Tetrahedron Letters, Vol. 33, No. 46, pp. 7003-7006, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

# REGIO- AND STEREO-CONTROLLED SYNTHESIS OF BICYCLIC α-METHYLENE-γ-BUTYROLACTONES CONTAINING A FLUORINE *VIA* HALOFLUORINATION-RADICAL CYCLIZATION

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***SUMMARY***: 3-Alkoxycycloalkenes undergo regio- and stereoselective halofluorination with pyridinium poly(hydrogen fluoride) and 1,3-dibromo-5,5-dimethylhydantoion or *N*-iodosuccinimide to give (1*S**,2*S**,3*S**)-1-alkoxy-3-fluoro-2-halocycloalkanes in good yields. Among the halofluorides, the 3-(2-propynyloxy) derivatives are in turn converted into bicyclic α-methylene-γ-butyrolactons containing a fluorine via radical cyclization followed by oxidation, leading to a stereospecific synthesis of (±)- 4-fluoro-1-*epi*-damsin.

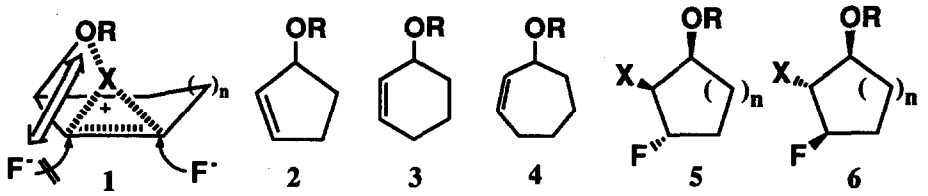
In conjunction with the rapidly growing interests in the field of specifically fluorinated bioactive compounds, natural products containing α-methylene-γ-butyrolactones have still received considerable attention due to the potentiality as drugs.[1] Among derivatizations, fluorination at the neighborhood of the unsaturation is important from the standpoint of modification and appearance of new biological activities due to the physical and biological properties imparted by fluorine,[2] although regio- and stereo-controlled introduction of a fluorine atom into a prototype molecule has not always been readily accomplished. For the introduction of a fluorine atom into a molecule, halofluorination[3] of an unsaturation is one of the methodologies of choice due to the highly selective *anti*-addition of an X-F species. In the addition of an X-F species to an olefin, the substituent at the neighborhood of the olefin is expected to effect the regio- and stereochemical course of the halofluorination, *e. g.*, the steric and electronic factors created by the allylic alkoxy substituent. Namely, as depicted in a plausible intermediate **1** in the initial step of the halofluorination of 3-alkoxycycloalkene **2-4**, the coordination of the hypohalite to the olefin and the oxygen would occur from the same side of the alkoxy substituent. In the second step, the fluoride ion can attack at the γ-carbon from the alkoxy functionality owing to the steric as well as electronic repulsion caused by the alkoxy substituent, leading to the selective formation of the halofluoride **5**. We would like to describe herein that based on the above assumption a regio- and stereo-controlled halofluorination of 3-alkoxycycloalkene **2-4** with pyridinium poly(hydrogen fluoride) ($(HF)_n$·Py ) and 1,3-dibromo-5,5-dimethylhydantoion (DBH) or *N*-iodosuccinimide (NIS) proceeds to give (1*S**,2*S**,3*S**)-1-alkoxy-3-fluoro-2-halocycloalkane **5** with high selectivity.

Treatment of 3-benzyloxycyclopentene **2a** with 2 equivalents of $(HF)_n$·Py and 2 equivalents of NIS in dichloromethane at -60°C-room temperature for 12 hr followed by quenching the reaction with aq. KF solution and the normal workup gave the iodofluoride **5a** (n = 1) and **6a** (n = 1) in 67 % yield with a ratio of 81 : 19 (Table 1, Entry 1). The iodofluorination using NIS gave better yields than the bromofluorination with DBH. The reaction solvent appears to be important in the cases with five- and six-membered derivatives **2b** and **3b**, and a better selectivity was obtained when the halofluorination was carried out in carbon tetrachloride, where

**Table 1. Halofluorination of 3-Alkoxycycloalkene 2-4[a)]**

| Entry | Substrate | R | NIS or DBH | X | Solvent | Temp/°C | Yield of 5&6/%[b)] | 5 : 6 |
|---|---|---|---|---|---|---|---|---|
| 1 | 2a | $CH_2Ph$ | NIS | I | $CH_2Cl_2$ | -60-rt | 67 | 81 : 19[c)] |
| 2 | 2a | $CH_2Ph$ | DBH | Br | $CH_2Cl_2$ | -60-rt | 33 | 87 : 13[c)] |
| 3 | 3a | $CH_2Ph$ | NIS | I | $CH_2Cl_2$ | -60--5 | 65 | 78 : 22[d)] |
| 4 | 3a | $CH_2Ph$ | DBH | Br | $CH_2Cl_2$ | -60--3 | 41 | 68 : 32[e)] |
| 5 | 4a | $CH_2Ph$ | NIS | I | $CH_2Cl_2$ | -78-rt | 89 | >99 : <1[c,e)] |
| 6 | 2b | $CH_2C{\equiv}CH$ | NIS | I | $CH_2Cl_2$ | -15-rt | 73 | 79 : 21[c)] |
| 7 | 2b | $CH_2C{\equiv}CH$ | DBH | Br | $CH_2Cl_2$ | -20-rt | 62 | 81 : 19[c)] |
| 8 | 2b | $CH_2C{\equiv}CH$ | DBH | Br | $CCl_4$ | -20-rt | 68 | 86 : 14[c)] |
| 9 | 3b | $CH_2C{\equiv}CH$ | NIS | I | $CH_2Cl_2$ | -20--5 | 73 | 71 : 29[d)] |
| 10 | 3b | $CH_2C{\equiv}CH$ | NIS | I | $CCl_4$ | -20--3 | 60 | 83 : 17[e)] |
| 11 | 4b | $CH_2C{\equiv}CH$ | NIS | I | $CH_2Cl_2$ | -78-0 | 78 | >99 : <1[c,e)] |
| 12 | 4b | $CH_2C{\equiv}CH$ | DBH | Br | $CH_2Cl_2$ | -60-5 | 45 | 83 : 17[d)] |
| 13 | 4c | $CH_2C{\equiv}CTBDMS$ | NIS | I | $CH_2Cl_2$ | -15-0 | 94 | >99 : <1[c,e)] |
| 14 | 4c | $CH_2C{\equiv}CTBDMS$ | DBH | Br | $CH_2Cl_2$ | -60-0 | 80 | 79 : 21[c)] |

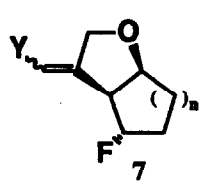
a) All the reactions were performed on a 0.3-1.0 mmol scale with a reactant ratio of the substrate : hypohalite : $(HF)_n$·Py = 1 : 2 : 2. b) Isolated yields by TLC. c) Determined by GLC. d) Determined after separation on TLC. e) Determined by 270 MHz $^1$H NMR.




**R = a: $CH_2Ph$, b: $CH_2C{\equiv}CH$, c: $CH_2C{\equiv}CTBDMS$**

ca. 85 : 15 stereoisomeric ratio of the halofluorides was obtained for 3-(2-propynyloxy)-cyclopentene and -cyclohexene (Entries 8 and 10). An excellent selectivity was observed in the cases of 3-alkoxycycloheptene **4**, and (1*S**,2*S**,3*S**)-1-alkoxy-3-fluoro-2-iodocycloheptane **5** (n = 3) was obtained as a sole product in a good yield (Entries 5, 11, and 13). The TBDMS-protected derivative **4c** enhanced the product yields without loss of the regio- and stereoselectivity (Entries 13 and 14), and the TBDMS group was readily removed as described later.

The regio- and stereoselective halofluorination can be used for the selective construction of α-methylene-γ-butyrolactone bearing a fluorine at the *anti*-homoallylic position via radical cyclization[4] followed by oxidation.[5] Radical cyclization of the 3-(2-propynyloxy) derivatives **5b** (n = 1-3, X = Br or I) with a catalytic amount of tributyltin chloride and a stoichiometric amount of sodium cyanoborohydride in the presence of a catalytic amount of AIBN in refluxing *t*-BuOH for 3 hr gave the cyclized fluoride **7** (n = 1-3, Y = H) in 44 -56 % yields, and the stereochemistry at the newly formed C-C bond was *cis* to the alkoxy group. In this radical cyclization the silyl-protected derivative **4c** (X = I) gave **7** (n = 3, Y = TBDMS) in 97% yield, and the desilylation was readily conducted with an excess of $(HF)_n$·Py in dichloromethane at -15 °C for 50 hr to give **7**

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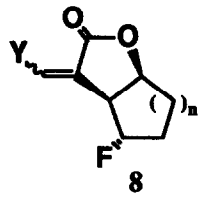


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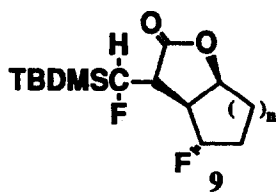


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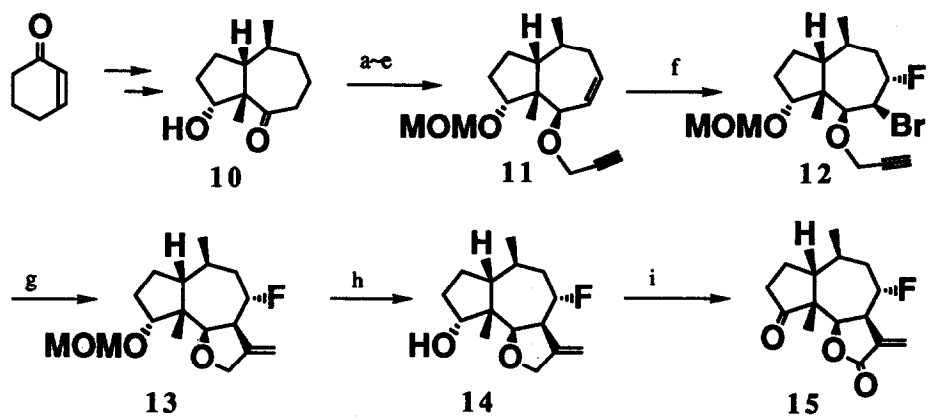
(n = 3, Y = H) in 93% yield. Oxidation of **7** (n = 1-3, Y = H) at the allylic position was readily carried out with chromium trioxide-pyridine in refluxing dichloromethane for 1 hr to give α-methylene-γ-butyrolactone **8** (n = 1-3, Y = H) in 44-66 % yield. Oxidation of the silyl substituted derivative **7** (n = 3, Y = TBDMS) also gave the butyrolactone **8** (n = 3, Y = TBDMS) in 82 % yield, which underwent addition of a fluoride anion to give **9** (n = 3) in 97 % yield upon treatment with 2 equivalents of tetra-*n*-butylammonium fluoride in THF at 0 °C.

The application of the present methodology was successfully demonstrated in the synthesis of a pseudoguaianolide skeleton containing a fluorine. The starting allyl 2-propynyl ether **11** was readily prepared from the octahydroazulene derivative **10**.[6] The transformations involving the protection of the hydroxyl group, the introduction of an unsaturation,[7] the reduction of the ketone,[8] and the 2-propynyl etherification gave **11** as a single stereoisomer. Initial examination with iodofluorination met with a disappointing result, and the starting allyl 2-propynyl ether **11** was recovered intact. However, the 2-propynyl ether **11** underwent bromofluorination in a stereo- and regiospecific manner to give the bromofluoride **12** as a single isomer in 61 % yield. Radical cyclization proceeded smoothly to give the cyclized product **13** in 70 % yield. After deprotection of the MOM group, the alcohol **14** was oxidized with the Collins reagent to give (±)-4-fluoro-1-*epi*-damsin **15**[9] in 52 % yield. The structure of **15**[10] was unambiguously established by $^{13}C$ NMR, $^{1}H$ NMR, and an NOE measurement, showing that the stereochemical integrity of the halofluoride **12** was not affected

**Scheme 1**[a]




[a] (a) NaH, cat. 18-crown-6, MOMCl, THF, rt, 24h, 42%; (b) LDA, $Me_3SiCl$, THF, -78 °C-rt, 3 hr; (c) $Pd(OAc)_2$, *p*-benzoquinone, MeCN, rt, 35 hr, 87% for two steps; (d) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C, 30 min, 60%; (e) $KN(SiMe_3)_2$, propargyl bromide, THF, 0 °C-rt, 3 hr, 75%; (f) DBH, $(HF)_n \cdot Py$, $ClCH_2CH_2Cl$,-60 °C-rt, 5.5 hr, 61%; (g) $NaBH_3CN$, cat. *n*-$Bu_3SnCl$, cat. AIBN, *t*-BuOH, 83 °C, 4 hr, 70%; (h) 6M HCl, THF, rt, 15.5 hr, 80%; (i) $CrO_3$, Py, $ClCH_2CH_2Cl$, rt-55 °C, 4 hr, 52%.

during the radical cyclization and oxidation processes: As shown in Fig.1, irradiation of the angular methyl group and $H_b$ resulted in 5 and 25 % enhancement of $H_c$ and $H_a$ signals, respectively.

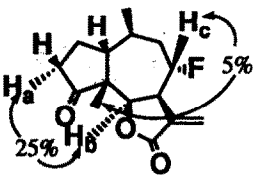


Fig. 1

Since the biologically active compounds possessing α-methylene-γ-butyrolactone skeletons are widespread and many of them pose a problem of the liability of the particular methylene moiety towards metabolism, the present methodology on a stereoselective approach to α-methylene-γ-butyrolactones containing a fluorine in a regio- and stereocontrolled fashion based on the directing ability of the allylic alkoxy group affords one of the solutions of modifying the substrate. Although the halofluorination of an olefin offers a straightforward approach to a fluorine-containing molecule, the application of the obtained halofluoride to further functional group manipulations has not been studied well. The high regio- and stereoselectivity in the present system coupled with the ready experimental procedure and availability of the starting allyl 2-propynyl ethers may broaden the applicability of this methodology to the construction of a variety of ring systems containg a fluorine from halofluorides.

**Acknowledgment:** The present work was partially supported by a grant from the Okasan-Kato Foundation.

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10. Mp 181-183 °C (from $Et_2O$); $^1H$ NMR (270 MHz, $CDCl_3$) δ 1.04 (d, 3H, $J$ = 6.60 Hz), 1.10 (s, 3H), 1.20-2.27 (m, 7H), 2.52-2.62 (m, 1H), 3.24-3.37 (m, 1H), 4.05 (dd, 1H, $J$ = 10.22 and 1.65 Hz), 4.88 (dm, 1H, $J$ = 49.15 Hz), 5.96 (d, 1H, $J$ = 2.64 Hz), 6.32 (dd, 1H, $J$ = 2.64 and 1.65 Hz); IR ($CHCl_3$) 2950, 2875, 1780, 1758, 1610, 1470, 1420, 1300, 1285, 1140, 1020, 980, and 970 $cm^{-1}$.

(Received in Japan 3 July 1992)