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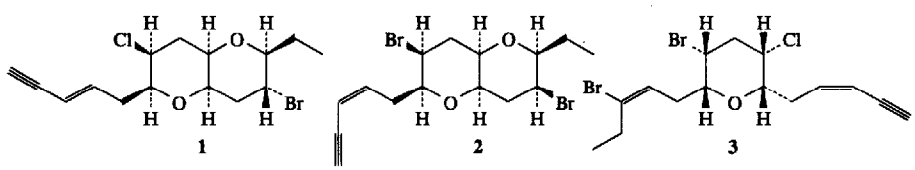
Stereocontrolled Synthesis of Chiral Nonracemic Halotetrahydropyrans

Victor S. Martín* and José M. Palazón
Centro de Productos Naturales Orgánicos "Antonio González"
Instituto Universitario de Bio-Orgánica
Carretera la Esperanza, 2
38206 La Laguna, Tenerife, SPAIN

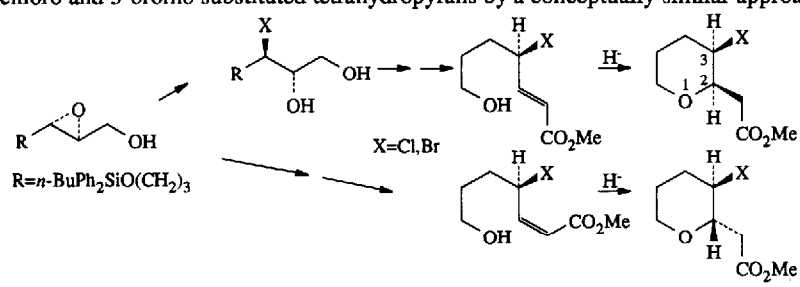
Abstract: The stereoselective synthesis of enantiomerically enriched *endo*-substituted halotetrahydropyrans by an intramolecular Michael addition of a suitable chiral γ-halo-α,β-unsaturated ester is described.

In the course of our programme directed towards the total synthesis of marine natural compounds[1] we have focussed our attention mainly in those containing polyfunctionalized cyclic ethers.[2] Of particular interest for us is a series of products containing halo-substituted tetrahydropyrans such as 3-*E*-dactomelyne[3] **1**, 3-*Z*-elatenyne[4] **2** and dactyline[5] **3**.



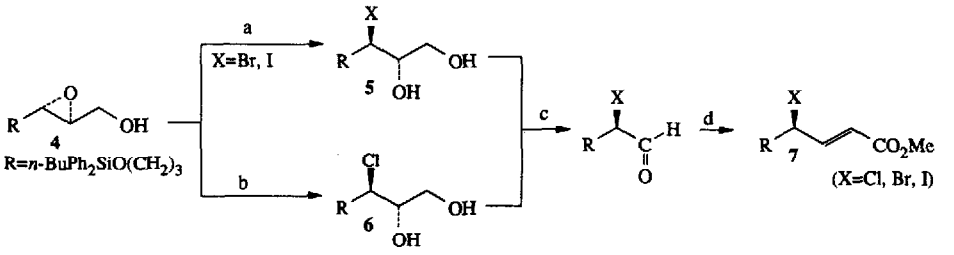
The structural features of such compounds together with the unknown biological activities make them very attractive targets for studies directed to their total synthesis. A challenging aspect to consider is the stereoselective introduction of the suitable halogen (Cl, Br) in the tetrahydropyran unities. To the best of our knowledge this synthetic problem has not been completely satisfactorily resolved.[6]

Very recently,[2a] we have described a procedure to synthesize enantiomerically enriched tetrahydropyrans functionalized with an ester in the C-3 position, making use of an intramolecular Michael type addition of a suitable α,β-unsaturated ester, controlling the ring closure stereochemistry by the proper choice of the double bond geometry. In this paper we present our results directed to the stereocontrolled synthesis of 3-chloro and 3-bromo substituted tetrahydropyrans by a conceptually similar approach.



In order to develop the idea we prepared the (*E*)-α,β-unsaturated esters **7** according to **Scheme I.**

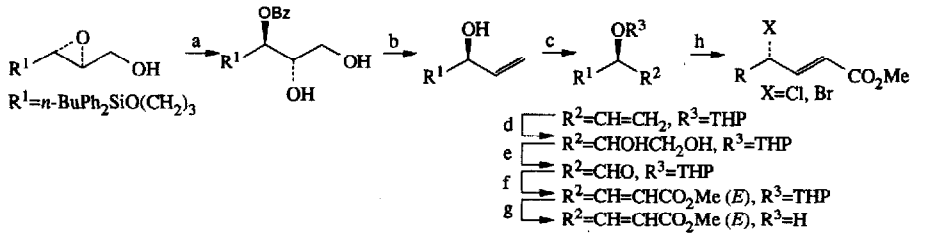
Scheme I



a) X_2-Ti(OPr-*i*)$_4$, CH_2Cl_2, 0°C, 86 % (X=Br), 78% (X=I); b) TiCl(OPr-*i*)$_3$, CH_2Cl_2, 0°C, 89%; c) $NaIO_4$, THF-H_2O (5:1) (no purification); d) $(MeO)_2P(O)CH^-CO_2Me$, toluene, -78°C (see text), 85% (X=Cl), 87% (X=Br), 75% (X=I), in both steps.

Although the cyclization step was performed only with the bromine and chlorine derivatives, this sequence was also extended to the iodine product. The regioselective opening of the epoxide **4** $[\alpha]_D^{25}$ -10.3° (c 2.3, $CHCl_3$) (>95% ee) was performed using a X_2-Ti(OPr-*i*)$_4$ mixture[7] in order to obtain the corresponding bromo and iodo halohydrins **5**. On the other hand, the chlorohydrin **6** was obtained using TiCl(OPr-*i*)$_3$ as the opening reagent.[8] Oxidative cleavage and Wadsworth-Emmons (Horner) reaction yielded the desired (*E*)-esters **7**. When the Wittig modification was performed at 0°C, complete racemization was obtained in the iodine case, as indicated by an $[\alpha]_D^{25}$ of zero. Although the optical rotation of the other cases (Cl, Br) was different to zero this result alerted us over a possible racemization. In order to analyse the enantiomeric excess, a known stereochemically controlled synthesis of such α,β-unsaturated esters was performed (**Scheme II**). Removal of the silyl protecting group [HF, CH_3CN, 94% (X=Cl), 89% (X=Br)] and analysis of the Mosher's esters[9] by high resolution NMR (400 MHz) showed a partial racemization (**Table I**).

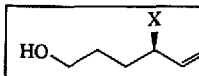
Scheme II



a) Ti(OPr-*i*)$_4$, PhCOOH, CH_2Cl_2, 0°C, 93%; b) i)MsCl, Et_3N, CH_2Cl_2, 0°C; ii) NaI, DMF, 80°C, 65% overall; iii) NaOMe, CH_2Cl_2, 0°C, 93%, c) DHP, CH_2Cl_2, CSA (cat), 95%; d) OsO_4, TBHP, CH_2CL_2, rt, 86%; e) $NaIO_4$, MeOH, 0°C; f) $(MeO)_2P(O)CH^-CO_2Me$, benzene, rt, 85% overall; g) MeOH, H^+ (cat), 93%; h) i)MsCl, Et_3N, CH_2Cl_2, 0°C; ii) LiX, DMF, rt, 78% (X=Cl), 74% (X=Br) overall.

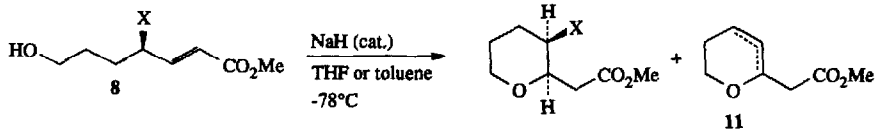
In order to overcome this problem the Wittig modification was performed at -78°C, in toluene.

Table I

	ee (0°C)	%ee (-78°C)	$[\alpha]_D^{25}$ (g/100mL, $CHCl_3$)
X=Cl	71	>94%	-8.4° (0.61)
X=Br	62	>94%	+6.8° (1.42)
X=I	0	–	–

Fortunately we found that at this temperature no substantial racemization occurred, obtaining α,β-unsaturated esters **7** of an enantiomeric purity almost identical with that obtained in the precursor 2,3-epoxy alcohols (**Table I**).

The cyclization reaction was performed over the free alcohol **8** in THF or toluene, at -78°C, yielding the *cis*-halopyrans **9**[11] and **10**[11] with no contamination of the *trans* isomer. A small amount (<5%) of the elimination products, easily removed by column chromatography, was detected when the solvents were not properly dried and/or the substrates were not desiccated by azeotropic distillation with benzene.

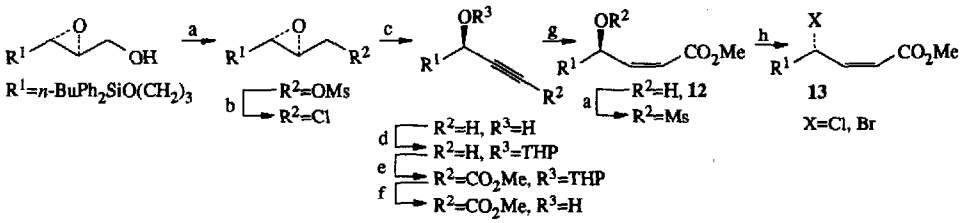


9, X=Cl 90%, $[\alpha]_D^{25}$ +5.3° (c 2.6, $CHCl_3$)

10, X=Br 81%, $[\alpha]_D^{25}$ +7.1° (c 1.3, $CHCl_3$)

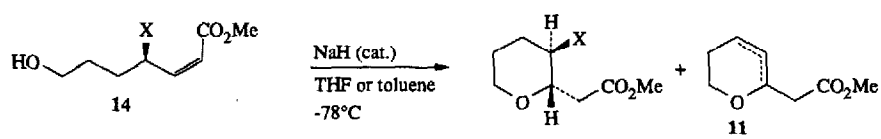
In order to achieve complete control over the cyclization step we prepared the (Z)-α,β-unsaturated ester **13** according with the **Scheme III**. The procedure makes use of the recently reported transformation of 1-chloro-2,3-epoxyalcohols into 3-propargylic alcohols.[10] The formation of the methyl propiolate under standard conditions, THP removal and Lindlar's hydrogenation afforded the alcohol **12** which after methylsulphonate derivatization was submitted to nucleophylic substitution with the suitable halide.

Scheme III



a) MsCl, Et_3N, CH_2Cl_2, 0°C; b) LiCl, DMF, rt, 83% overall; c) *n*-BuLi (3 equiv), THF , -35°C, 85%; d) DHP, PPTS (cat.), CH_2Cl_2, rt, 95%; e) *n*-BuLi, THF, -78°C, then $ClCO_2Me$, 83%; f) MeOH, HCl conc. (cat.), 94%; g) H_2, Lindlar, quinoline, AcOH, 89%; h) LiX, DMF, rt, 78% (X=Cl), 74% (X=Br) overall (a + h).

Finally, the free alcohol **14** was submitted to basic conditions (NaH, toluene, -78°C) yielding the expected *trans*-halopyrans **15**[12] and **16**[12] with no traces of the *cis* isomer. The same requirements of dryness of solvent and substrate were necessary to avoid contamination with the elimination products **11**.



15, X=Cl 90%, $[\alpha]_D^{25}$ +5.3° (c 2.6, $CHCl_3$)

16, X=Br 81%, $[\alpha]_D^{25}$ +7.1° (c 1.3, $CHCl_3$)

The application of the procedure to the enantiomeric total synthesis of dactyline **3** is underway and will be published elsewhere.

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11. **9**, ^{1}H-NMR (C_6D_6) δ: 0.80 (1H, m), 1.40 (1H, m), 1.77 (1H, m), 1.96 (1H, m) 2.49 (1H, dd, J = 16.3 and 5.5 Hz), 2.80 (1H, dd, J = 16.3 and 7.5 Hz), 3.09 (1H, ddd, J = 11.5, 11.5 and <2.5 Hz), 3.34 (3H, s), 3.73 (1H, m), 3.81 (1H, m), 3.86 (1H, s broad); ^{13}C-NMR (C_6D_6) δ: 19.98 (t), 31.98 (t), 38.92 (t), 51.29 (q), 59.79 (d), 68.32 (t), 75.59 (d), 171.12 (s); 10, ^{1}H-NMR (C_6D_6) δ: 0.86 (1H, m), 1.54 (1H, m), 1.90 (1H, m), 2.05 (1H, m), 2.51 (1H, dd, J = 16.4 and 5.4 Hz), 2.83 (1H, dd, J = 16.4 and 7.4 Hz), 3.15 (1H, ddd, J = 11.6, 11.6 and 2.5 Hz), 3.39 (sH, s), 3.61 (1H, ddd, J = 7.4, 5.4 and <2.5 Hz), 3.77 (1H, m), 4.1 (1H, ddd, J = 3.0, 3.0 and <2.5 Hz); ^{13}C-NMR (C_6D_6) δ: 20.70 (t), 32.71 (t), 40.76 (t), 51.33 (s), 55.18 (d), 68.44 (t), 75.58 (d), 171 (s).
12. **15**, ^{1}H-NMR (C_6D_6) δ: 1.01 (1H, m), 1.26 (1H, m), 1.48 (1H, m), 1.95 (1H, m), 2.53 (1H, dd, J = 15.5 and 8.9 Hz), 3.01 (1H, dd, J = 15.5 and 2.8 Hz), 3.03 (1H, ddd, J = 12.1, 12.1 and <2.5 Hz), 3.43 (3H, s), 3.44 (1H, m), 3.59 (1H, m), 3.84 (1H, ddd, J = 8.9, 8.9 and 2.8 Hz), ^{13}C-NMR (C_6D_6) δ: 27.21 (t), 34.87 (t), 38.67 (t), 51.35 (q), 58.67 (d), 67.85 (t), 79.85 (d), 171.1 (s); **16**, ^{1}H-NMR (C_6D_6) δ: 0.82 (1H, m), 1.17 (1H, m), 1.54 (1H, m), 1.92 (1H, m), 2.44 (1H, dd, J = 15.5 and 8.9 Hz), 2.96 (1H, ddd, J = 11.9, 11.9 and 2.2 Hz), 2.98 (1H, dd, J = 15.5 and 2.8 Hz), 3.32 (3H, s), 3.5 (1H, m), 3.52 (1H, m) 3.84 (1H, ddd, J = 8.9, 8.9 and <2.5 Hz); ^{13}C-NMR (C_6D_6) δ: 28.19 (t), 35.75 (t), 39.49 (t), 51.21 (q), 51.35 (d), 67.92 (t), 79.52 (d), 171.2 (s).
13. Satisfactory spectroscopic and analytic data for the new products were obtained.

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