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REGIOSELECTIVE RING OPENING OF UNSYMMETRICAL CYCLIC ETHERS WITH THE $AlCl_3$-NaI-ACETONITRILE SYSTEM: APPLICATION TO HYDROXYLATION OF *ent*-KAURENE.

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Summary: Unsymmetrically substituted 5-membered cyclic ethers were effectively cleaved with the $AlCl_3$-NaI-CH_3CN system at the less hindered carbon atom to afford δ-iodoalcohols. Conversion of *ent*-kaurene to *ent*-14α- and *ent*-12β-hydroxykaurene was achieved through the ring opening of the cyclic ether with the present system as a key step.

A number of combination systems of a hard Lewis acid and a soft nucleophile have been developed for cleavage reactions of various carbon-oxygen bonds.[1] Very recently, we reported the selective demethylation of aliphatic methyl ethers in the presence of an aromatic methyl ether with an $AlCl_3$-NaI-CH_3CN combination system.[2] This system was found to be effective for the ring opening of 5-membered cyclic ethers giving δ-iodoalcohols. Here we describe the regioselective ring opening of unsymmetrical 5-membered cyclic ethers with this system and its application to the functionalization at C(12) and C(14) of *ent*-kaurene.

2-Substituted tetrahydrofurans were easily cleaved to furnish δ-iodoalcohols in high yield as shown in Table, when treated with $AlCl_3$ and NaI in acetonitrile. Benzoate (run 4) required a longer reaction time than 2-benzyltetrahydrofuran (run 3), because aluminum chloride was consumed by a coordination with oxygen atoms in the molecule. An S_N2 character of this reaction can be assumed by the formation of the products in which the less hindered C(5) was attacked by iodide ion regioselectively. Several reagent systems including AcOTs,[3] $MgBr_2$-Ac_2O,[4] and RCOCl-Pd(II)-R_3SnX[5] have been reported for the cleavage of 2-methyl-tetrahydrofuran (1). In all cases, the product 2 arising from the C-O bond cleavage at the more substituted site

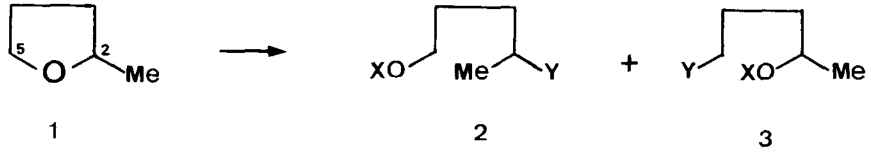
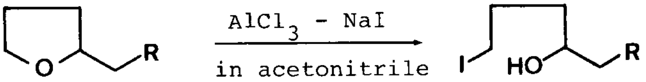


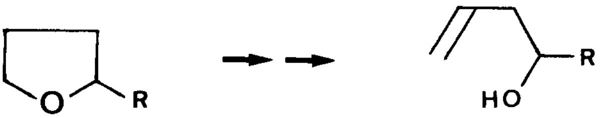
Table. Regioselective Ring Opening Reaction of 2-Substituted Tetrahydrofurans



Substrate R	Reagent[a] (mol. equiv.)	Temperature	Time	Yield[b] (%)
H	1.5	r.t.	5 h	76[c]
H	5	0°C	2 h	∿ 100[c]
Ph	5	r.t.	40 min.	88
OCOPh	5	r.t.	4 h	95

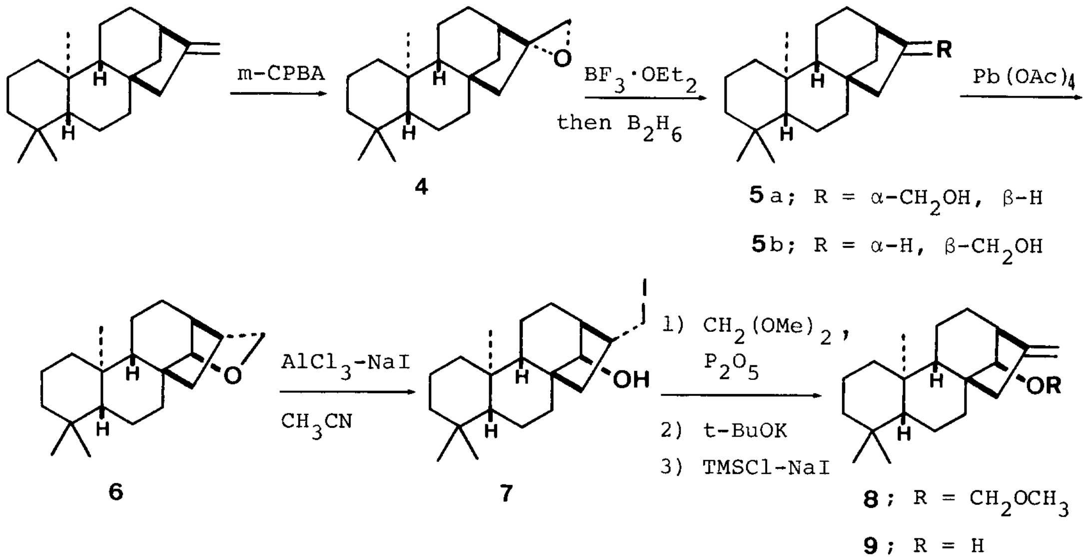
a) Equivalent molar amount of aluminum chloride and sodium iodide were used. About 1 ml of acetonitrile was used for 1 mmol of substrate. b) Isolated yield. c) Crude yield of the material pure on the NMR spectrum.

was obtained predominantly or exclusively. The only exception reported involves the pivaloyl chloride-NaI system,[5] with which the cleavage of the ether bond in 2-methyltetrahydrofuran (1) occurred at the less hindered C(5) to give 3 ($X=CO^tBu$, Y=I). Difficulties involve the hydrolysis of acylated δ-iodoalcohols with a base to obtain unprotected alcohols, since recyclization to the parent ether is generally observed under the basic conditions. Although the ring opening mode with our reagent system is the same as the latter, the advantage exists in obtaining the unprotected δ-iodoalcohol directly. If elimination of hydrogen iodide from the resulting δ-iodoalcohol can be achieved, the overall process constitutes of the regioselective transformation of tetrahydrofuran derivatives to homoallylic alcohols (eq 1). This sequence of the reactions was utilized for the hydroxylation of *ent*-kaurene.

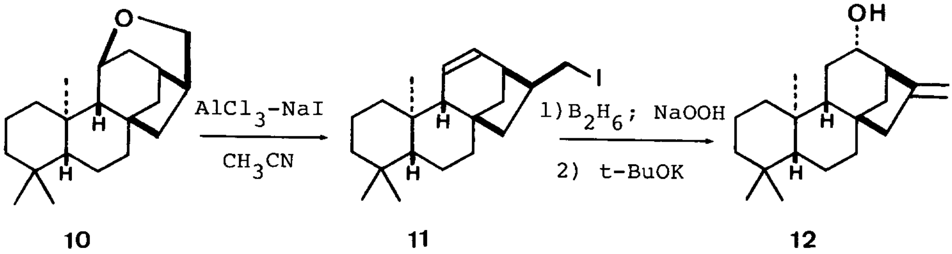


(eq. 1)

The epoxide 4[7] was converted to a 4:1 mixture of 5a[8] and 5b[9] in 82% overall yield from *ent*-kaurene on refluxing with $BF_3\cdot OEt_2$ in tetrahydrofuran for 15h[10] under nitrogen followed by reduction with B_2H_6 in one-pot. Treatment of 5a with $Pb(OAc)_4$ in a refluxing mixture of cyclohexane-benzene (1:1) for 1.5h afforded the cyclic ether 6[8] in 35% yield. The regioselective ring opening reaction of 6 with the $AlCl_3$-NaI-CH_3CN system proceeded easily at room temperature for 3h to afford 7 in 95% yield. Protection of a hydroxyl group at C(14) with a methoxymethyl group,[11] and elimination of hydrogen iodide with *t*-BuOK in dimethyl sulfoxide converted 7 to 8 in 87% overall yield. The desired *ent*-14α-hydroxykaurene(9)[8] was obtained by removal of the protecting group with trimethylsilyl chloride and sodium iodide.[12]



Generally, 6-membered cyclic ethers are stable with this reagent system. Cyclic ether 10,[13] however, provided 11[8] in 84% yield by the use of 20 eq. of reagents at room temperature for 3h, where the resulting hydroxyl group was eliminated under the reaction conditions. The preparation of 10 was achieved in 75% overall yield from *ent*-kaurene by the slight modification of the reported method.[14] Iodoolefin 11 was converted to the desired *ent*-12β-hydroxykaurene(12)[15] by hydroboration in refluxing tetrahydrofuran followed by elimination of hydrogen iodide in 63% overall yield.



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