Tetrahedron Letters Vol. 21, pp 2643 - 2646 0040-4039/80/0701-2643$02.00/0

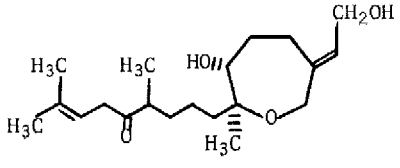
A NOVEL TRANSFORMATION OF 7-MEMBERED RING LACTONES TO β-KETO ETHERS

Vinayak V. Kane,*[1] Donald L. Doyle and Paul C. Ostrowski

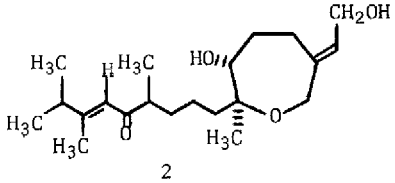
Division of Chemical Research, Ortho Pharmaceutical Corporation, Raritan, New Jersey 08869

Abstract: The development of an efficient and regioselective transposition of a 7-membered lactone to a corresponding β-keto ether is reported.

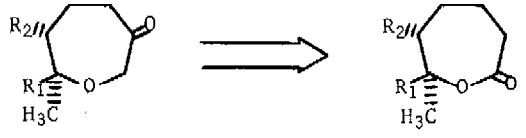
Recently, the isolation and structural elucidation of two new diterpenoids, zoapatanol (1) and montanol (2) from the zoapatle plant, Montanoa tomentosa, has been reported.[2] During synthetic studies related to 1 and 2, we needed an efficient, general and selective method for the synthesis of β-keto ether 3 from a readily available intermediate such as the 7-membered lactone 4. In recent years, several new methods for transposing a ketone carbonyl[3] by one carbon atom have been described, but no such transformation has been reported[4] for a lactone to a β-keto ether. In this communication, we report such a transformation.



1



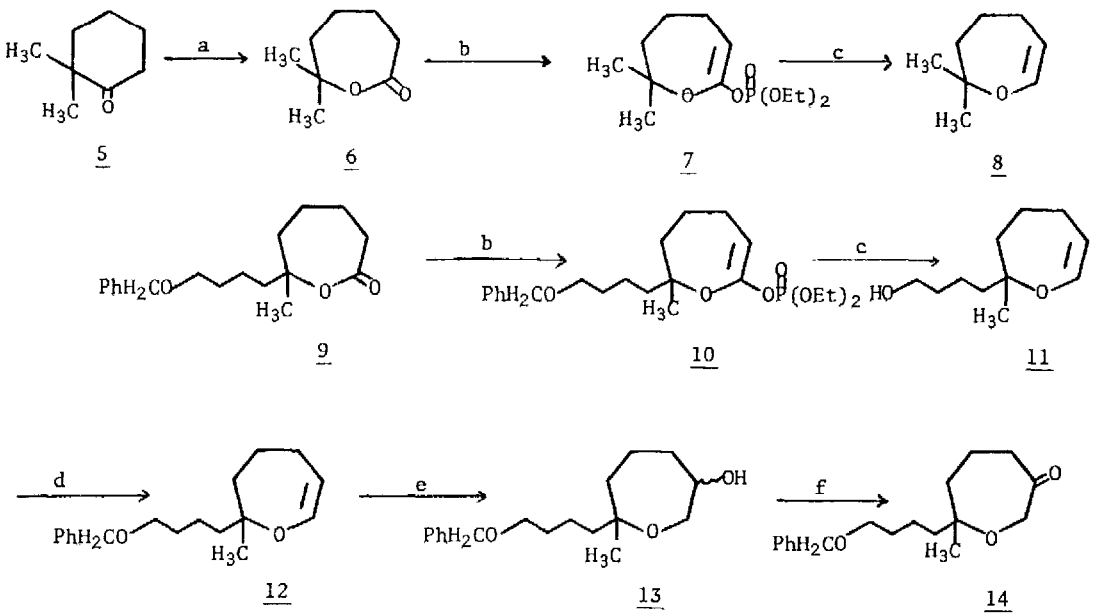
2



3 4

One such scheme[5] was suggested by the results of both Ireland and Fetizon[6] on the deoxygenation of a diethyl enol phosphate or an enol tetramethylphosphorodiamidate by lithium-ammonia reduction to give an olefin. If the diethyl enol phosphate of a lactone behaved in a similar

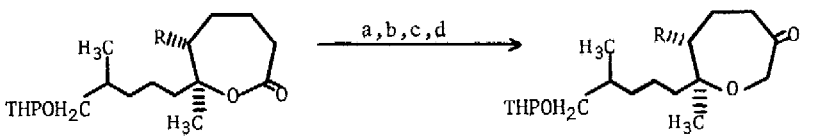
manner, then an enol ether should result. The desired selectivity in hydroxylation of the enol ether should be obtained by hydroboration-oxidation, since it has been observed that enol ethers undergo hydroboration predominantly at their β-position.[7] Oxidation of the resulting alcohol with a suitable oxidizing reagent would then give the desired β-keto ether in a regioselective manner.



a, MCPBA/NaOAc/CH_2Cl_2,Δ; b, LDA/$(EtO)_2\overset{O}{\overset{\|}{P}}Cl$/THF/TMEDA/HMPA; c, Na/t-BuOH/liq. NH_3; d, $PhCH_2Br$/NaH/C_6H_6; e, BH_3/THF; $NaOH/H_2O_2$; f, CrO_3/Pyr/CH_2Cl_2.

The lactone 6[8,9] selected as the starting material to examine this sequence was readily prepared by Baeyer-Villiger oxidation (MCPBA) of the known ketone 5.[10] Reaction of 6 in THF with LDA at -78°C and treatment of the resulting enolate solution with diethyl phosphorochloridate gave the diethyl enol phosphate 7 (80%). However, reduction of the diethyl enol phosphate led to the tetrahydrooxepene 8 in only 5 to 10% yield. It is assumed that the low yield of the tetrahydrooxepene 8 is due to the highly volatile nature of this compound. In view of this difficulty, the lactone 9,[11] which has a hydroxy substituted longer side chain was chosen in the hope that the tetrahydrooxepene formed would be more suitable than 8. Reaction of lactone 9 with diethyl phosphorochloridate in the presence of LDA in THF solution gave the

diethyl enol phosphate 10 (84%).[12] Reduction of the crude diethyl enol phosphate 10 with Na (7.5 eq.) in a mixture of NH_3/t-BuOH/THF led to the tetrahydrooxepene 11 (52%). The alcohol 11 on treatment with NaH/$PhCH_2Br$ in benzene gave the benzyl ether 12 (99%). Treatment with borane (BH_3) in THF followed by alkaline H_2O_2 oxidation afforded a mixture of epimeric alcohols 13 (66%), which without separation was oxidized with Collins reagent in CH_2Cl_2[13] to give the desired β-keto ether 14 (85%).



15, R = H; 16, R = OCH_3 17, R = H; 18, R = OCH_3

a, LDA/$(EtO)_2\overset{O}{\overset{\|}{P}}Cl$/THF/TMEDA/HMPA; b, Na/t-BuOH/liq NH_3; c, BH_3/THF; NaOH/H_2O_2; d, CrO_3/Pyr/CH_2Cl_2

Likewise, transposition of the lactones 15 and 16[11] gave the β-keto ethers 17 and 18 both in 24% overall yield. The application of this novel transformation to other lactones is currently under investigation and will be reported at a later date.

Acknowledgment

The authors thank Dr. M. L. Cotter, Mr. J. Grodsky and Ms. R. Naldi for the NMR and IR data and Mr. C. Shaw for the mass spectral data. We also thank Professor James A. Marshall for helpful discussions.

References and Notes

1. Present Address - College of Pharmacy, University of Arizona, Tucson, AZ 85721.
2. S. D. Levine, R. E. Adams, R. Chen, M. L. Cotter, A. F. Hirsch, V. V. Kane, R. M. Kanojia, C. Shaw, M. P. Wachter, E. Chin, R. Huettemann, P. Ostrowski, J. L. Mateos, L. Noriega, A. Guzman, A. Mijarez and L. Tovar, J. Am. Chem. Soc., 101, 3404 (1979).
3. a) B. M. Trost, K. Hiroi and S. Kurozumi, ibid, 97, 438 (1975); b) B. M. Trost, T. N. Salzmann and K. Hiroi, ibid, 98, 4887 (1976); c) Y. K. Lee and A. G. Schultz, J. Org. Chem., 44, 719 (1979); d) W. E. Fristad, T. R. Bailey and L. A. Paquette, ibid, 43, 1620 (1978) and references cited therein.

4. Although a transformation of a lactone to a β-keto ether has not been reported in the literature, it should be more readily achieved in 5 and 6-membered lactones. Their reduction products, the corresponding lactols are cyclic and readily converted to cyclic enol ethers through dehydration. Hydroboration oxidation, followed by Collins oxidation should lead to the β-keto ether. However, in the case of a 7-membered ring lactone, treatment of 15 with diborane in THF gave an open chain diol. This is the result of the equilibrium between the lactol and the open chain hydroxy aldehyde, C. D. Hurd and W. H. Saunders, J. Am. Chem. Soc., 74, 5324 (1952). The formation of the diol, thus precludes the formation of the intermediate cyclic enol ether.

5. Recently, Trost and co-workers[2a,b] have described a 1,2-carbonyl transposition based on sulfenylation of a ketone enolate with a disulfide to give an α-sulfenylated ketone. Mono and bis-sulfenylation of the 7-membered lactones 6 and 9 were successful. However, the subsequent steps described by Trost[2a,b] for conversion of these mono and di-sulfenylated ketones to the transposed ketones were unsuccessful, due to the opening of the 7-membered lactone during reduction, V. V. Kane and P. C. Ostrowski, unpublished work.

6. a) R. E. Ireland and G. Pfister, Tetrahedron Letters, 2145 (1969); b) M. Fetizon, M. Jurion and N. T. Anh, J. Chem. Soc., Part D, 112 (1969).

7. G. Zweifel and J. Plamondon, J. Org. Chem., 35, 898 (1970).

8. Satisfactory ^{1}H NMR, IR and mass spectral data were obtained for all compounds described in this communication, with the exception of 10 (nmr only).

9. All intermediates were purified using Silica gel column chromatography and yields mentioned are of pure products.

10. R. E. Ireland and J. A. Marshall, J. Org. Chem., 27, 1615 (1962).

11. The synthesis of lactones 9, 15 and 16 will be described in a subsequent paper.

12. Although we were able to purify the diethyl enol phosphate on a small scale by column chromatography on Silica gel (Baker), purification was not possible on a large scale (100 g, batch) leading instead to the lactone and unidentified polar compounds.

13. R. Ratcliffe and H. Rodehurst, J. Org. Chem., 35, 4000 (1970).

(Received in USA 23 April 1980)