Acetylation of **4** (10 mg in 0.2 mL each of acetic anhydride and pyridine, 16 h at ambient temperature) after crystallization from ether–hexane gave acetate **4a**, identical in all respects (mixture melting point, ^{1}H NMR spectrum, and TLC) with the natural compound isolated below.

Verrucarin L Acetate (4a). Fraction E was subjected to MPLC (30–40% ethyl acetate in hexane) to give 100 mg of verrucarin B, 70 mg of verrucarin L acetate (**4a**), and 2.8 g of a mixture of verrucarin A and roridin J. Recrystallization of **4a** from ether–hexane gave crystals: mp 132–135 °C; $[\alpha]^{27}_D$ +29.7° (*c* 0.52, $CHCl_3$), UV (EtOH) 261 nm (log ϵ 4.28); mass spectrum (chemical ionization, methane gas reagent), *m/e* 543.2217 (M^+ + H, calcd 543.2230); ^{1}H NMR ($CDCl_3$) δ 0.86 (3 H, s, 14-H), 1.80 (3 H, s, 16-H), 1.94 (acetate), 2.27 (3 H, d, J = 1 Hz, 12′-H), 2.97 (2 H, AB, J = 4 Hz, 13-H), 3.75 (1 H, d, J = 5 Hz, 11-H), 4.40 (2 H, AB, J = 12 Hz, 15-H), 5.70 (1 H, d, J = 5 Hz, 10-H), 5.96 (1 H, d, J = 16 Hz, 7′-H), 6.07 (1 H, d, J = 11 Hz, 10′-H), 6.61 (1 H, dd, J's = 11 Hz, 9′-H), 8.01 (1 H, dd, J = 11, 16 Hz, 8′-H).

Roridin K Acetate (10). Fraction F was subjected to MPLC (30–60% ethyl acetate in hexane) to yield a fraction (6 g) composed principally of a mixture of roridin E and isororidin E in a ratio of ca. 1:4.[34] The following fraction (320 mg) was subjected to HPLC (20% ethyl acetate in hexane, 40 mg/injection) to give 100 mg of roridin D and 65 mg of roridin K acetate, which was recrystallized from dichloromethane–hexane to give **4a**: mp 255–257 °C; $[\alpha]^{25}_D$ +2.1° (*c* 5.6, $CHCl_3$), UV (EtOH) 263 nm (log ϵ 4.21); mass spectrum (chemical ionization, methane gas reagent), *m/e* 573.2692 (M^+ + H, calcd 573.2700); ^{1}H NMR ($CDCl_3$) δ 0.78 (3 H, s, 14-H), 1.19 (3 H, d, J = 6 Hz, 14′-H), 1.76 (3 H, s, 16-H), 1.19 (acetate), 2.30 (3 H, d, J = 1.2 Hz, 12′-H), 2.52 (1 H, dd, J = 7, 15 Hz, 3α-H), 2.97 (2 H, AB, J = 4 Hz, 13-H), 3.84 (1 H, d, J = 5 Hz, 2-H), 3.90 (1 H, d, J = 5 Hz, 11-H), 4.31 (2 H, AB, J = 12 Hz, 15-H), 5.75 (1 H, d, J = 11 Hz, 10′-H), 5.78 (1 H, d, J = 16 Hz, 7′-H), 6.10 (1 H, dd, J = 4, 8 Hz, 4-H), 6.57 (1 H, dd, J's = 11 Hz, 9′-H), 7.47 (1 H, dd, J = 11, 16 Hz, 8′-H).

Hydrolysis of Esters. All new compounds (ca. 10 mg each) were transesterified at room temperature in 0.3 M sodium methoxide (2–3 h reaction time). The reaction was quenched by passage through a small column packed with Dowex 50W-X4 acidic resin. The solvent was removed, and the crude product was purified by preparative TLC. Trichodermadiene (**13**), **14**, and **15** yielded trichodermol (**11**), mp 116–117 °C (lit.[6] mp 117.5–118 °C). Roridin J (**9**) and **16**–**19** each gave verrucarol; compounds **4**, **4a**, and **10** gave 4β,8α,15-trihydroxy-12,13-epoxytrichothec-9-ene (**20**), mp 177–178 °C (undepressed upon admixture with an authentic sample).[3]

Acknowledgment. This investigation was supported by Grant No. CA 25967 awarded by the National Cancer Institute, DHSS. We thank Dr. Gary McCluskey of the Frederick Cancer Research Facility, Frederick, Maryland for mass spectral measurements. G. P. Stahly thanks Gillette Corp. for a fellowship.

Registry No. **1**, 3148-09-2; **2**, 2290-11-1; **3**, 4643-58-7; **4**, 77101-87-2; **4a**, 77101-88-3; **5**, 14729-29-4; **6**, 14682-29-2; **7**, 16891-85-3; **7a**, 64726-84-7; **8**, 29953-50-2; **9**, 74072-83-6; **9** acetate, 74098-61-6; **10**, 80326-33-6; **11**, 2198-93-8; **12**, 2198-92-7; **13**, 75323-72-7; **14**, 76740-74-4; **14** diacetate, 80326-34-7; **15**, 76685-81-9; **15** diacetate, 80374-38-5; **16**, 76739-71-4; **16** triacetate, 80326-35-8; **17**, 76685-83-1; **17** triacetate, 80374-39-6; **18**, 76739-70-3; **18** triacetate, 80326-36-9; **19**, 76685-82-0; **19** triacetate, 80408-18-0; **20**, 74516-69-1.

(34) These isomers are very difficult to separate. They may be separated with difficulty on a silica column (HPLC) by using 60% ethyl acetate in hexane. Reverse-phase HPLC (C-18 column, MeOH–H_2O) works somewhat better.

Notes

Dehalogenation of α-Chloro and α-Bromo Ketones. Use of Sodium *O,O*-Diethyl Phosphorotelluroate

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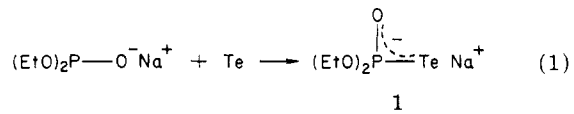
Conversion of α-halo ketones into the parent ketones is a reaction that is sometimes used in synthesis,[1] and several new reagents have been introduced recently[2] for this transformation. We have found that sodium *O,O*-diethyl phosphorotelluroate (**1**) is a mild and convenient reagent for such dehalogenations.

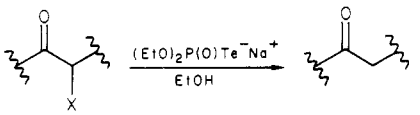
The salt **1** is readily prepared[3] (eq 1) by dissolving



(1)

1

metallic tellurium in an ethanol solution of sodium diethyl phosphite. As reported previously,[3] compound **1** converts epoxides into olefins. It also dehalogenates α-halo ketones (eq 2), and our results are collected in Table I for a number



(2)

X = Cl, Br

of α-chloro and α-bromo ketones. In each case the halo ketone, usually in ethanol but sometimes in THF, was injected into a solution containing a stoichiometric amount of the phosphorotelluroate. The reaction was then allowed to proceed at room temperature or at 80 °C with the results indicated.

One of the reaction products is elemental tellurium, and entry 4, parts b and c (Table I) shows that less than 1 equiv of the metal can be used, although, for best results, a

(1) (a) Stork, G.; MacDonald, T. L. *J. Am. Chem. Soc.* **1975**, *97*, 1264. (b) Deprês, J.-P.; Greene, A. E. *J. Org. Chem.* **1980**, *45*, 2036. (c) For conversion of olefins into α-halo ketones see: Cardillo, G.; Shimizu, M. *Ibid.* **1977**, *42*, 4268. Sharpless, K. B.; Teranishi, A. Y. *Ibid.* **1973**, *38*, 185.

(2) Olah, G. A.; Arvanaghi, M.; Vankar, Y. D. *J. Org. Chem.* **1980**, *45*, 3531. Alper, H.; Pattee, L. *Ibid.* **1979**, *44*, 2568. Alper, H.; Des Roches, D. *Ibid.* **1976**, *41*, 806. Luh, T.-Y.; Lai, C. H.; Lei, K. L.; Tam, S. W. *Ibid.* **1979**, *44*, 641. Ho, T.-L.; Wong, C. M. *Ibid.* **1974**, *39*, 562. Sauers, R. R.; Hu, C. K. *Ibid.* **1971**, *36*, 1153. Borowitz, I. J.; Kirby, K. C., Jr.; Rusek, P. E.; Lord, E. *Ibid.* **1969**, *34*, 2687. Kuivila, H. G.; Menapace, L. W. *Ibid.* **1963**, *28*, 2165. Denis, J. N.; Krief, A. *Tetrahedron Lett.* **1981**, 1431. Alper, H. *Ibid.* **1975**, 2257. Townsend, J. M.; Spencer, T. A. *Ibid.* **1971**, 137. Olah, G. A.; Vankar, Y. D.; Fung, A. P. *Synthesis* **1979**, 59. Ho, T.-L.; Olah, G. A. *Ibid.* **1976**, 807. Ho, T.-L. *Synth. Commun.* **1979**, *9*, 241. Ho, T.-L.; Wong, C. M. *Ibid.* **1973**, *3*, 237.

(3) Clive, D. L. J.; Menchen, S. M. *J. Org. Chem.* **1980**, *45*, 2347.

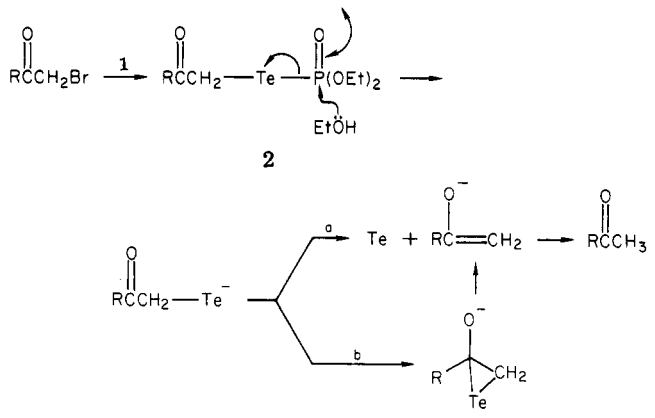
0022-3263/82/1947-1124$01.25/0

Table I[a]

expt	halo ketone	temp, °C	time, h	ketone yield,[b] %
1	(1*R-endo*)-3-bromo-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one	80	5.0	79
2	2-bromo-3,4-dihydro-1(2*H*)-naphthalenone	25	3.0	91
3	2,4′-dibromoacetophenone	25	2.5	78
		60	0.25	78
4	2-bromocycloheptanone a	25	3.5	89[c]
	b	25	15.0	86[c,d]
	c	25	5.0	67[c,e]
5	2α-bromocholestan-3-one	25	4.0	81
6	16α-bromo-3-methoxyestra-1,3,5(10)-trien-17-one	25	0.75	96
7	2-bromo-2,4-dimethylpentan-3-one	80	3.5	48[c]
8	2-bromocyclohexanone	80	2.0	56[c]
9	2-chlorocyclohexanone	80	7.0	36[c]
10	2-chloro-2-methylcyclohexanone	80	15.0	19[c]
11	2-chloroacetophenone	25	1.0	84

[a] Experiments were run on a 1-mmol scale except for no. 5 and 6 which were on a 0.125-mmol scale. A stoichiometric amount of tellurium was used escept, as noted in footnotes *d* and *e*, for the experiments with 2-bromocycloheptanone. Runs 1, 3, 5, and 6 were in EtOH–THF, and the others were in EtOH. [b] Yields refer to pure isolated material, except where indicated. [c] Yield determined by VPC with an internal standard. [d] For this experiment 0.67 equiv of tellurium was used. [e] For this experiment 0.14 equiv of tellurium was used.

Scheme I



stoichiometric amount is needed. No ethyl bromide was produced (VPC) in the dehalogenation, as a test case, of 2-bromoacetophenone, and triethyl phosphate was formed [ca. 100% yield (VPC)] in an experiment with 2,4′-dibromoacetophenone. A chemically reasonable mechanism that accounts for these observations is shown in Scheme I.

Analogy for intervention of the ester **2** is provided by our observation that the selenium salt[4] corresponding to **1** reacts with 2,4′-dibromoacetophenone to give the selenium analogue of **2**[5] although further reaction does not occur under conditions in which the tellurium reagent effect smooth dehalogenation. The pathway b in Scheme I is consistent with the known[6] tendency of epitellurides to extrude the heavy element.

Finally, in control experiments sodium diethyl phosphite itself was found to effect slow dehalogenation in poor yield (see Table II) as judged by experiments with 2-chloro- and 2,4′-dibromoacetophenone.

Table II

halo ketone[c]	stoichiometric reagent[a]	time, h	yield,[b] %
2-chloro-	$(EtO)_2P(O)TeNa$	1	84
acetophenone	$(EtO)_2PONa$	72	~60
	$(EtO)_2PONa$	1	0
2,4′-dibromo-	$(EtO)_2P(O)TeNa$	2.5	78
acetophenone	$(EtO)_2PONa$	24	18

[a] Reactions run in EtOH plus THF. [b] Yield refers to isolated ketone. [c] The temperature was 25 °C in all cases.

The general procedure for dehalogenation was as follows. Finely divided tellurium[7] (128 mg, 1.0 mmol) was placed in a two-necked oven-dried flask containing a Teflon-covered stirring bar. One neck of the flask was connected by hose adaptor to a vacuum/argon line, and the other neck was closed with a septum or, for reactions done above room temperature, was fitted first with a reflux condenser. The system was evacuated and filled with argon (three cycles). A standard ethanolic solution[3] (1.0 M, 1.5 mL, 1.5 mmol) of sodium diethyl phosphite was injected, the mixture was stirred (ca. 5 min) until a clear solution of sodium *O,O*-diethyl phosphorotelluroate had formed, and the α-halo ketone (1.0 mmol) in dry ethanol or THF (1.5 mL plus a 0.5 mL rinse) was injected. The mixture was stirred at the specified temperature (see Table I) for the time indicated and was then filtered with the aid of ether (ca. 25 mL) through a pad of Celite (2.5 × 2.0 cm). The orange filtrate was evaporated at room temperature under waterpump vacuum, and the residue was applied in 8:2 hexane–ethyl acetate to a column of silica gel (Merck Silica Gel 60, 70–230 mesh ASTM, 1.5 × 20 cm) made up in the same solvent. The material was allowed to penetrate the column for a distance of about 2 cm, development was then stopped for 30 min to allow decomposition of residual tellurium species (deposition of black tellurium), and development was resumed to elute the product, which was obtained pure by removal of solvent and, where necessary, crystallization or distillation.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for support and Dr. S. M. Menchen for preliminary work. P.L.B. is an

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(5) IR ($CDCl_3$) 1680 cm^{-1}; ^{31}P NMR ($CDCl_3$, 36.43 MHz) $\delta_{^{31}P}$ 18.6 ppm downfield from 85% H_3PO_4 as an external standard (s, satellite signals with $J_{^{31}P-^{77}Se}$ = 450 Hz); ^1H NMR ($CDCl_3$, 60 MHz) δ 1.05–1.56 (w, 6 H), 3.75–4.55 (m, 6 H), 7.4–8.06 (m, 4 H); exact mass, *m/e* 413.9145 (calcd for $C_{12}H_{16}BrO_4PSe$, *m/e* 413.9134). Cf.: Glidewell, C.; Leslie, E. J. *J. Chem. Soc., Dalton Trans.* **1977**, 527.

(6) (a) Connor, J.; Van Roodselaar, A.; Fair, R. W.; Strausz, O. P. *J. Am. Chem. Soc.* **1971**, *93*, 560. (b) The dehalogenation does not proceed efficiently in THF (i.e., in the absence of EtOH), and attempts to trap enolate species in THF by addition of MeI were unsuccessful.

(7) Brauer, G. "Handbook of Preparative Inorganic Chemistry", 2nd ed.; Academic Press: New York, 1963; Vol. I, p 447. Goldstein, J. *Rev. Chem. (Bucharest)* **1963**, *14*(3), 164; *Chem. Abstr.* **1963**, *59*, 12425*g*.

NSERC Postgraduate scholar.

Registry No. 1, 65857-68-3; (1*R*-*endo*)-3-bromo-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one, 10293-06-8; 2-bromo-3,4-dihydro-1-(2*H*)-naphthalenone, 13672-07-6; 2,4′-dibromoacetophenone, 99-73-0; 2-bromocycloheptanone, 766-65-4; 2α-bromocholestan-3-one, 23737-88-4; 16α-bromo-3-methoxyestra-1,3,5(10)-trien-17-one, 10324-68-2; 2-bromo-2,4-dimethylpentan-3-one, 3212-63-3; 2-bromocyclohexanone, 822-85-5; 2-chlorocyclohexanone, 822-87-7; 2-chloro-2-methylcyclohexanone, 10409-46-8; 2-chloroacetophenone, 532-27-4; sodium diethylphosphite, 2303-76-6.

Synthesis of (Aryloxy)propanolamines via a Palladium-Promoted Oxyamination

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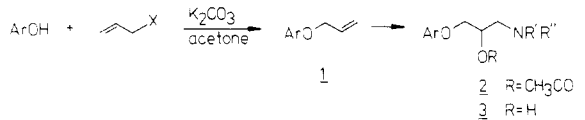
We recently reported a method for direct vicinal oxyamination of alkenes utilizing palladium.[1] An important aspect on the reaction is the high stereospecificity resulting in an overall cis oxyamination. The addition to certain alkenes is also regioselective. In this work we have taken advantage of the regioselectivity of the reaction and applied the oxyamination to transformation of allyl aryl ethers **1** into (aryloxy)propanolamines **3**. Compounds **3** are an important class of biologically active substances with β-adrenergic receptor blocking effects.[2] The oxyamination reaction now also proceeds with primary amines, an improvement over our previous report. It has previously been reported that oxyamination of phenyl allyl ether with stoichiometric amounts of a (*tert*-butylimido)osmium reagent gives **3** (R′ = H, R″ = *t*-Bu).[3]

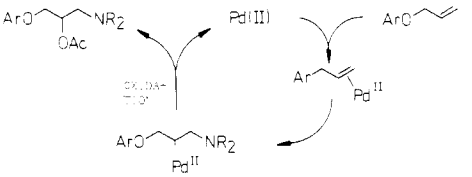
The procedure, which has generally been used to prepare (aryloxy)propanolamines **3**, involves reaction of an epihalohydrin with a phenoxide, followed by amination of the product obtained, which is either a 3-arylpropene oxide[2a,2d] or a 1-halo-3-arylpropen-2-ol,[2e] or a mixture of both. Another common method utilizes 5-(hydroxymethyl)-2-phenyl-1,3-oxazolidine.[2f,2g] Here, we have utilized a mild, direct vicinal oxyamination of **1**, which proceeds through an aminopalladation oxidation sequence. The allyl aryl ethers **1** are obtained by allylation of the corresponding phenol in high yield[4] (Scheme I).

Oxyamination of the double bond in **1** at −50 °C, using the aminopalladation–oxidation sequence described previously,[1] gives the aminoacetate **2**. Hydrolysis of **2**, which is quantitative, yields the desired amino alcohol **3**. Secondary amines gave fair to good yields of oxyamination products (Table I). It was found that lead tetraacetate is the most efficient oxidant for oxyamination of olefins **1**. This is in contrast to the oxidation of styrene, where *N*-bromosuccinimide (NBS) as the oxidant gave the best yields.[1]

Scheme I

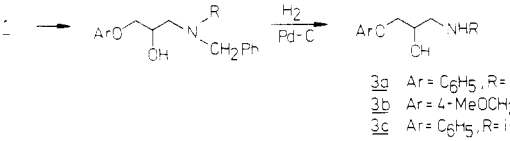


Scheme II



We have now succeeded in obtaining oxyamination products from primary amines. In our previous study we were only able to isolate aziridines when primary amines were used. We have now found that the formation of aziridines is depressed on addition of a silver salt. However, the amino acetates **2** obtained in this way from primary amines are not conveniently isolated due to acetyl migration from oxygen to nitrogen.[6] The crude product from these reactions was therefore hydrolyzed[7] with base to afford the corresponding amino alcohol **3**. Thus, oxyamination of allyl phenyl ether with isopropylamine followed by hydrolysis gave **3c** in 50% yield.

An alternative method for obtaining secondary oxyamines **3**, via the benzyl derivatives, was also used. Thus, oxyamination utilizing an *N*-alkylbenzylamine, followed by hydrogenolysis (Pd/C) of the benzyl group in the amino alcohol obtained, affords secondary oxy amines **3a–c** (eq 1). This route to secondary oxy amines should be useful



in cases where a protecting group is desired on the oxygen or nitrogen atoms. Another synthetic application of this procedure is in asymmetric oxyamination using an amine with an optically active benzyl group (e.g., α-methylbenzyl) which can be removed at the end.[8]

The inhibition of aziridine formation on addition of a silver salt needs some comment. We previously observed[1a] that it was not possible to inhibit formation of an aziridine by protonating the amino group β to palladium. To account for these results we suggested that a β-chloro amine is first formed, which on treatment with base would give the aziridine. The present results provide strong support for such a mechanism under acidic conditions. In fact, we were able to isolate β-chloro amines in several cases using the general procedure in the absence of a silver salt.

In principle, the oxyamination can be considered to be a catalytic reaction since palladium(II) is regenerated in the oxidative cleavage of the palladium–carbon bond (Scheme II). However, the palladium(II) regenerated is

(1) (a) Bäckvall, J. E.; Björkman, E. E. *J. Org. Chem.* **1980**, *45*, 2893. (b) Bäckvall, J. E. *Tetrahedron Lett.* **1975**, 2225.

(2) (a) Shtacher, G.; Rubenstein, R. *J. Med. Chem.* **1978**, *21*, 678. (b) Danilewics, J.; Kemp, J. *Ibid.* **1973**, *16*, 168. (c) Tucker, H. *J. Org. Chem.* **1979**, *44*, 2943. (d) Nelson, W. L.; Burke, T. R. *Ibid.* **1978**, *43*, 3641. (e) Lemke, T. L.; Boblitt, R. L.; Capiton, G. A.; Cates, L. A.; Martin, G. E. *Ibid.* **1978**, *43*, 2079. (f) Weinstock, L. M.; Mulvey, D. M.; Tull, R. *Ibid.* **1976**, *41*, 3121. (g) Baldwin, J. J.; Hirschman, R.; Lumma, P. K.; Lumma, W. C.; Ponticello, G. S.; Sweet, C. S.; Scriabine, A. *J. Med. Chem.* **1977**, 20, 1024.

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(4) Tarbell, D. S. *Org. React.* **1944**, *2*, 22.

(5) Bäckvall, J. E. *J. Chem. Soc., Chem. Commun.* **1977**, 413.

(6) Similar acyl migrations are well-known and have been observed in analogous systems: Pavlova, L. V.; Rachinskii, F. Yu. *Russ. Chem. Rev.* (*Engl. Transl.*) **1968**, *37*, 587. Welsh, L. H. *J. Org. Chem.* **1967**, *32*, 119. Welsh, L. H. *J. Am. Chem. Soc.* **1949**, *71*, 3504; **1947**, *69*, 128.

(7) The base hydrolysis proceeds via the amide: $RCH(OAc)CH_2NHR \rightarrow RCH(OH)CH_2N(Ac)R \rightarrow RCH(OH)CH_2NHR$ (cf. ref 6). In fact, it was difficult to isolate the amino acetate without O → N acetyl migration.

(8) Preliminary results show that oxyamination of allyl phenyl ether with optically active *N*-methyl-1-phenethylamine gives an optical yield of approximately 20–30%: Bäckvall, J. E.; Björkman, E. E.; Byström, S.; Solladié-Cavallo, A. *Tetrahedron Lett.*, in press.

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