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Conversion of Lactones into Substituted Cyclic Ethers

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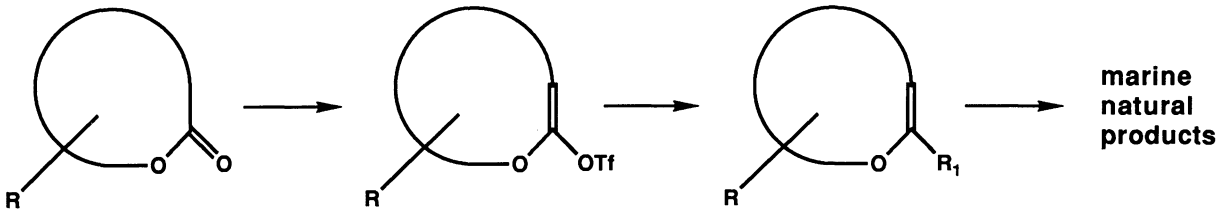
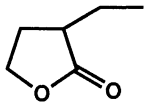
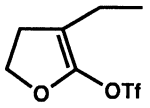
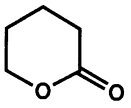
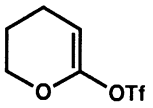
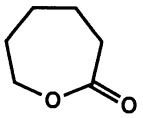
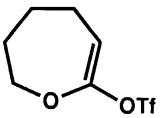
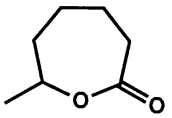
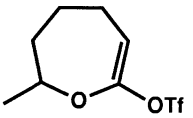
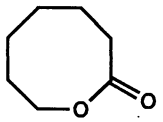
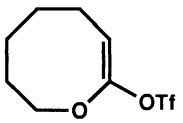
Lactone enolates were treated with N-phenyl triflimide in the presence of hexamethylphosphoric triamide to afford smoothly the corresponding enol triflates, which, on reaction with lithium dialkylcuprates, gave rise to alkylated cyclic ethers in good yields.

Enol trifluoromethanesulfonate (triflate) has now recognized widely as one of important functional groups in organic synthesis. While preparation and reactivity of enol triflates derived from aldehyde or ketone have been studied extensively, those from ester or lactone carbonyl compounds have not yet been reported.[1-3] In the course of synthetic studies on marine natural products including cyclic ether ring systems, we have investigated a new synthetic strategy involving conversion of lactones into substituted cyclic ethers via enol triflates, whose results are described in this communication. Our synthetic strategy is shown below.



After many fruitless attempts, we found a new reaction condition for preparation of enol triflate starting with lactone in a stable state. A general procedure is as follows: To a solution of ε-caprolactone (342 mg, 3.0 mmol) in tetrahydrofuran (THF) (2 ml) was added a solution of lithium hexamethyldisilazide (LiHMDS) (3.9 mmol) in THF (10 ml) and hexamethylphosphoric triamide (HMPA) (807 mg, 4.5 mmol) at -78 °C, and the solution was stirred at -78 °C for 2 h. A solution of N-phenyl triflimide ($PhNTf_2$) (1.28 g, 3.6 mmol) in THF (5 ml) was then added and the mixture was stirred at 0 °C for 1 h and 20 °C for 2 h. After evaporation of the solvents *in vacuo*, the oily residue was extracted with hexane (3 x 8 ml). The extracts were concentrated *in vacuo* to yield the crude lactone enol triflate (2c, 752 mg), which contained 12.6% of HMPA (checked by 400 MHz ^{1}H NMR spectrometer). Therefore, the yield of 2c was calculated as 89%. 2c: MS, m/z 246 (M^+, 8.8%), 69 (25.0), 55 (100.0), and 41 (70.9); IR (neat), 2940, 1705, 1430, and 1145 cm^{-1}; ^{1}H NMR [400 MHz, $(CD_3)_2CO$], δ1.63-1.93 (4H, m), 2.16 (2H, dt, J=6.3 and 5.4 Hz), 4.14 (2H, dd, J=4.9 and 5.4 Hz), and 5.14 (1H, t, J=6.3 Hz). We applied the reaction condition to several lactones. The results are summarized in Table 1. The data

Table 1. Conversion of lactones into triflates

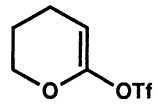
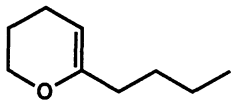
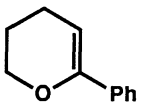
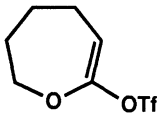
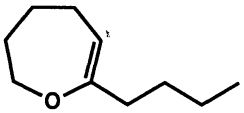
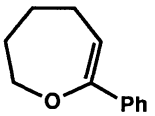
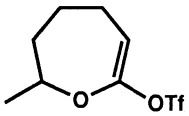
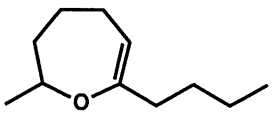
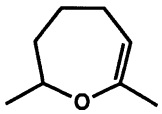
Run	Lactone	Enol triflate	Yield/%[a]
1	 1a	1. LiHMDS/THF-HMPA 2. $PhNTf_2$	 2a	32 (64)[b]
2	 1b		 2b	75
3	 1c		 2c	89
4	 1d		 2d	95
5	 1e		 2e	0

a) Since each product contains a trace amount of HMPA, the yield in the Table is estimated by 400 MHz ^{1}H NMR analysis. b) The value in parenthesis denotes the yield based on the recovered starting material.

indicate that (i) six- or seven-membered lactones could be converted efficiently to the corresponding enol ethers (runs 2,3, and 4); (ii) although the reaction with five-membered lactone (1a) proceeded completely, the desired product (2a) was isolated only in a poor yield because of its labile property (run 1);[4] (iii) eight-membered lactone (1e) led to no production of 2e under the present conditions, resulting in oligomerization (run 5); (iv) a trace amount of HMPA is indispensable for stocking the enol triflates in a stable state.

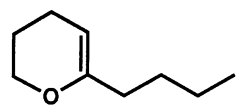
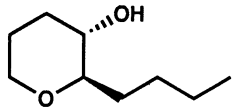
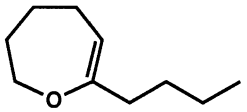
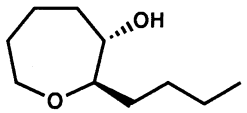
Enol triflates obtained thus were smoothly coupled without further purification with various lithium dialkylcuprates (R_2CuLi)[5] to give the corresponding α-alkylated cyclic enol ethers in good yields, respectively, as summarized in Table 2. A typical reaction is as follows: Enol triflate (2c) (crude 563 mg, net 2.0 mmol) in THF (4 ml) was added at -50 °C to a solution of lithium dibutylcuprate prepared freshly from 1.5 M butyllithium in hexane (6.7 ml, 10.0 mmol) and copper(I) iodide (1.05 g, 5.5 mmol) in THF (15 ml) at 0 °C and the mixture was stirred

Table 2. Conversion of lactone enol triflates into alkylated cyclic enol ethers

Run	Enol triflate	R_2CuLi	Product	Yield/%
1	 **2b**	Bu_2CuLi	 **3b**	65
2		Ph_2CuLi	 **3e**	40
3	 **2c**	Bu_2CuLi	 **3c**	60
4		Ph_2CuLi	 **3f**	71
5	 **2d**	Bu_2CuLi	 **3d**	72
6		Me_2CuLi	 **3g**	58

at 0 °C for 12 h. After concentration of the solution in vacuo, the residue was extracted with hexane (3 x 10 ml) and the extracts were filtered through a pad of neutral alumina to afford 3c (183 mg, 60% yield). 3c: MS, m/z 154 (M^+, 8.1%), 112 (100.0), 97 (47.9), and 55 (99.0); IR (neat), 2935, 1680, and 1170 cm^{-1}; ^1H NMR [400 MHz, $(CD_3)_2CO$], δ0.88 (3H, t, J=7.3 Hz), 1.25-1.62 (8H, m), 1.78 (2H, dt, J= 5.5 and 11.0 Hz), 1.95 (2H, t, J=7.3 Hz), and 4.69 (1H, t, J=5.5 Hz). The data in Table 2 reveal that the reaction proceeded as expected in each case. These enol ethers were transformed naturally by hydroboration followed by oxidation into trans-α-alkyl-β-hydroxy cyclic ethers in moderate yields, respectively (Table 3). These whole results would be valuable as providing a new general strategy for the synthesis of various marine natural products with cyclic ether ring systems,[6] and further extention is now under investigation.

Table 3. Hydroboration reaction of α-alkylated cyclic enol ethers

Run	Cyclic enol ether	Product	Yield/%
1	 3b	1. $BH_3 \cdot Me_2S$ 2. H_2O_2, NaOH  4b	45
2	 3c	 4c	30

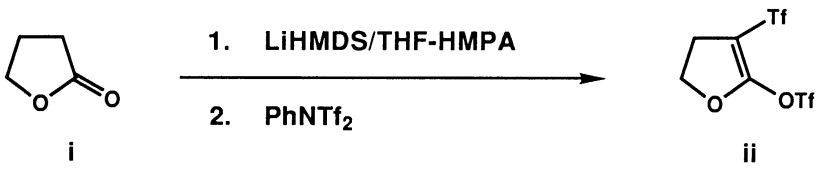
References

1) J. E. McMurry and W. J. Scott, Tetrahedron Lett., 21, 4313 (1980); 24, 979 (1983).

2) S. Cacchi, E. Morera, and G. Ortar, Tetrahedron Lett., 25, 2271 (1984); 26, 1109 (1985).

3) For a recent review on the conversion of ketones into olefins via the corresponding enol triflates, see W. J. Scott and J. E. McMurry, Acc. Chem. Res., 21, 47 (1988).

4) Reaction of γ-butyrolactone (i) with LiHMDS in THF-HMPA, followed by $PhNTf_2$ under the same conditions in the text afforded 2-trifluoromethanesulfonyloxy-3-trifluoromethanesulfonyl-4H,5H-dihydrofuran (ii) in 43.1% yield, along with the recovered starting material (i, 40.0%).



i ii

Usual conditions with use of lithium diisopropylamide only in THF led to almost the same results as above, no trace amount of the desired enol triflate being detected.

5) For a review of organocuprate coupling reactions, see G. H. Posner, Org. React., 22, 253 (1975).

6) Cf., K. L. Erickson, "Constituents of Laurencia," in "Marine Natural Products, Chemical and Biological Perspectives," ed by P. J. Scheuer, Academic Press, New York (1983), Vol. 5, Chap. 4, pp. 131-257.

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