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Stereoselective Allylic Transposition by means of Allylic *n*-Pentenyl Ethers

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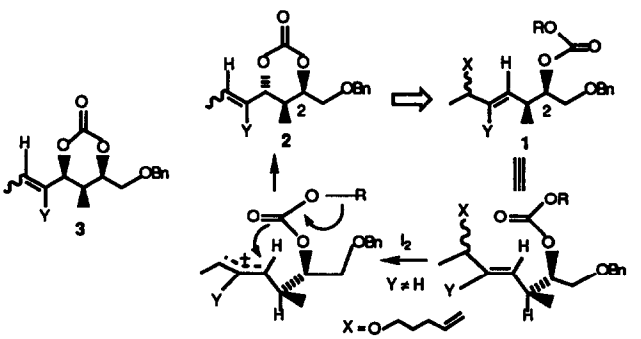
Abstract: *Stereospecific formation of optically active tetrahydrofurans and dihydropyrans was obtained via an allylic rearrangement by means of allylic n-pentenyl ethers.*

In our synthetic programm directed towards natural products, we were recently faced with the problem of having to perform an allylic transposition of **1**, with the stereospecific introduction of the C(4)-hydroxy group *anti* to the C(3)-methyl in **2** (Scheme 1).

Scheme 1

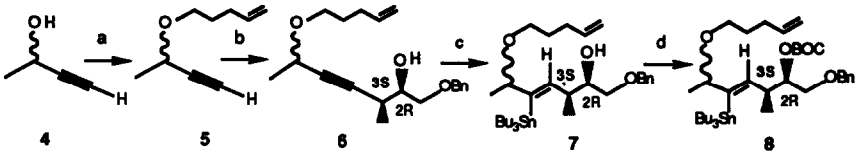


We anticipated that assistance from the C(2)-hydroxyl of **1** could be made by intramolecular cyclisation of its corresponding carbonate and with a suitable leaving group X. However, as presented in **1** (Y=H), such an approach could possibly lead to an undesired mixture of epimers **2** and **3**. On the other hand, by installation of a removable ligand in **1** (Y≠H), 1,3-allylic strain[1] would be imposed, forcing **1** into the conformation as indicated in Scheme 1, and thus favouring attack on the required α-face. In order to promote this cyclization, we required the formation of an initial allylic cation. To this end, *n*-pentenyl ethers (**1**, X=O-pentenyl), which previously have been employed by the group of Fraser-Reid as glycolisating agent in the presence of I^+, were explored.[2] In essence, the *n*-pentenyl group would serve as a dual purpose: initially as an O-protecting group, and eventually as as switch for the generation of an allylic cation on subjection to iodonium ions.

We wish to report our studies in this line and the unexpected findings that compounds of the type **1** (Y≠H) lead to the stereospecific formation of optically active tetrahydrofurans and dihydropyrans.

The required *n*-pentenyl ether **8** was easily obtained in four steps. Alkylation of racemic butyn-3-ol **4** with 1-tosyloxypenten-2-ene gave *n*-pentenyl ether **5**. Subsequent conversion to its corresponding alanate and treatment with 1-benzyloxy-2(*S*)-3(*S*)-epoxybutane[3] in the presence of BF_3: OEt_2,[4] afforded alcohol **6** as a 1:1 diastereomeric mixture, in 80% yield. Hydrostannylation[5] provided the *trans* alkene **7** in 84% yield, which was eventually transformed quantitatively to its BOC ester **8**, thus setting the stage for the allylic transposition studies.[6]

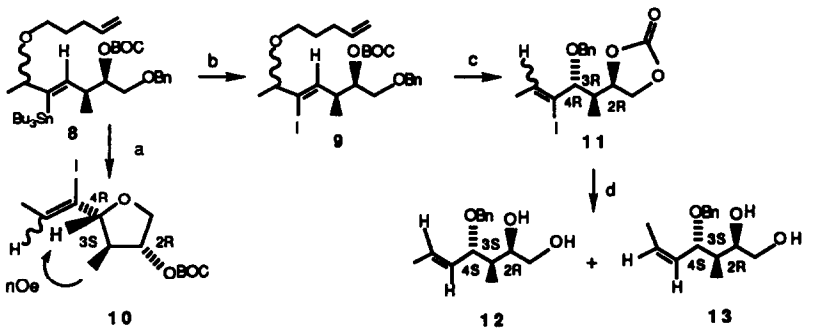
Scheme 2



a) HNA, 1.2 eq, DMF, 0°C, 20 min, then 1-tosyloxypent-4-ene, 1.2 eq, 0°C to rt, overnight, quantitative; b) *n*-BuLi, 1 eq, -78°C, 10 min, then $MeAl_3$, 1 eq, -35°C, 1 h, then, -78°C, 1-benzyloxy-2(*S*),3(*S*)-epoxybutane, 1 eq, 10 min, then BF_3,OEt_2, 1 eq, -78°C, 1h, 80%; c) *n*-Bu_3SnH, neat, 1 eq, AIBN, catalytic, 120°C, 3 h, 84%; d) *n*-BuLi, 1 eq, 0°C, 10 min, then $(BOC)_2O$, 1.2 eq, rt, overnight, quantitative.

Treatment of **8** with 4 equivalents of I_2 in acetonitrile, overnight, at room temperature, did not give rise to the expected carbonate, but, instead to the tetrahydrofuran **10**, in 86% yield, as single stereomer with respect to the three contiguous chiral centers. Benzyl iodide and 2-iodomethyltetrahydrofuran were also isolated. Cyclisation had apparently occurred with participation of the C(1)-benzyl ether and concommittant loss of CH_2Ph (Scheme 3). Such participation of ether oxygen in iodocyclisation reaction had been previously observed.[7]

Scheme 3



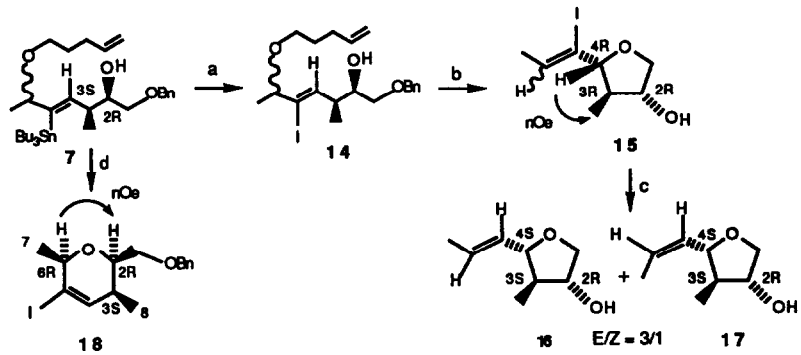
a) I_2, 4 eq, CH_3CN, $NaHCO_3$, excess, rt, overnight, 86%; b) I_2, 1.5 eq, CH_3CN, $NaHCO_3$, excess, -20°C, 15 min, quantitative; c) I(collidine)$_2^+$, BF_4^-, 4 eq, $CHCl_3$, 0°C, 3 d, 14 70%; d) *n*-BuLi, 3 eq, THF, -78°C, 90%.

On the other hand, examination of vinylstannane **8** by sequential treatment first with 1.5 equivalent of iodine[8] and then, an iodine free reagent, I(collidine)$_2$ tetrafluoroborate,[9] for three days, at room temperature, afforded the cyclic carbonate **11**,[10] in 70% yield. Shorter reaction times led to mixtures of **10** and **11**. ^1H NMR

analysis of **11** indicated that protons C(1)-H_2 (*ABX*, δ ppm: 4.24 and 4.49) and C(2)-H (*m*, δ ppm: 5.02) were esterified and not C(4)-H (*d*, δ ppm: 3.2). Information about the stereochemical outcome of the newly formed double bond of **11** was obtained by metallation[11] and subsequent protonation supplying a 3:1 mixture of the *trans* and *cis* compounds **12** and **13**, respectively, according to HPLC and ^{1}H NMR analyses.

In the absence of the BOC ester, subjection of alcohol **7** to first 1.5 equivalent of I_2 to give vinyl iodide **14** and then additionnal treatment with excess I_2, afforded a 86% yield of tetrahydrofuran **15**.[12] As with carbonate **11**, metallation and subsequent protonation supplied a 3:1 mixture of the *trans* and *cis* compounds **16**[13] and **17**.[14] Catalytic hydrogenation of both **16** and **17** afforded the same dihydro derivative, ($[\alpha]_D$=-16.4, $CHCl_3$, c=0.5). Quite surprising, by the use of I(collidine)$_2$ perchlorate,[8] dihydropyran **18**[15] could be isolated in 48% yield. In this case, the C(2)-hydroxyl had attacked at C(6) (Scheme 4).

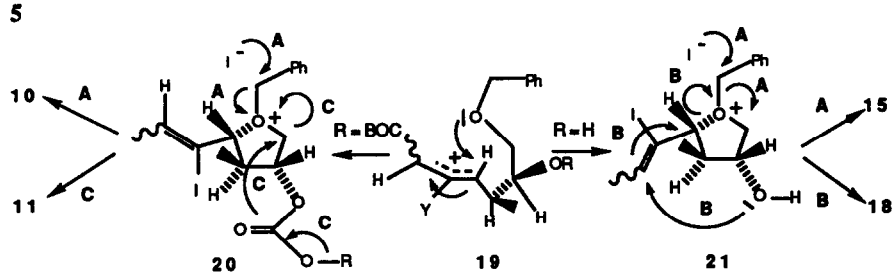
Scheme 4



a) I_2, 1.5 eq, CH_3CN, $NaHCO_3$, excess, -20°C, 15 min, quantitative; b) I_2, 4 eq, CH_3CN, $NaHCO_3$, excess, rt, overnight, 86%; c) *n*-BuLi, 1 eq, THF, -78°C, 3 h, 95%; d) I(collidine)$_2^+$ ClO_4^-, 4 eq, $CHCl_3$, 0°C, 3 h, 48%.

The relative stereochemistry of the three stereogenic centers in **10**, 2(*R*), 3(*R*), 4(*R*), **15**, 2(*R*), 3(*R*), 4(*R*), and **18**, 2(*R*), 3(*S*), 6(*R*), were unambiguously assigned by the observed nOe interactions, in 2D NOESY experiments, as indicated in Schemes.

Scheme 5



These various results are consistent with attack of C(2)-oxygen on the α-face of the initially allylic carbonium ion **19** to give either oxonium **20** or **21** and which upon debenzylation with iodide led to **10** or **15** respectively (path A) (Scheme 5).

In the absence of iodide, compound **18**, however, could come from **21**, *via* allylic substitution at C(6) by the C(2)-hydroxyl, to give the six-membered ring with the given stereochemistry (path **B**). Similarly, attack of the intermediate **20** by the carbonyl of the BOC group could lead to carbonate **11** of which configuration according to this mechanism has to be 2(*R*), 3(*R*), 4(*R*) (path C) (Scheme 5).

It is not clear as to which mechanism is participating in the stereochemical output of the newly formed double bond.[16] As our starting material is an epimeric mixture at the leaving group center, it will be necessary to examine each epimer separately, to explain these results.

In conclusion, a novel approach to optically active tetrahydrofurans and dihydropyrans, through transposition of allylic *n*-pentenyl ethers has been presented. Further investigations to the generality of this reaction as well as their application to the synthesis of natural products are currently in progress in these laboratories.

References and Notes

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6 Satisfactory spectroscopic data were obtained for all the new compounds.

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10 Compound **11**, oil; CIMS: MH^+ 403, peaks at 341, 213;IR ν^{cm-1}: 1795 (C=O), 1653 C=C), 1157, 1067 (C-O); ^1H NMR, 250 MHz, $CDCl_3$, δ ppm: 0.86 (3H, d, J=7 Hz, C(8)-H_3), 1.92 (3H, d, J=6 Hz, C(7)-H_3), 2.1 (1H, m, C(3)-H), 3.2 (1H, J=6 Hz, C(4)-H),4.14 and 4.24 (2H, ABX, J=8, J'=, C(1)-H_2), 4.2 (1H, m, C(6)-H), 4.49 (2H, AB, J=10 Hz, O$\underline{CH_2}$Ph), 5.02 (1H, dt, J=5 Hz, J'=8 Hz, C(2)-H), 6.1 (1H, q, J=7 Hz, C-6H), 7.3 (5H, broad s, Ar); ^{13}C NMR, $CDCl_3$, δ ppm: 10.1 (C-8), 21.6 (C-7), 41.9 (C-3), 69.0 (C-1), 70.3 (O$\underline{CH_2}$Ph), 76.9 (C-2), 76.8 (C-6), 86.0 (C-4), 113.1 (C-5), 128.1 (ArCH), 128.3 (ArCH), 128.6 (ArCH), 137.2 (C-10), 137.6 (ArC), 156.7 (C=O).

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12 Compound **15**, oil, EIMS: M^+ 268, m/z 197, 141; ^1H NMR, 250 MHz, $CDCl_3$, δ ppm: 1.0 (3H, d, J=7 Hz,C(8)-H_3), 1.7 (3H, d, J=6 Hz, C(7)-H_3), 2.0 (1H, m, C(3)-H), 3.4 (1H, d, J=7 Hz C(4)-H), 3.8 (3H, m, C-2H, C(1)-H_2), 6.0 (1H, q, J=6 Hz, C(6)-H); ^{13}C NMR, $CDCl_3$, δ ppm: 15.0 (C-7), 21.5 (C-8), 48.2 (C-3), 73.9 (C-1), 78.9 (C-2), 91.2 (C-4), 113.0 (C-6), 132.7 (C-5).

13 Compound **16**, $[\alpha]_D$=+ 29.1, $CHCl_3$, c=0.59, ^1H NMR: C(5)-H) at 5.5.ppm , ddd, J=15 Hz, J'=7 Hz, J"=2 Hz, , C(6)-H at 5.7 ppm, dq, J=15 Hz, J'=6 Hz.

14 Compound **17**, $[\alpha]_D$= -64.4 ,$CHCl_3$, c=0.58, ^{1}HNMR: C(5)-H and C(6)-H) at 5.1ppm).

15 Compound **18**, oil, $[\alpha]_D$= +71.3 ,$CHCl_3$, c=1.43) ; EIMS: M^+ 358, m/z 267, 231, 208; ^1H NMR, 250 MHz, $CDCl_3$, δ ppm: 0.9 (3H, d, J=7 Hz, C(8)-H_3), 1.4 (3H, d, J=6 Hz, C(7)-H_3), 2.1 (1H, m, C(3)-H), 3.4 (2H, ABX, J_{AB}=10 Hz, J_{AX}=6 Hz, J_{BX}=7 Hz, C(1)-H_2) 3.9 (1H, m, C(2)-H), 4.2 (1H, m, C-6H), 4.5 (2H, AB, J=10 Hz, O$\underline{CH_2}$Ph), 6.4 (1H, d, J=7 Hz, C(4)-H), 7.3 (5H, broad s, Ar); ^{13}C NMR, $CDCl_3$, δ ppm:13.2 (C-7), 22.7 (C-8), 36.3 (C-3), 70.3 (O$\underline{CH_2}$Ph), 73.4 (C-1), 74.9 (C-2), 76.8 (C-6), 102.2 (C-5), 127.6 (ArCH), 127.7 (ArCH), 128.3 (ArCH), 136.5 (ArC) 141.9 (C-4).

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