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SYNTHESES OF TETRAHYDROPYRANS BY PPh_3/CBr_4 INDUCED CYCLIZATION OF ACETALS : APPLICATION TO A SYNTHESIS OF ROSE OXIDE

A. WAGNER, M.-P. HEITZ, C. MIOSKOWSKI*

Laboratoire de Chimie Bio-Organique, associé au CNRS, Université Louis Pasteur, Faculté de Pharmacie, 74 route du Rhin F- 67401 Strasbourg Cédex, FRANCE.

Summary : Substituted tetrahydropyrans are prepared in good yields by PPh_3/CBr_4 induced cyclization of acetals. The utility of this new procedure is illustrated by the synthesis of cis-2-(2-methyl-1 propenyl)- 4 methyltetrahydropyran (rose oxide).

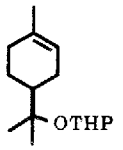
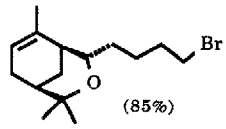
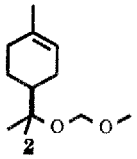
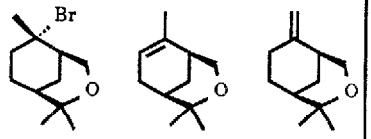
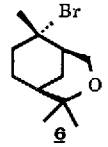
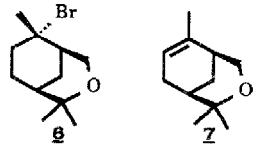
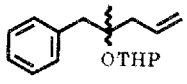
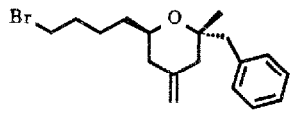
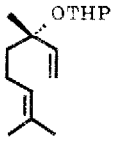
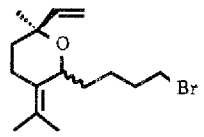
The tetrahydropyran nucleus is a common structural feature of many naturally occuring compounds[1] and there is still an active interest in developping efficient methods for preparing these oxacyclic products[2]. During our exploratory study for the direct conversion of THP protected ethers to the corresponding bromides[3], we found that γ- and δ- unsaturated THP or MOM protected alcohols are converted by intramolecular induced PPh_3/CBr_4 cyclization to substituted tetrahydropyrans. We wish now to report our preliminary results on the first use of this method to prepare 6-membered oxygenated rings and to synthesize cis-rose oxide, a minor but important olfactive ingredient of rose otto and geranium oil[4].

The THP and MOM ether cyclization reactions we examined are summarized in the table.

The cyclization reactions of **1-4** were carried out either with PPh_3/CBr_4 following the general procedure described for the direct bromination of THP ethers[3] or with 1.3 eq PPh_3,Br_2 in dichloromethane as solvent. In all cases, good yields of cyclization products were obtained (see table).

The reaction can be rationalized by a pathway involving a PPh_3,Br_2 induced acetal activation followed by an intramolecular addition of the double bond leading to a carbocationic species. This intermediate is deprotonated in the case of a THP ether (entries A, B, D) or trapped by a bromine ion in the case of a MOM ether (entry B_2). A mixture of elimination and bromination products can be observed under certain reaction conditions (entries B_1, B_3).

Table

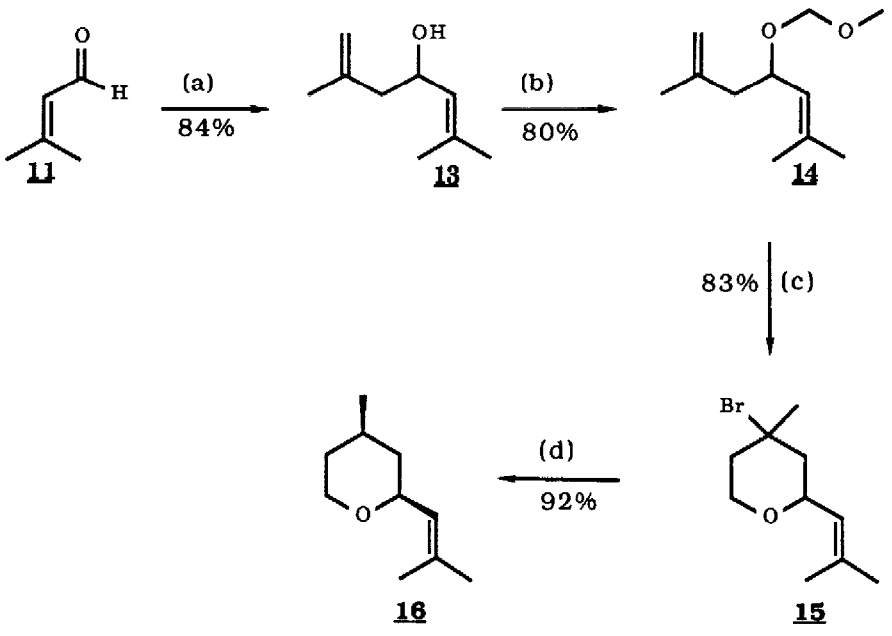
Entry	substrat	reagent	temp.	products[a] (yield)[b]
A	 **1**	PPh_3/CBr_4	r.t.	 **5** (85%)
B_1	 **2**	PPh_3/Br_2 [c]	r.t.	 **6** (65%) **7** (15%) **8** (5%)
B_2	**2**	PPh_3/Br_2	reflux	 **6** 86%
B_3	**2**	PPh_3/CBr_4	r.t.	 **6** (78%) **7** 10%
C	 **3**	PPh_3/CBr_4	r.t.	 **9** (84%)
D	 **4**	PPh_3/CBr_4	r.t.	 **10** (82%)

[a] All products are fully spectroscopically characterized (IR, ^1H NMR, ^{13}C NMR, MS); some spectral data are shown in footnote 8.

[b] Yield of isolated products. [c] PPh_3/Br_2 is commercially available from Fluka.

The high flexibility of this reaction is finally demonstrated in the synthesis of cis-rose oxide. The synthetic pathway for the preparation of this product is outlined in scheme I.

Scheme I



Reagents and conditions : (a)  / THF / 0°C; (b) $BrCH_2OCH_3$ / $EtN(iPr)_2$ / 0°C to r.t.; (c) PPh_3/CBr_4/ CH_2Cl_2 / r.t.; (d) Bu_3SnH / ether / hν

The key intermediate **14** was prepared by addition of aldehyde **11** to the Grignard reagent **12** followed by protection of the alcohol function as a MOM ether[5]. Treatment of **14** with PPh_3/CBr_4 and photocatalyzed tin hydride reduction[6] of the bromotetrahydropyran **15** gave cis-rose oxide (purity > 95% by GC analysis). The product shows the same spectroscopic features as previously reported in the litterature[7].

The potential of this cyclisation reaction, as a general route to oxygen-, sulfur- and nitrogen- containing rings, is currently under investigation.

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Reference and notes.

1. See, e.g. : Katritzky, A., Rees, C.W., Eds. "Comprehensive Heterocyclic Chemistry"; Pergamon Press : Oxford, 1984; vol. 1-6.
2. (a) Sworin, M., Neumann, W.L., J. Org. Chem. 1988, 53, 4894 and references therein. (b) Coppi, L., Ricci, A., Taddei, M., J.Org.Chem.1988, 53, 911. (c) Lolkema, L.D.M., Hiemstra, H., Mooiweer, H.H., Speckamp, W.N. Tetrahedron Lett. 1988, 29, 6365.
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4. For a review on the rose oxides see Thomas, A.F. in "The Total Synthesis of Natural Products", vol.2, 167-169, ed. J. ApSimon, John Wiley & Sons, New-York (1973).
5. Stork, G., Takahashi, T. J.Am.Chem.Soc. 1977, 99, 1275.
6. Luh, T.Y., Stock, L.M., J.Org.Chem. 1977, 42, 2790.
7. (a) Metera, A., Naves, Y.R., Compt. Rend. Acad. Sc. Paris 1961, 252, 1937. (b) Vidari,G., De Benardi, M., Pavan, M., Ragozzino, L. Tetrahedron Lett. 1973, 4065.
8. Some selected data are : **5** : ^{1}H NMR (200 Mz, $CDCl_3$) δ 1.20 (s, 3H), 1.29 (s, 3H), 1.32-1.55 (m, 4H), 1.55-1.70 (m, 3H), 1.70-1.85 (m, 3H), 1.85-2.00 (m,2H), 2.00-2.18 (m, 2H), 2.25-2.42 (m, 1H), 3.41 (t, J=6.8Hz, 2H), 3.67 (td, J=6.8 and 1.8 Hz), 5.50-5.60 (m,1H); ^{13}C NMR (50Mz, $CDCl_3$) δ 23.8, 25.1, 25.2, 27.7, 28.3, 28.5, 32.7, 33.8, 34.0, 38.3, 73.3, 74.7, 123.7, 133.1. **6** ^{1}H NMR ($CDCl_3$) δ 1.21 (s, 3H), 1.28 (s, 3H), 1.42-1.50 (m, 1H), 1.82-2.05 (m, 5H), 1.98 (s, 3H), 2.05-2.17 (m, 2H), 3.48 (apparent dt, J=11 and 1.9 Hz, 1H), 3.79 (apparent dd J=11 and 2.2 Hz); ^{13}C NMR ($CDCl_3$) δ 23.8, 25.1, 21.7, 28.1, 33.7, 35.4, 39.6, 43.8, 62.9, 75.7, 76.9. **7** ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 3H), 1.31 (s, 3H), 1.48-1.57 (m, 1H), 1.57-1.65 (m,1H), 1.65-1.73 (m, 3H), 1.84-1.95 (m, 1H), 2.02-2.25 (m, 2H), 2.27-2.40 (m, 1H), 3.73 (apparent dd, J=12.0 and 3.0 Hz, 1H), 3.83 (apparent dt, J=12.0 and 2.0 Hz, 1H), 5.50-5.58 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 22.0, 23.5, 26.7, 27.7, 28.5, 34.7, 35.3, 63.1, 74.8, 122.4, 134.5. **8** ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 3H), 1.33 (s, 3H), 1.42-1.65 (m, 3H), 1.94-2.31 (m, 4H), 2.85-3.08 (m, 1H), 3.64 (apparent dt, J=12.0 and 2.0 Hz, 1H), 4.02 (apparent dd, J=12.0 and 2.0 Hz, 1H), 4.60-4.66 (m, 2H). **9** ^{1}H NMR ($CDCl_3$) δ 1.42-1.67 (m, 4H), 1.58 (s, 3H), 1.73-2.06 (m, 4H), 2.08-2.25 (m, 2H), 2.76 and 2.85 (AB system, J=12.0Hz, 2H), 3.44 (t, J=6.7Hz, 2H), 3.48-3.60 (m, 1H), 4.62-4.67 (m, 1H), 4.73-4.82 (m, 1H), 7.13-7.38 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 11.4, 20.2, 24.2, 25.3, 29.1, 32.7, 34.6, 44.6, 70,6, 75,1, 109,9, 126,1, 127,6, 130.8, 137.8, 143.5. **10** ^{1}H NMR ($CDCl_3$) δ 1.12-2.17 (m, 15H), 1.25-1.37 (m, 3H), 3.42 (t, J=6.8 Hz), 4.67-4.78 (m, 1H), 4.87-5.25 (m, 2H), 5.66-6.08 (m, 1H), ^{13}C NMR ($CDCl_3$, mixture of two isomers) δ 20.3, 20.6, 24.3, 24.9, 26.0, 26.7, 29.9, 31.1, 32.6, 32.7, 34.0, 34.5, 42.3, 43.0, 48.7, 48.8, 71.8, 72.3, 73.3, 73.5, 74.7, 75.1, 110.7, 111.7, 113.4, 114.7, 143.2, 144.2, 146.1,147.1.

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