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The Mitsunobu Reaction of *ortho*-Ethers of Secondary Benzylic Alcohols. Concise Enantioselective Synthesis of a Key Intermediate of the Novel β-Adrenergic Receptor Antagonist MY336-a

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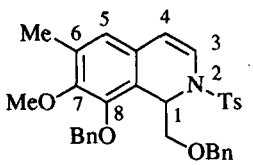
Abstract: Chiral secondary benzylic alcohols bearing an *ortho*-alkoxy substituent suffer ring-assisted racemization during the Mitsunobu reaction; however, their congeners bearing also a 3-substituent undergo virtually complete Mitsunobu inversion. A concise enantioselective synthesis of a key intermediate of the β-adrenergic receptor antagonist MY336-a was achieved exploiting this observation.

One of the most useful attributes of the Mitsunobu reaction[1] is to provide complete configurational inversion at the carbinyl carbon of alcohols under mild conditions. However, certain secondary benzylic alcohols are an exception; it has been reported the obtention of a 1:1 mixture of epimeric products upon Mitsunobu amination of a derivative carrying a *para*-methoxy group[2] and also it has been demonstrated that reactions of *para*-methoxy phenols led to racemization at the benzylic centre while, under the same conditions, *para*-acetoxy and -pivaloxy phenols gave inverted products.[3] In addition, the same ring-assisted racemization process was observed during the Mitsunobu conversion of *exo*-benzonorbornen-2-yl alcohols to amines.[4]

Surprisingly, there are no relevant publications concerning the result of the Mitsunobu reaction of *ortho*-substituted benzylic alcohols, except for the work of Ku[5] and Rao,[6] showing respectively that the thioacetoxylation of 2-methyl benzyl alcohols and the esterification of a vinylogous of a secondary benzyl alcohol bearing a methoxy group proceeded with complete configurational inversion at their carbinyl centers.



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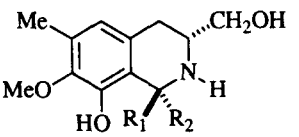
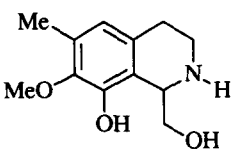


2 R^1= H, R^2= CH_2OH
3 R^1= CH_2OH, R^2= H



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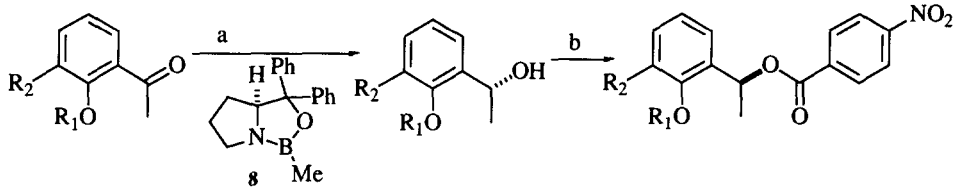
Reported in this letter is a study on the stereochemical outcome of the Mitsunobu reaction of secondary benzylic alcohols carrying phenolic ether groups at the *ortho*-position, which resulted in the elaboration of (+)-**1**, employing our Mitsunobu-based methodology for the enantioselective synthesis of 1-substituted 1,2,3,4-tetrahydroisoquinolines.[7] The 1,2-dihydroiosquinoline derivative **1** has been employed for the total synthesis

of the β-adrenergic receptor antagonist MY336-a (**2**), as well as its epimer (**3**)[8a] and their partial analog **4**.[8b] This accomplishment is important because chiral 1-alkyl tetrahydroisoquinoline derivatives displaying a 7,8-substitution pattern on the isocyclic ring are relatively uncommon and difficult to obtain.

In order to understand the influence of the nature of the *ortho*-ether and the substitution pattern on the degree of racemization, alcohols **6a-d** were enantioselectively synthesized from the related ketones **5a-d**[9] (Scheme 1), employing the CBS reduction process[10] with oxazaborolidine **8** as catalyst, and subsequently reacted with *para*-nitrobenzoic acid under Mitsunobu conditions, modified by Martin,[11] to afford esters **7a-d**.



5a R_1= Me, R_2= H
5b R_1= Bn, R_2= H
5c R_1= Me, R_2= OMe
5d R_1= Bn, R_2= OMe

6a R_1= Me, R_2= H
6b R_1= Bn, R_2= H
6c R_1= Me, R_2= OMe
6d R_1= Bn, R_2= OMe

7a R_1= Me, R_2= H
7b R_1= Bn, R_2= H
7c R_1= Me, R_2= OMe
7d R_1= Bn, R_2= OMe

Scheme 1. *Reagents and conditions:* a) $BH_3.SMe_2$, THF, TEA, **8** (10 mol%), 0°C, 8 h; b) 4-NO_2-C_6H_4-COOH (3 equiv.), PPh_3 (3 equiv.), DEAD (3 equiv.), toluene, RT, 3 h.

The results of these transformations are summarized in the Table. As shown, while the reactions of the 2-substituted benzylic alcohols **6a** and **6b** occurred with partial racemization (less extensive, however, than that observed in the 4-methoxy counterparts), their 2,3-disubstituted congeners **6c** and **6d** underwent essentially complete Mitsunobu inversion.

Table. Chemical yields, optical yields and optical rotation data of alcohols **6a-d** and their inverted *para*-nitrobenzoates **7a-d**.

Compd.	Yield (%)	ee (%)	$[\alpha]_D^{20}$/conc.[c]	Compd.	Yield	ee (%)	$[\alpha]_D^{20}$/conc.[c]
6a	96	94[a,b]	+32.3/2.00	**7a**	88	57[a,b]	+53.7/2.20
6b	94	> 95[a]	+26.1/1.44	**7b**	85	76[a]	+67.3/2.18
6c	92	97[a,b]	+24.5/2.51	**7c**	89	93[a,b]	+95.2/1.05
6d	96	> 95[a]	-11.1 /2.17	**7d**	87	95[a]	+24.9/0.69

a. Determined by ^1H NMR with (+)-Eu(hfc)$_3$ in C_6D_6; b. Determined by HPLC with a Chiralcel OD column; mobil phase: hexane/2-propanol (9:1) at 0.5 mL/min; c. All measurements in $CHCl_3$; concentration in g/dL.

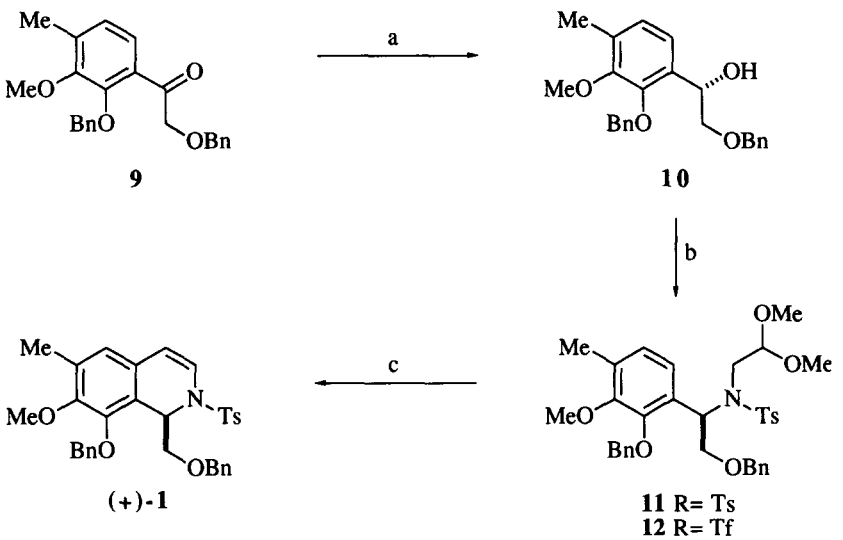
By analogy with related systems,[3] this ring-assisted racemization seems to be a consequence of the strongly electron donating ability of the *ortho*-alkoxy substituent, which causes the Mitsunobu's phosphonium salt intermediate[12] to have significant carbocation character. Thus, the reaction products arise partly from an S_N1 reaction pathway.

The synthetically useful inversion observed in **7c** and **7d** could be a result of a diminished participation of the *ortho*-substituent in the activation of the aromatic moiety, being detrimental for the S_N1 pathway. This

effect is probably originated in the known out of plane preferred conformation of *ortho*-disubstituted phenolic ethers, resulting in steric inhibition of the resonance.[13]

That the 3-substituent *per se* does not affect the reaction course, being crucial in these 1,2,3-trisubstituted compounds only by providing the required steric bulk[14] to produce resonance inhibition of the *ortho*-ether, is further demonstrated by previous observations indicating that 3,4-dimethoxy-α-phenethyl alcohol suffered similar degree of racemization than the related 4-methoxy susbtituted benzylic alcohol, upon submission to Mitsunobu conditions[3,7] and that 3-methoxy -α-phenethyl alcohol undewent this transformation with clean inversion.[15]

In view of these highly promising results, ketone **9**[8b] (Scheme 2) was submitted to the CBS reduction with 10 mol% of oxazaborolidine **8**, yielding alcohol **10**;[16] this, in turn, was reacted with toluene-*p*-sulfonamide **13** under Mitsunobu conditions with the addition of pyridine[17] (to avoid elimination by-products), providing 64% of the completely inverted *N*-benzyl-*N*-tosylaminoacetal **11**. In an attempt to improve yields, use of the TMAD-TBP couple[18] (3 equiv. each, toluene, 100°C, 32 h) was used, providing 69% of partially racemized **11** (ee 85%), probably due to the extensive heating required for the reaction to proceed. In addition, the potentially more efficient Mitsunobu amination of **10** with triflamide **14** was carried out,[19] however it gave a complex mixture and none of the desired product **12** could be isolated. Therefore, tosylamide **11** was cyclized with HCl under the Jackson protocol,[7] furnishing (+)-**1** in 80 % yield and > 95% ee, as expected.



Scheme 2. *Reagents and conditions:* a) $BH_3.SMe_2$, THF, TEA, **8** (10 mol%), RT, 8 h (> 95% ee); b) $TsNHCH_2CH(OMe)_2$ (**13**, 3 equiv.), PPh_3 (3 equiv.), DEAD (3 equiv.), pyridine (1 equiv.), toluene, RT, 3 h (64%, >95% ee) or $TfNHCH_2CH(OMe)_2$ (**14**), PPh_3, DEAD, toluene, RT, 3 h, complex mixture; c) 6 N HCl, dioxane, reflux (82%, > 95% ee).

In conclusion, a short enantioselective synthesis of a key intermediate of MY336-a has been achieved based on the observation that *ortho*-ethers of chiral secondary benzylic alcohols undergo virtually complete Mitsunobu inversion when a 3-substituent is present in their structure. The synthesis of related compounds in optically active form employing the same strategy is currently under study.

Acknowledgements

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