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2,4,5-Trisubstituted Tetrahydrofuran의 입체 선택적 합성

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A Stereoselective Synthesis of 2,4,5-Trisubstituted Tetrahydrofuran

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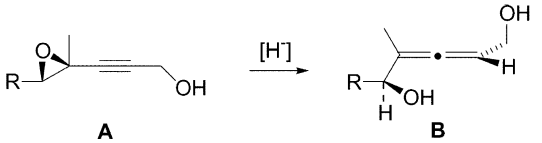
주제어: 테트라하이드로퓨란, S_N2' 하이드라이드 첨가반응, 입체선택적 수소화반응
Keywords: Tetrahydrofuran, S_N2' Hydride Addition, Stereoselective Hydrogenation

The synthesis of substituted tertrahydrofuran (THF) has been important because they are ubiquitous in many natural products such as annonecious acetogenins, polyether antibiotics and C-nucleosides.[1-3] The efficient and stereoselective manner of the preparation of the substituted THF has been a significant challenge for synthetic chemists. There are numerous synthetic methodologies that involve the preparation of the multisubstituted THFs.[4,5] Among those, the formation of carbon-oxygen or carbon-carbon bonds *via* intramolecular S_N1, S_N2 or S_N2' addition reactions is worthy to mention as the effective approaches to these hetero cyclic compounds.[6]

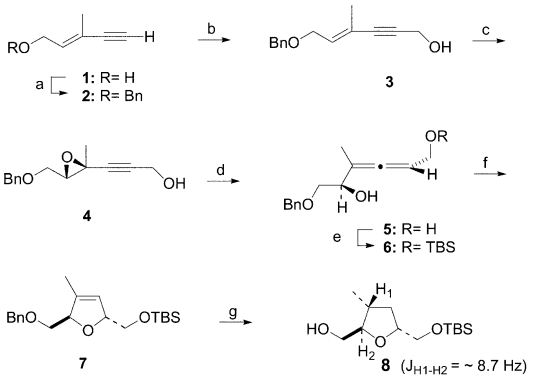
An approach that has been envisioned by us is to employ a methodology involving a stereoselective preparation of allenes by the S_N2' hydride addition to an alkynyloxirane.[7]



A **B**

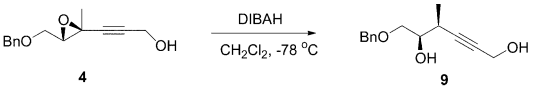
The *syn* addition of the hydride to the alkynyloxirane **A** afforded the highly stereoselective allenediol **B**. The stereo-defined allene would be subsequently converted to a *trans*-dihydrofuran and the following hydrogenation of the corresponding olefin of the dihydrofuran would offer the trisubstituted THF.

The synthesis was initiated with commercially available enynol **1**.[8] The alcohol was protected as a benzyl group. One carbon homoligation of the corresponding lithium acetylide with gaseous formaldehyde at 78 °C first then, warmed to room temperature afforded the propargylic alcohol **3**. The epoxidation of the compound **3** with *meta*-chloroperbenzoic acid gave the alkynyl epoxide **4**. The addition of diisobutyl aluminium hydride (DABAH) to the alkynyloxirane **4** at 0 °C gave the *cis*-allenediol **5** in 60% yield with the high diastereoselectivity. The ^{1}H NMR analysis showed exclusively the *syn* addition product. The previous example of this type of reaction showed exclusively *syn* addition that was contrasted with CuH addition resulting an *anti* addition product.[7] Presumably the hydroxy group might assist the aluminium hydride addition resulting the *syn* addition product exclusively. Interestingly the addition of DABAH to the alkynyloxirane at -78 °C gave the S_N2 addition adduct **9** in 76% yield with a small amount of the allendiol.



a. NaH, BnCl, PhH, reflux (70%); b. n-BuLi, formaldehyde, THF, -78 °C to rt (67%); c. m-CPBA, CH_2Cl_2 (52%); d. DIBAH, CH_2Cl_2 (60%);e. TBSCl, Et_3N, DMAP, CH_2Cl_2; f. $AgNO_3$, $CaCO_3$, acetone, water (80%, 2 steps); g. Pd/C, H_2, EtOH (88%).

The stereo-defined allenediol **5** was mono-protected as a *tert*-butyldimethylsilyl ether in the presence of dimethylamino pyridine (DMAP). The subsequent ring-closure under the condition of catalytic silver nitrate and calcium carbonate in the acetone/water (3:1) medium afforded the *trans*-dihydrofuran **7** in 80% yield in two steps starting the allendiol **5**. The hydrogenation of the dihydrofuran **7** with palladium on charcoal in the hydrogen atmosphere gave the trisubstituted hydrofurans **8** in 88 % yield with an excellent diastereoselectivity. The J value between H_1 and H_2 was observed to be about 8.7 Hz, indicating *trans* stereochemistry between C-1 and C-2. The high selectivity could be envisioned from the hydroxy-assisted hydrogenation after the reductive cleavage of the benzyl group of the dihydrofuran **6**.[9]



In conclusion, the synthesis herein allows us to prepare stereo-defined trisubstituted tetrahydrofurans. The diastereoselective hydride addition to lead the *syn*-allendiol and hydroxy-assisted hyrogenation of the dihydrofuran **6** are note-worthy in this synthetic route. The synthetic method of the trisubstituted THF shown here could be utilized to the synthesis of annonecious acetogenins and polyether antibiotics.

EXPERIMENTAL SECTION

General

^{1}H NMR and ^{13}C NMR spectra were recorded using 200 and 300 MHz NMR spectrometers. The chemical shifts are reported in ppm using $CDCl_3$ as solvent and TMS as an internal standard. Infrared spectra were recorded Perkin Elmer Paragon 500 FT-IR spectrometer. Flash chromatography was performed using E. Merck silica gel 60 (200-400 mesh).

(E)-3-Methyl-5-(benzyloxy)-3-penten-1-yne (2)

To a solution of 3.30 g (0.0343 mol) of the *trans*-alcohol **1** in 10 mL benzene was added 1.50 g (0.0377 mol) of NaH in 60% mineral oil at 0 °C. After the hydrogen evolution stopped 6.20 g (0.036 mol) of benzyl bromide was added. The solution was stirred at 80 °C for 24 hrs. Water was added slowly at 0 °C and then 3% HCl was added. The aqueous layer was separated and extracted with ether three times. The extracts were washed with saturated sodium bicarbonate and subsequently with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with 2% ether in hexanes afforded 4.26 g (67%) of the benzyl ether **2**:

IR (film) ν 3300, 2100, 1470, 1600, 1450 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34 (5H, s, phenyl Hs), 6.10 (1H, t, J=12.0 Hz, vinyl H), 4.51 (2H, s, benzyl H), 4.10 (2H, d, J=13 Hz, -OCH_2-), 2.84 (1H, s, acetylenic H), 1.08 (3H, s, vinyl CH_3) ppm; MS(EI), m/z(real intensity) 185(27), 149(22), 107(74), 91(100), 77(33), 65(20), 53(12).

(E)-4-Methyl-6-(benzyloxy)-4-hexen-2-yn-1-ol (3)

To a solution of 2.0 g (0.011 mol) of the benzyl ether **2** in 20 mL of THF was added 4.8 mL (0.012 mol) of 2.5 M n-BuLi in hexanes at -78 °C. The solution was stirred for 1 hr and then an excess gaseous formaldehyde was passed into the solution. The solution was stirred for the additional hour. The reaction mixture was warmed to room temperature and quenched with water. The aqueous layer was separated and extracted with ether three times. The extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with

40% ether in hexanes afforded 1.22 g (52%) of the alcohol **3**: IR (film) ν 3400, 1030, 1600, 1450 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33 (5H, m, phenyl Hs), 6.02 (1H, brt, J=12 Hz, vinyl H), 4.50 (2H, s, benzyl CH_2) 4.38 (2H, s, -CH_2OH), 4.09 (2H, d, J= 13 Hz, -OCH_2-), 1.78 (3H, s, vinyl CH_3) ppm.

(E)-4-Methyl-4,5-epoxy-6-(benzyloxy)- 4-hexen-2-yn-1-ol (4)

To a solution of 2.30 g (0.0106 mol) of the enynol **3** in 25 mL of $CHCl_3$ was added 3.67 g (0.0213 mol) of m-CPBA. The solution was stirred for 3.6 hrs at room temperature. The solution was quenched with saturated $NaHCO_3$. The aqueous layer was separated and extracted with ether three times. The extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with 50% ether in hexanes afforded 1.36 g (56%) of the epoxide **4**: IR (film) 3450, 2250, 1600, 1450; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34 (5H, m, phenyl Hs), 4.56 (2H, ABX, J_{AX}=11 Hz, J_{BX}=10 Hz, J_{AB}= 22 Hz, benzylic CH_2), 4.28 (2H, s, -CH_2OH), 3.50 (2H, m, -OCH_2-), 3.41 (1H, dd, J_{AX}=11, J_{BX}=10 Hz epoxide H), 1.49 (3H, s, vinyl CH_3) ppm.

***rel*-(2S,5R)-4-Methyl-6-(benzyloxy)-2,3-hexadien-1,5-diol (5)**

To a solution of 200 mg (0.696 mmol) of the *trans*-alkynyloxirane **4** in 3 mL of CH_2Cl_2 was added 0.23 mL of 1 M DIBAH in hexanes at 0 °C. The solution was stirred for 1.5 h and extracted with ether three times. The extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with 75% ether in hexanes afforded 120 mg (60%) of the *trans*-allenediol **5a**: IR (film) 3400, 1980, 1450; ^{1}H NMR (200 MHz, $CDCl_3$) 7.37 (5H, m, phenyl Hs), 5.54 (1H, brs, vinyl H), 4.60 (2H, s, benzylic Hs) 4.25 (1H, m, methane H), 4.10 (2H, d, J=2.0 Hz, C**H**$_2$OH), 3.62 and 3.52 (2H, m, methylene), 3.20 (1H, brs, -OH), 2.91 (1H, brs, -OH), 1.77 (3H, s, vinyl CH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 199.70, 137.63, 128.45, 127.84, 102.98, 94.26, 73.45, 72.55, 71.22, 59.96, 15.64.

***rel*-(2R,5R)-(5-Benzyloxymethyl-4-methyl-2,5-dihydro-furan-2-ylmethoxy)-*tert*-butyl-dimethyl-silane (7)**

To a solution of 110 mg (0.460 mmol) of the diol **5** in 3 mL of CH_2Cl_2 was added 77 mg (0.51 mmol) of *tert*-butyldimethylsilyl chloride, 0.38 mL (0.23 mmol) of DMAP and 0.38 mL (2.80 mmol) freshly distilled triethylamine. The reaction mixture was stirred for 2 hrs. Water was added. The aqueous solution was separated and extracted with ether three times. The extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to afford the clean crude allenol **6**. The allenol was treated with 70 mg (0.41 mmol) of silver nitrate and 41 mg (0.41 mmol) of calcium carbonate in 2 mL of a mixture of acetone and water (5:1). The solution was stirred overnight. The mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with 30% ether in hexanes afforded 130 mg (80%) of the dihydrofuran **7**: IR (film) 3450, 1940, 1262; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34 (5H, m, phenyl Hs), 5.54 (1H, brs , vinyl H), 4.88 (2H, m, methane Hs), 4.59 (2H, d, J=16 Hz, benzylic CH_2), 3.69-3.52 (4H, m, -OCH_2), 1.71 (3H, s, vinyl CH_3), 0.89 (9H, s, $SiC(CH_3)_3$), 0.06 (6H, s, -$Si(CH_3)_2$) ppm: ^{13}C NMR (75.5 MHz, $CDCl_3$) 138.34, 137.34, 128.79, 128.27, 127.64, 127.47, 123.47, 87.29, 86.05, 73.39, 71.47, 66.29, 25.88, 18.31, 12.62, -5.33; MS(EI), m/z (rel intensity) 291(17), 203(18), 183(6), 145(6), 91(100), 73(33), 65(6).

***rel*-(2R,3R,5R)-[5-(*tert*-Butyl-dimethyl-silanyloxymethyl)-3-methyltetrahydrofuran-2-yl]-methanol (8)**

To a solution of 130 mg (0.037 mmol) of the dihydrofuran in 2 mL of ethyl acetate was added 65 mg of palladium on charcol. The suspension was stirred for 2 days. The reaction mixture was filtered. The filtrate was concentrated undr reduced pressure. The residue was chromatographed on silica gel. Elution with 60% ether in hexanes afforded 81 mg (88%) of the tetrahydrofuran **8**: IR (film) 3450, 1480, 1250; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98 (1H, m, H-5), 3.69 (1H, dt, J=8.7 Hz and 2.4 Hz , H-1), 3.57 (2H, d, J= 4.5 Hz, -CH_2OTBS), 3.50-3.42 (3H, m, -CH_2OH), 2.09 (2H, m, methylene), 0.97 (3H, d, J=6.0 Hz, -CH_3), 0.84 (9H, s, $SiC(CH_3)_3$), 0.08 (6H, s, -$Si(CH_3)_2$) ppm.

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