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An Efficient Method for the Reductive Transposition of Allylic Alcohols.

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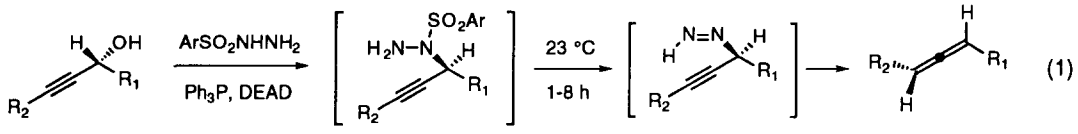
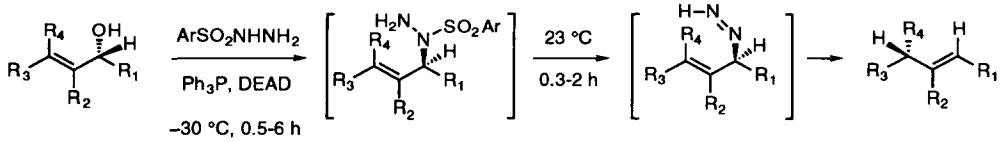
Abstract: The Mitsunobu reaction of allylic alcohols with *o*-nitrobenzenesulfonylhydrazine (NBSH) as nucleophile proceeds at –30 °C with invertive displacement; warming the resultant *N*-allylic sulfonylhydrazine derivative to 23 °C then leads to allylic diazene formation followed by sigmatropic elimination of dinitrogen. This one-step method for reductive 1,3-transposition is shown to be efficient and highly regio- and stereocontrolled within a wide range of allylic alcohol substrates. Copyright © 1996 Elsevier Science Ltd

We have developed a new and efficient one-step method for the reductive 1,3-transposition of allylic alcohols that proceeds with excellent regio- and stereochemical control. Such reductive transposition reactions are highly useful in complex synthesis, as demonstrated, e.g., in key steps of routes to the bergamotenes, cafestol, and protosterol by Corey and co-workers, and, more recently, as a key step in the synthesis of the core structure of dynemicin A by Schreiber et al.[1] In common with these precedents, our method involves the transformation of an allylic alcohol to an allylic diazene intermediate (with subsequent sigmatropic elimination of dinitrogen); however, the mode of diazene generation is different. The new method proceeds in direct analogy to our recently reported stereospecific synthesis of allenes from propargylic alcohols (eq 1)[2] and involves a low-temperature Mitsunobu inversion reaction of an allylic alcohol with *o*-nitrobenzenesulfonylhydrazine (NBSH) as



(1)



(2)

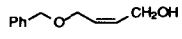
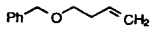
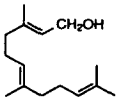
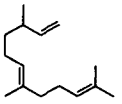
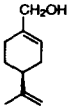
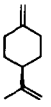
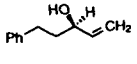
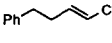
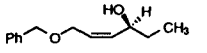
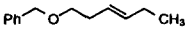
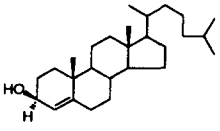
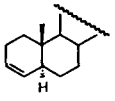
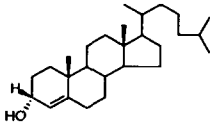
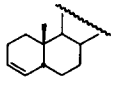
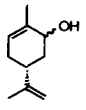
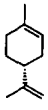
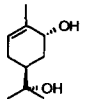
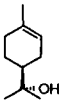
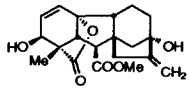
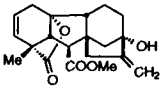
Ar = *o*-$O_2NC_6H_4$

nucleophile, followed by warming of the reaction mixture to 23 °C to induce diazene formation by thermal elimination of *o*-nitrobenzenesulfinic acid (eq 2).

Although conceptually identical to our allene synthesis, it was necessary to modify the earlier process in order to achieve a generally efficacious procedure for the reductive transposition of allylic alcohols. We found that, in general, Mitsunobu inversion reactions of allylic alcohols are more complicated than are the analogous propargylic alcohol substrates, presumably a consequence of the greater steric hindrance of allylic alcohols and the greater propensity of intermediates derived from them to undergo cation-based side reactions (e.g., elimination to form a 1,3-diene). In addition, our experiments suggest that the *N*-allylic sulfonylhydrazine intermediates undergo elimination at lower temperature than the corresponding propargyl derivatives, releasing *o*-nitrobenzenesulfinic acid which can then compete with NBSH in the Mitsunobu inversion reaction. By conducting the Mitsunobu inversion reaction at a lower temperature than was used in the prior method (–30 °C versus –15 °C), the reaction was cleaner, with fewer by-products from elimination and sulfinate displacement. Although tetrahydrofuran was a suitable medium for rapidly reacting substrates such as primary alcohols, we encountered solubility problems over the extended reaction periods at –30 °C required for more sterically demanding substrates. After an extensive survey of alternative solvents, we found that the somewhat unconventional solvent *N*-methylmorpholine (NMM) provided a nearly ideal reaction medium. The reactants were found to be readily soluble in *N*-methylmorpholine at –30 °C to the extent that substrate concentrations of 0.3 M were easily accomodated. In addition, NMM has the desirable feature of being freely water soluble, thus facilitating the isolation of the reaction products, particularly in the case of volatile products.

As illustrated by the examples of Table 1, this new method has proven to be highly effective for the reductive 1,3-transposition of a wide variety of allylic alcohols. Entries 4 and 5 show that the rearrangement proceeds with high trans selectivity in the formation of 1,2-disubstituted olefins. This outcome was anticipated on the basis of simple allylic strain arguments and parallels our earlier studies of the stereochemistry of allylic diazene decomposition.[3] As a consequence of this finding, a two-step sequence involving the addition of a vinyl anion of cis or trans (or mixed) configuration to an aldehyde followed by reductive 1,3-transposition can be envisioned as a simple alternative to the Julia olefin synthesis.[4] The regioselectivity (1,3-transposition versus direct displacement) of the reduction reaction is complete in every example we have examined, but is perhaps best illustrated in example 8, where (*R*)-(+)-limonene was formed with 97% ee. This finding is noteworthy in light of the many examples of "anomalous" or S_N2' products reported in Mitsunobu reactions of allylic alcohols with standard nucleophiles such as carboxylic acids and phenols.[5] The invertive nature of the initial displacement reaction is only discernible in the examples of entries 6 and 7. When NMM was used as the reaction solvent in the latter examples, each diastereoisomeric product was formed to the exclusion of the other with >20:1 selectivity. Interestingly, when tetrahydrofuran was employed as the solvent the stereospecificity of the transformation of entry 6 was reduced to 10:1 (75% yield) while that of entry 7 was 15:1 (56% yield). These

Table 1. Reductive 1,3-Transposition of Allylic Alcohols

Entry	Substrate	Solvent	equiv PPh_3	equiv DEAD	equiv NBSH	Product	Yield (%)[a]
1		THF	1.3	1.2	1.3		88
2		THF	1.3	1.2	1.5		79 (85)
3		THF	1.3	1.2	1.2		76 (84)
4[b]		NMM	1.3	1.2	1.3		81 (*E*:Z 94:6)[c]
5[b]		NMM	1.3	1.2	1.2		77 (*E*:Z >99:1)[c]
6		NMM	2.2	2	2		76
7		NMM	3.3	3	3		70
8[d]		NMM	2.2	2	2		78[e]
9[b]		NMM	2.2	2	2		70
10		NMM	3.3	3[f]	3		66

[a] Isolated yield; the yields in parentheses were obtained by gas chromatography. [b] Racemic substrate. [c] Determined by capillary gas chromatography. [d] The starting material was a 9:1 mixture of cis and trans isomers, obtained by reduction of (*R*)-carvone (98% ee) with sodium borohydride. [e] The product gave $[\alpha]_D^{20}$ = + 121° (neat), corresponding to (*R*)-(+)-limonene of 97% ee. [f] Diisopropyl azodicarboxylate was used instead of DEAD in order to avoid the difficult separation of the product from 1,2-dicarbethoxyhydrazine.

examples demonstrate a 1,3-transfer of stereochemistry from the hydroxylic center to the β-olefinic carbon. Although these examples were cyclic allylic alcohols, in principle, this 1,3-transfer of stereochemistry could proceed with high fidelity in acyclic systems as well, given the observed preference for trans stereochemistry in the olefinic products of entries 4 and 5 (see eq 2). As we found in our allene synthesis methodology, the reductive transposition reaction is tolerant of a wide variety of functional groups. The reductive transposition of GA_3 methyl ester (entry 10) is notable in this regard. It is also illustrative of the difficulty we encountered with sterically hindered substrates; the alcohols of entries 6-10 were the most challenging substrates we encountered, undoubtedly a consequence of steric hindrance in the Mitsunobu inversion step. For these substrates we found it beneficial to use an excess of the Mitsunobu reagents and to operate at higher substrate concentrations (~0.3 M versus 0.1 M in tetrahydrofuran for entries 1-3) in NMM as solvent. Experimental detail is provided in the procedure below. In conclusion, we have developed an efficient one-step process for the 1,3-reductive transposition of allylic alcohols that we believe will find great utility as a synthetic method.

(*E*)-1-benzyloxy-3-hexene (entry 5) Diethylazodicarboxylate (DEAD, 0.19 mL, 1.2 mmol, 1.2 equiv) was added to a solution of triphenylphosphine (0.34 g, 1.3 mmol, 1.3 equiv) in *N*-methylmorpholine (3.5 mL) at –30 °C. After 5 min, (*Z*)-1-benzyloxy-2-hexen-4-ol (0.21 g, 1.0 mmol, 1 equiv) was added to the cold reaction mixture, followed 10 min later by solid NBSH[2a] (0.26 g, 1.2 mmol, 1.2 equiv). The reaction mixture was held at –30 °C for 1 hr, after which time thin-layer chromatographic analysis indicated complete consumption of the starting alcohol. The reaction mixture was warmed to 23 °C, and was allowed to stand at that temperature for 30 min. The reaction solution was then partitioned between ethyl ether (30 mL) and water (30 mL). The organic layer was separated and washed with a second 30-mL portion of water, then was dried over sodium sulfate and concentrated. Purification of the residue by chromatography on silica gel provided the title olefin (146 mg, 77%).

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