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Iodocyclization of Olefinic t-Butyl Ethers : An easy Stereocontrolled Synthesis of Cis-Substituted Tetrahydrofurans.

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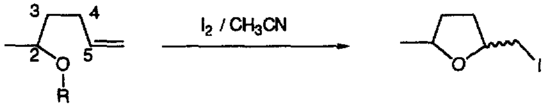
Key Words : Iodocyclisation. Olefinic t-Butyl ethers. Tetrahydrofurans. Tetrahydropyrans.

Abstract : The iodoalkoxylation of δ,ε olefinic t-butyl ethers leads, with a very high selectivity, to cis substituted tetrahydrofurans.

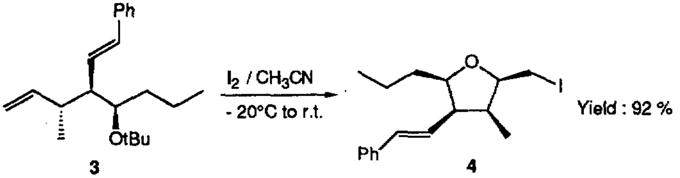
A particularly challenging aspect of the synthesis of polyether antibiotics[1], is the stereocontrolled construction of the substituted tetrahydrofuran unit found in many of these natural products, particularly those in which there is a cis relationship between substituents at the 2 and 5 positions. An elegant solution to this problem has been brought by Bartlett[2] who showed that in iodoalkoxylation cyclizations, the more bulky the ether, the better the diastereoselection :



1 2

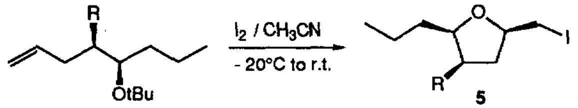
Cis / Trans ratio.	
R = Me	0.5
Bu	2
tBuPh$_2$Si	8
2,6 dichlorobenzyl	21

Curiously, one of the most promising candidate for this electrophilic internal addition, namely the t-butyl ether has not been tested, although such protection of an alcohol is much easier, general, and cheap when compared to the preparation of substituted 2,6 dichlorobenzyl ethers. We describe here, that such is indeed the case: starting from the t-butyl ether[3] of the preceding alcohol, we obtained the tetrahydrofurans (2) with a cis:trans ratio of 28:1. It occurs that protection of acetylenic alcohols as t-butyl ethers is of prime importance for subsequent carbocupration[4] or hydroalumination[5] of the triple bonds, leading to the desired starting material. Thus, their use for the cyclization according to the Bartlett procedure[2] in a straightforward way is to be considered. We recently disclosed an other application of this procedure[6].



3 4

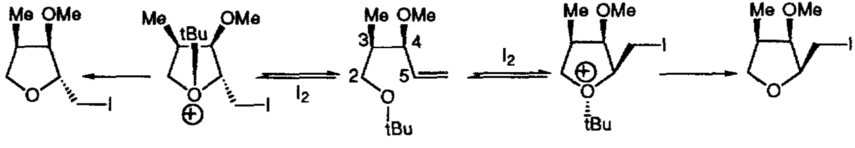
Compound (3) was directly submitted to iodine in acetonitrile[7] to give a single isomer whose NMR spectroscopy (NOE) proved that all substituents are located on the same face[8]. An intermediate case between disubstituted (2) and tetrasubstituted (4) cases shows a quantitative diastereoselection[9]: (5) is obtained as a single isomer :



5a R = Me. Yield : 94 %

5b R = styryl. Yield : 92 %

Subsequently, we have looked at the influence of substituents at C-3 and C-4 on the diastereoselection. Thus, starting with the ether (**6**)[10]: we observed an important drop of diastereoselection.



8 **6** **7**

The 60:40 ratio of (**7**:**8**), yield = 78%, shows that substituents on C-3 / C-4 are not involved in a steric interaction with a cis t-butyl moiety for the intermediate oxonium ion leading to **8**[11], as was the case for a C-2 substituent.

Iodocyclizations leading to tetrahydropyrans are less common than those leading to tetrahydrofurans[1], in general they proceed, quite predictably to give the equatorially substituted isomer whenever possible. The same holds true for t-butyl ethers.

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References and notes

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7. Typical procedure: To a solution of 5mmol of δ,ε olefinic t-Butyl ethers in 10 ml anhydrous acetonitrile is added, at -20°C, 1.5 eq.of iodine (7.5 mmol) in 10 ml CH_3CN. This solution, which turns instantaneously dark red, is stirred at -20°C during 3 hours and slowly warmed to room temperature overnight. 50 ml of ether and 10 ml of a saturated aqueous solution of $Na_2S_2O_3$ are added and the mixture is stirred until decoloration. The aqueous layer is extracted twice with 10 ml ether and the organic phases are dried over $MgSO_4$, then concentrated. The dark residue is purified by chromatography. The yield of the purified material is usually higher than 90 %.
8. The introduction of a styryl group was made purposedly so that all C-H signals of the tetrahydrofuran were perfectly separated in ^1H NMR: 7.32-7.19 (m,5H); 6.42 (d,1H,J = 15.6); 6.27 (dd, 1H,J = 15.6, J = 10.7); 4.29 (q,1H,J = 7.15); 3.95 (q,1H,J = 5.77); 3.2 (dd, 2H,J = 2.2, J = 7.43) 3 (dt, 1H,J = 10.72, J = 6.33); 2.55 (q,1H,J = 7.42); 1.65-1.1 (m,4H); 0.9 (d,3H,J = 6.33); 0.88(t,3H,J = 7) ^{13}C NMR: 137.2; 132.8; 128.6; 127.3; 126.7; 126.1; 81.6; 80.8; 51; 41.1; 34.4; 19.7; 14.2; 10.9; 6.
9. The pure products, isolated by chromatography on silica gel, gave satisfactory ^1H and ^{13}C NMR data. **5a**: ^1H NMR: 3.95-3.88 (m,2H) ;3.3 (dd,1H,J = 4.95, J = 9.9); 3.15 (dd,1H,J = 7.15, J = 9.9); 2.3-2.2 (m,2H); 1.48-1.20 (m,5H); 0.9 (d,3H,J = 7); 0.9 (t,3H,J = 7).^{13}C NMR: 85.9; 77.3; 40.0; 36; 33.2; 19.4; 14.6; 14.1; 10.8
   5b ^1H NMR: 7.3-7.19 (m,5H); 6.39 (d,1H,J = 15.7); 6.15 (dd,1H,J = 15.7, J = 9.53); 4-3.95 (m,2H); 3.4 (dd,1H,J = 5.13, J = 9.89); 3.24 (dd,1H,J = 6.96, J = 9.89); 3.08-3.04 (m,1H); 2.39-2.34 (m,1H); 1.66-1.59 (m, 1H); 1.51-1.25 (m, 4H); .87 (t,3H,J = 7).^{13}C NMR: 137.1; 130.7; 129.3; 128.5; 127.2; 126; 85.8; 77.9; 46.3; 38.8; 34.1; 19.4; 14.1; 10.4
10. Made by a metalla Claisen reaction, to be published shortly.
11. Treatment by DBU converts **7** to the exomethylene tetrahydrofuran whereas the minor isomer **8** remains intact.

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