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Conversion of a Silylated Hemiacetal Into an α-Bromoether Using Trimethylsilylbromide. Synthesis of Platelet Activating Factor Antagonist L-659,989.

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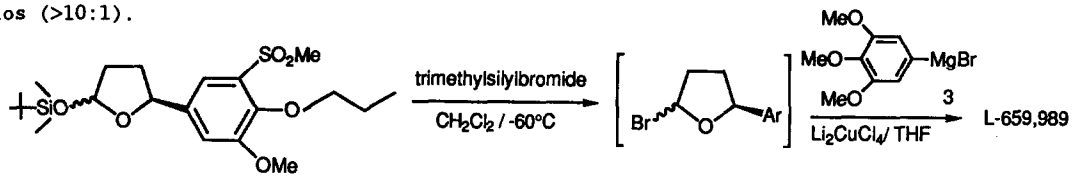
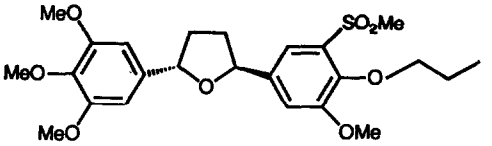
Abstract: An efficient synthesis of platelet activating factor antagonist L-659,989 has been achieved in ten steps from commercially available 5-iodovanillin. The key transformation converts a silylated hemi-acetal into an α-bromoether followed by a highly stereoselective Grignard coupling.

The ability to design receptor antagonists for platelet activating factor (PAF) may lead to a therapy for human ailments such as acute allergy, inflammation, toxic shock and asthma[1,2]. Lignans of the 2,5-diaryl tetrahydrofuran series have been identified as potent, selective and competitive PAF-receptor antagonists[3]. Several approaches toward the synthesis of the requisite trans 2,5-diaryl tetrahydrofuran have been reported[4,5]. The most promising, in terms of controlling relative and absolute stereochemistry, is the report by Corey and co-workers.[4] Using Corey's strategy, α-bromoether 2 (generated in situ) is coupled with Grignard reagent 3, resulting in diaryltetrahydrofurans with high trans:cis ratios (>10:1).



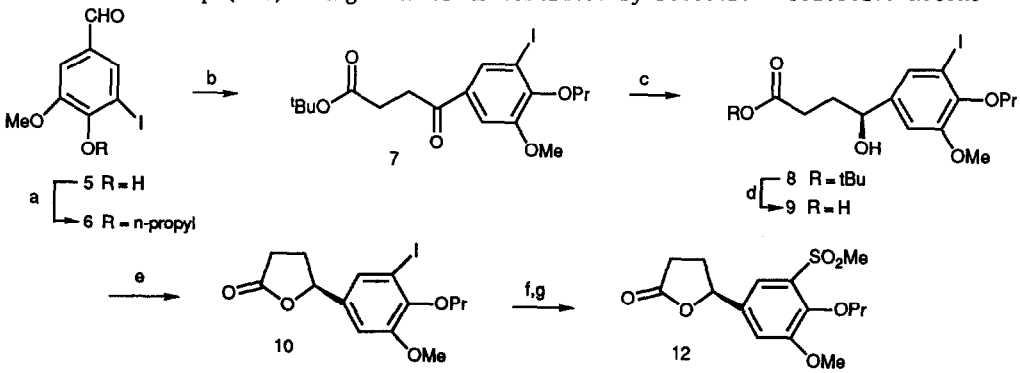
1 2

This paper describes significant improvements to the literature procedure, both in terms of anomeric activation and organometallic used. In particular, we have developed a new activation method. Using this method, silylated hemiacetal 1 can be cleanly converted into 2. The highly unstable bromoether 2 is produced without forming reactive by-products, allowing for an efficient copper-mediated Grignard coupling. Application of the improved sequence is demonstrated in a synthesis of L-659,989, a potent PAF antagonist.[5a]



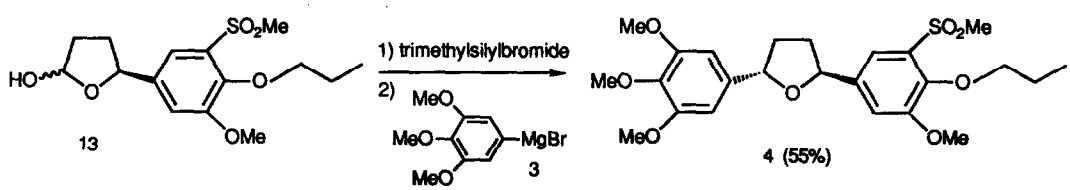
L-659,989

The synthesis of silylated hemiacetal 1 in optically pure form is shown in Scheme 1. Commercially available 5-iodovanillin is alkylated with n-propylbromide affording aldehyde 6. Construction of keto-ester 7, the carbon backbone of the tetrahydrofuran ring is achieved in one-step (83%) using conditions described by Stetter.[6] Selective ketone

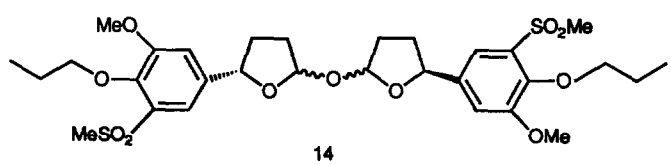


(a) n-propyl bromide/DMF/70°C (98%) (b) t-butyl acrylate/NaCN 0.25 eq./DMF
(c) β-chlorodiisopinocampheylborane/THF (d) KOH/MeOH/H_2O (e) Pyridinium-p-toluenesulfonate (1 mol %)/toluene (f) dimethyldisulfide/Cu°/pyridine/100°C, (g) Magnesium monoperoxyphthalate/CH_3CN/H_2O.

reduction using β-chlorodiisopinocampheylborane[7] affords alcohol 8 in 92% ee as determined by a Mosher ester derivative.[8] Ester hydrolysis results in hydroxy acid 9 and allows for the facile separation of product from α-pinene which is produced upon reduction. Lactonization under mildly acidic conditions with azeotropic removal of water produces lactone 10[9] in 65% overall yield from keto-ester 7. One recrystallization from ethyl acetate/hexanes produces material of >99.5% ee as determined by HPLC (chirosphere™). The iodide is converted to sulfone 12[9] using a two step procedure involving Ullmann coupling and sulfide oxidation, (88% from 10). Lactone reduction with diisobutylaluminum hydride in toluene at -60°C furnishes the corresponding lactols 13 (97% as a 1:1 mixture of trans and cis isomers). Application of the literature method[4] for conversion of 13 into L-659,989 met with limited success.

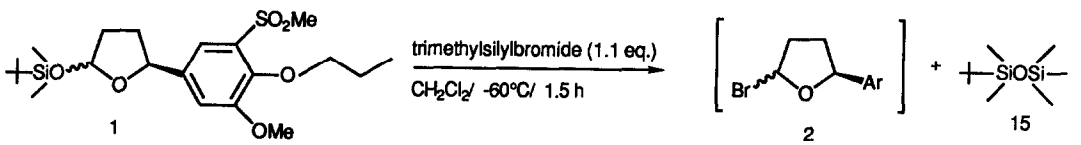


The trans:cis ratio was an encouraging 15:1 respectively. However, the yield for this procedure was 45% (from lactol 13). Use of excess Grignard reagent (2.5 eq.) increased the yield to 55%. The major impurity was shown to be acetals 14 (mixture at the acetal carbons) which accounts for up to 20% of the yield loss.



14

In addition, acetals 14 are comprised of 3-separate diastereomers necessitating a tedious purification. Formation of acetals 14 can be prevented by protecting the lactol hydroxyl prior to activation with trimethylsilylbromide (TMSBr). Several protecting groups were examined. Activation of a glycosyl acetate with TMSBr is known,[10] however with our substrate, a less than optimum equilibrium was obtained with the acetate[11]. We have found, however, that the t-butyldimethylsilyl ether of lactol 13 (prepared under the standard silylation conditions) is cleanly converted into α-bromoether 2 using TMSBr. Thus, employing stoichiometric quantities of reagents, silyl ether 1 is converted into α-bromoether 2[12,13] (>99% conversion). A balanced equation for this reaction is shown below. In addition to bromide 2, the reaction also yields disiloxane 15. The high converion is due to the thermodynamic stability of by-product 15 which provides a strong driving force to the right.



1 2 15

In addition siloxane 15 is not a reactive by-product, thus allowing the subsequent Grignard coupling to proceed unimpeded. This is in contrast to the reaction of lactol 13 with trimethylsilylbromide. A balanced equation for lactol activation (free OH) indicates that trimethylsilanol should be a by-product. Low temperature (-80°C) NMR studies (^{1}H and ^{29}Si) show only the presence of hexamethyldisiloxane. This indicates that any trimethylsilanol formed is dimerizing to hexamethyldisiloxane and H_2O. The presence of water explains the need to use excess Grignard reagent and also accounts for the formation of acetals 14. With the silyl acetal method, no proton source is produced and 1.25 equivalents of Grignard reagent are sufficient to achieve complete reaction. This method is well suited for C-glycoside synthesis since a readily available shelf stable silyl acetal is the precursor for anomeric actiation, the conversion into α-bromoether 2 is >99% complete and handling of the highly unstable α-bromoether 2 is kept to a minimum. Our method is unique among glycosyl activation techniques in that the activation by-product is not a potential electrophile.

Finally, we explored the effect of various metal salts on the aryl coupling step.[14] The reactivity of the Grignard reagent could be attenuated with metals such as $ZnCl_2$ or copper salts. Transmetallation of Grignard reagent 3 with $ZnCl_2$ (1 equivalent) followed by aryl coupling results in a low trans:cis ratio (4:1). Alternatively, co-mixing copper salts such as copper I cyanide (0.5 eq) or dilithium tetrachlorocuprate[15] (1.5%) increase the trans:cis ratio from 15:1 to 40:1.[14] With these two changes in place, i.e. silyl acetal activation and copper catalyzed Grignard coupling, the yield for the transformation of 1 into 4 (L-659,989) is 86%. The trans:cis ratio is 40:1 and the optical purity of the final product is >98% ee.

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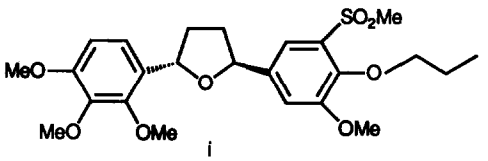
8) Dale, J.A.; Dull, D.L.; Mosher, H.S. J. Org. Chem. 1969, 34, 3543.
9) All compounds reported in this communication exhibited ^{1}H NMR charactristics in agreement with their structures. 10 $[\alpha]_D$ = -24.1 (c=1.06, $CHCl_3$), MP=82.5-83°C, ^{1}H NMR (300 MHz $CDCl_3$) δ=7.27 (d,J= 1.9 Hz,1H), 6.84(d,J=1.9 Hz,1H), 5.38(dd,J=6.1,8.2 Hz,1H), 3.92(t,J=6.8 Hz,2H), 3.84(s,3H), 2.69-2.57(m,3H), 2.20-2.13(m,1H), 1.84(sextet, J=7.1 Hz, 2H), 1.06(t,J=7.3 Hz,3H). 12 $[\alpha]_D$ = -21.2 (c=0.96, $CHCl_3$), MP=105°C, ^{1}H NMR (300 MHz $CDCl_3$) δ=7.45 (d,J= 2.0 Hz,1H), 7.19(d,J=2.0 Hz,1H), 5.49(dd,J=8.6,5.8 Hz,1H), 4.13(t,J=6.8 Hz,2H), 3.92(s,3H), 3.25(s,3H), 2.78-2.60(m,2H), 2.30-2.10(m,1H), 1.88(s,J=7.1 Hz,2H), 1.05(t,J=7.4 Hz,3H).
10) Gillard, J.W.; Israel, M. Tetrahedron Lett. 1981, 513.
11) The reaction of trimethylsilylbromide and the acetate corresponding to lactol 13 is an equilibrium reaction. Use of 1 equivalent of TMSBr results in 90% α-bromoether and 10% starting material. The details of these results will be the subject of a future report.
12) The chemical shifts (in CD_2Cl_2) for the anomeric proton is 5.72 ppm for the trans isomer of 1 and 5.60 ppm for the cis-isomer. Once converted to the bromide, these chemical shifts are 6.7 and 6.9 ppm.
13) The reaction is incomplete with trimethylsilylchloride.
A conceptually similar reaction using trimethylsilyliodide on a silylated hemi-thio-acetal has been reported see: Aida, T.; Harpp, D.N.; Chan, T.H. Tetrahedron Lett., 1980, 3247.
14) Reaction of Grignard reagent 3 with 2 produces 6% of i in addition to 4. We assume this product results from a competitive Friedel-Crafts arylation of bromoether 2. More Lewis acidic metals such as zinc increase the proportion of this impurity while cooper salts virtually eliminate (<0.5%) this impurity.



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15) Kochi, J; Tamura Synthesis 1971, 303.

Experimental

The silylated acetal 1 (12 gm, 27.1 mmol) was dissolved in dry CH_2Cl_2 (100 mL) and cooled to -60°C under N_2. To this mixture was added neat trimethylsilylbromide (4.2 mL, 31.8 mmol) and the reaction stirred at -60°C for 1.5 h. To the reaction was added a solution of Grignard reagent 3 (0.85M, 42 mL, 35.7 mmol) containing dilithium tetrachlorocuprate (0.5M, 0.6 mL, 0.30 mmol). The reaction was stirred at -60°C for 1/2 h then quenched with 10:1 v:v of saturated NH_4Cl:concentrated NH_4OH. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification by silica gel chromatography afforded 4 11.3 gm, 23.6 mmol (87%).

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