solution of 1,2-dioxine (1 mmol) in chloroform (5 mL) was added triphenylphosphine (393 mg, 1.5 mmol) and the mixture heated to reflux until complete by ^{1}H NMR or TLC. The mixture was then concentrated in vacuo, and the products were purified by flash chromatography.

(±)-(1a*R*,2*R*,4*R*,4a*S*)-2,4-Diphenyltetrahydrooxireno[2,3-*c*]furan 9a: colorless oil purified by column chromatography (Florisil); R_f 0.82 (CH_2Cl_2); IR (neat) 3031, 2863, 1494, 1451, 1056, 739, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300) δ 3.92 (d, J = 2.6 Hz, 1H), 3.94 (dd, J = 2.6, 0.6 Hz, 1H), 5.16 (s, 1H), 5.40 (s, 1H), 7.33−7.55 (m, 10H); ^{13}C NMR ($CDCl_3$, 50) δ 59.7, 60.1, 78.7, 79.8, 125.9, 127.3, 128.1, 128.3, 128.4, 128.8, 136.8, 138.4; EIMS *m*/*z* 238 (M^+, 20), 211 (30), 105 (100); HRMS calcd for (M + Na, ESI) $C_{16}H_{14}O_2Na$ 261.0891, found 261.0886.

(±)-(1a*R*,2*R*,4*R*,4a*S*)-2,4-Dicyclohexyltetrahydrooxireno-[2,3-*c*]furan 9b: colorless oil; R_f 0.58 (90:10 hexane/ethyl acetate); IR (neat) 2924, 1449, 1062, 868, 732 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300) δ 0.94−1.74 (m, 21H), 1.80−2.0 (m, 1H), 3.48 (d, J = 5.8 Hz, 1H), 3.57 (d, J = 2.0 Hz, 1H), 3.64 (dd, J = 2.0, 0.6 Hz, 1H), 3.75 (d, J = 5.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75) δ 25.7,

25.8, 25.9, 25.9, 26.3, 26.4, 28.8, 29.1, 29.3, 30.6, 39.2, 40.0, 56.8, 57.7, 81.7, 82.0; EIMS *m*/*z* 251 (MH^+, 100), 233 (85), 95 (50); HRMS calcd for (M + Na, ESI) $C_{16}H_{26}O_2Na$ 273.1830, found 273.1827.

1a-Hexyltetrahydrooxireno[2,3-*c*]furan 9c: colorless oil; R_f 0.15 (CH_2Cl_2); IR (neat) 2930, 2857, 1466, 1078, 908, 758 cm^{-1}; ^1H NMR ($CDCl_3$, 300) δ 0.88 (t, J = 6.9 Hz, 3H), 1.23−1.46 (m, 8H), 1.74−2.04 (m, 2H), 3.55 (s, 1H), 3.61 (d, J = 10.2 Hz, 1H), 3.67 (dd, J = 10.5, 0.6 Hz, 1H), 3.89 (d, J = 10.2 Hz, 1H), 3.67 (d, J = 10.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75) δ 13.9, 22.4, 25.4, 27.9, 29.2, 31.5, 60.5, 67.0, 67.6, 69.0; EIMS *m*/*z* 170 (M^+, 4), 152 (4), 55 (95), 43 (100); HRMS calcd for (M + Na, ESI) $C_{10}H_{18}O_2Na$ 193.1204, found 193.1212.

1a-(1-Adamantyl)tetrahydrooxireno[2,3-*c*]furan 9d: colorless oil; R_f 0.16 (CH_2Cl_2); IR (neat) 2904, 1453, 1080, 860 cm^{-1}; ^1H NMR ($CDCl_3$, 300) δ 1.65−1.80 (m, 12H), 2.01 (br s, 3H), 3.61 (br d, 10.5 Hz, 1H), 3.62 (br s, 1H), 3.83 (dd, J = 9.9, 0.9 Hz, 1H), 3.88 (d, J = 9.9 Hz, 1H), 3.97 (d, J = 10.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75) δ 27.8, 31.9, 36.5, 38.8, 57.7, 65.6, 67.5, 73.0; EIMS *m*/*z* 220 (M^+, 20), 191 (30), 135 (100). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 75.73; H, 9.10.

1a-Cyclohexyltetrahydrooxireno[2,3-*c*]furan 9e: colorless oil; R_f 0.11 (CH_2Cl_2); IR (neat) 2927, 2852, 1449, 1081, 909, 863 cm^{-1}; ^1H NMR ($CDCl_3$, 300) δ 1.09−1.29 (m, 5H), 1.66−1.77 (m, 6H), 3.59 (s, 1H), 3.65 (dd, J = 10.5, 0.6 Hz, 1H), 3.66 (d, J = 10.2 Hz, 1H), 3.89 (d, J = 10.2 Hz, 1H), 3.97 (d, J = 10.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75) δ 25.8, 25.9, 26.0, 28.8, 29.4, 36.5, 59.4, 67.6, 67.7, 70.4; EIMS *m*/*z* 150 ($M^+ - H_2O$, 35), 111 (70), 95 (90), 67 (100). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.10; H, 9.65.

2,2-Diphenyltetrahydrooxireno[2,3-*c*]furan 9f: colorless solid; mp 115−117 °C; R_f 0.50 (80:20 hexane/ethyl acetate); IR (Nujol) 1048, 867, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300) δ 3.86 (dd, J = 3.0, 0.6 Hz, 1H), 3.91 (dd, J = 10.8, 0.6 Hz, 1H), 4.29 (d, J = 3.0 Hz, 1H), 4.31 (d, J = 10.8 Hz, 1H), 7.25−7.48 (m, 10H); ^{13}C NMR ($CDCl_3$, 75) δ 56.3, 61.0, 67.2, 85.9, 126.0, 127.1, 127.6, 128.2, 128.6, 141.3, (2 masked aromatics); EIMS *m*/*z* 238 (30), 182 (20), 105 (100); HRMS (ESI) calcd for (M + Na) $C_{16}H_{14}O_2Na$ 261.0891, found 261.0887.

(±)-(1a*R*,2*R*,5a)-1a-Methyl-2-phenylperhydrooxireno-[2,3-*c*]furan 11:[25] colorless oil; R_f 0.48 (70:30 hexane/ethyl acetate); IR (neat) 3031, 2931, 2866, 1493, 1455, 1063, 832, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 300) δ 1.29 (s, 3H), 3.78 (s, 1H), 4.16 (d, J = 10.8 Hz, 1H), 4.19 (d, J = 10.8 Hz, 1H), 4.89 (s, 1H), 7.22−7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 75) δ 14.4, 63.1, 67.1, 68.4, 82.8, 126.6, 128.1, 128.6, 140.0; EIMS *m*/*z* 176 (M^+, 5), 133 (10), 105 (100).

2-Cyclohexyl-2,5-dihydrofuran 12a: unstable colorless oil; R_f 0.40 (90:10 hexane/ethyl acetate); ^1H NMR ($CDCl_3$, 300) δ 0.97−1.72 (m, 11H), 4.60−4.61 (m, 3H), 5.79 (ddd, J = 6.3, 2.4, 1.2 Hz, 1H), 5.86 (br d, J = 6.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75) δ 26.1, 26.1, 26.5, 28.4, 28.6, 43.4, 75.2, 90.6, 126.7, 128.1; EIMS *m*/*z* 168 (M + O), 152 (M^+, 10), 151 (70), 135 (100).

3-(1-Adamantyl)-2,5-dihydrofuran 12b: colorless solid which decomposed over several days; R_f 0.50 (30:70 hexane/CH_2Cl_2); IR (Nujol) 1651, 1102, 1082, 906, 784 cm^{-1}; ^1H NMR ($CDCl_3$, 300) δ 1.65−1.76 (m, 12H), 1.99 (br s, 3H), 4.63−4.64 (m, 4H), 5.38 (m, 1H); ^{13}C NMR ($CDCl_3$, 75) δ 28.3, 33.8, 36.8, 41.7, 73.7, 76.0, 116.0, 150.1; EIMS *m*/*z* 204 (M^+, 20), 176 (20), 135 (100); HRMS calcd for (MH^+, ESI) $C_{10}H_{21}O_1$ 205.1592, found 205.1597.

3-Cyclohexyl-2,5-dihydrofuran 12c: unstable colorless oil; R_f 0.28 (90:10 hexane/ethyl acetate); IR (neat) 2925, 2852, 1448, 1071 cm^{-1}; ^1H NMR ($CDCl_3$, 300) δ 1.16−1.28 (m, 5H), 1.66−1.78 (m, 5H), 1.83 (br s, 1H), 4.55−4.59 (m, 2H), 4.61−4.65 (m, 2H), 5.40−5.42 (m, 1H); ^{13}C NMR ($CDCl_3$, 75) δ 26.1, 26.2, 31.9, 36.6, 75.7, 75.9, 116.9, 145.7; EIMS *m*/*z* 152 (M^+, 40), 123 (40), 69 (100).

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Supporting Information Available: Full characterization data for **8c**−**e**,**g** and **10**. ^1H or ^{13}C NMR spectra for **1c**, **8c**,**e**, **9a**−**c**,**f**, **10**, and **12a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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