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Mitsunobu Reactions with Methanesulfonic Acid; The Replacement of Equatorial Hydroxyl Groups by Azide with Net Retention of Configuration

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Abstract: Treatment of equatorial cyclohexanols with Ph_3P/DEAD/MsOH gives clean conversion to the axial mesylates. Subsequent reaction with NaN_3 gives the equatorial azides in overall yields of 74-87%. Axial hydroxyl groups are not affected, allowing the regioselective conversion of methyl cholate into a 3α-azidodiol intermediate for steroid-based synthetic receptors.
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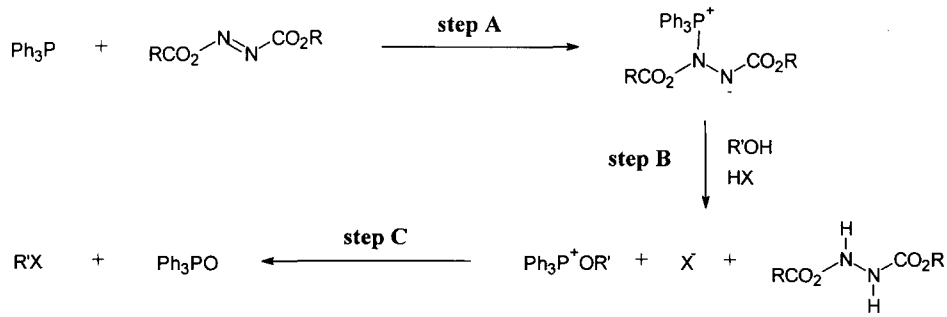
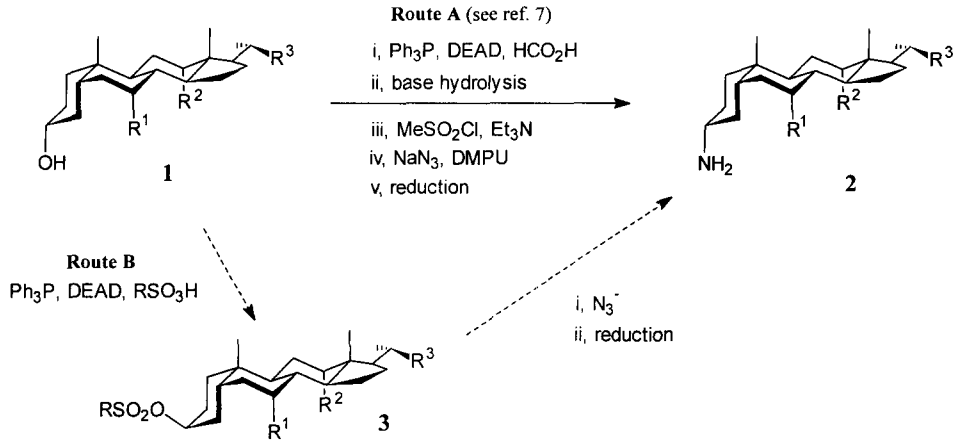
The Mitsunobu reaction is one of the most versatile and widely-used transformations in organic chemistry.[1] As shown in Scheme 1, the combination of an alcohol, triphenylphosphine, a diazodicarboxylate (e.g. diethyl azodicarboxylate, DEAD), and an acidic species HX, results in direct replacement of the hydroxyl group by X, usually with strict inversion of configuration. The method can be applied to a wide range of conversions, dependent on the pK_a of HX. The upper limit of $pK_a \approx 13.5$, resulting from deceleration of step **B** in Scheme 1, has been explored quite extensively.[2] However, a lower limit also appears to exist, presumably related to the low nucleophilicity of X^- for strongly acidic HX. For example, while the reaction succeeds when HX is a phosphonic acid,[3] or trifluoroacetic acid,[4] it is reported to fail when *p*-toluenesulfonic acid (TsOH) is employed.[5] We now describe the successful deployment of *methane*sulfonic acid (MsOH) in the Mitsunobu reaction, as part of a new and efficient method for the stereoretentive displacement of equatorial hydroxyl by azido groups in cyclohexanols.



Scheme 1

Our work in this area arose from our interest in the bile acids as building blocks for supramolecular chemistry.[6] In order to prepare "cyclocholamides"[7] and podand-type receptors[8] from cholic acid, we had needed to replace the 3α-OH in derivatives **1** with an α-NH_2 as in **2** (Scheme 2). The method used (Route A) involved conventional Mitsunobu inversion with formic acid, hydrolysis of the 3β-formate, mesylation and displacement with azide.



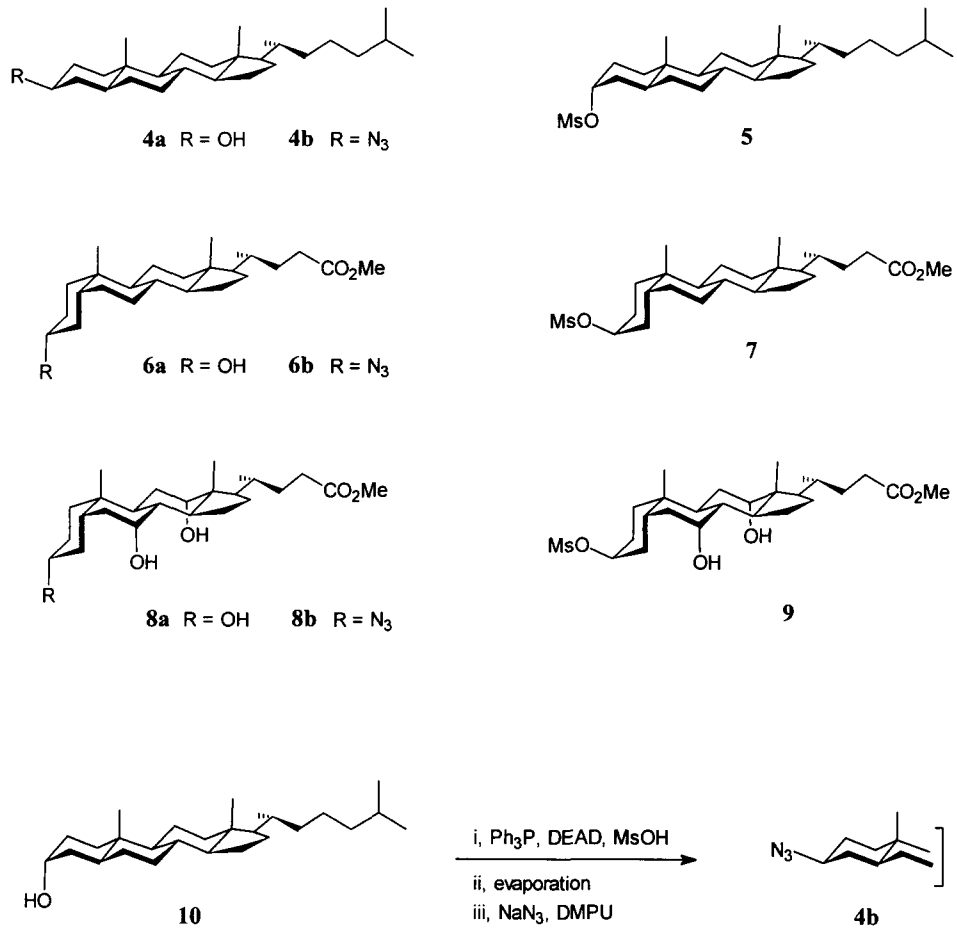
Scheme 2

Although this process was workable and high yielding, it seemed desirable to seek a shorter sequence. In particular, direct access to β-sulphonates **3** *via* Mitsunobu reactions with RSO_3^- as nucleophiles would reduce the number of steps by two (Route B in Scheme 2). As mentioned above, other workers had found that the first step in Route B was infeasible for RSO_3H = TsOH.[5] On foot of this result, Galynker and Still[5a] had proceeded to develop a successful method in which $Zn(OTs)_2$ replaced the acid. However, in our hands it gave modest yields (*ca.* 30%) of **3** (R = *p*-tolyl), and the requirement for large excesses of reagents (5 equiv each of Ph_3P and DEAD) discouraged large scale use.

Exploring alternatives,[9] *we were pleased to find that a Mitsunobu reaction employing MsOH as the acidic/nucleophilic component can be a highly efficient method for generating mesylates.* Thus, addition of DEAD (3 equiv) to 3β-cholestanol (**4a**), methyl lithocholate (**6a**) or methyl cholate (**8a**), dissolved in dry THF in the presence of Ph_3P (3 equiv) and MsOH (2 equiv), gave the corresponding mesylates **5**, **7** and **9**. These compounds were partially purified by chromatography, then treated with sodium azide in DMPU. Azides **4b**, **6b**, and **8b** were isolated in overall yields of 87%, 74% and 75% respectively.[10]

As might be expected, the Mitsunobu inversion with MsOH is somewhat slower than the analogous reactions employing carboxylic acids, requiring 24 hours at 40 °C to reach completion. A notable feature is its selectivity for equatorial hydroxyl groups. For example, in the conversion of **8a** to **8b** the reaction seems to be entirely regioselective, there being no evidence of attack at either of the axial hydroxyl groups in the starting material.[11] Similarly, when 3α-cholestanol (**10**) was subjected to the conditions, it was recovered largely unchanged. Interestingly, evaporation of the reaction mixture in this case, followed by addition of NaN_3/DMPU, resulted in the Mitsunobu reaction proceeding with N_3^- as nucleophile, giving **4b** as product in a yield of 75 % (Scheme 3). This result implies that a mixture of 3α- and 3β-cholestanols should undergo a

stereoconvergent transformation to the equatorial azide if treated with DEAD/Ph_3P/MsOH then NaN_3/DMPU, without an intermediate work-up.[12] When cholesterol was used as substrate, the reaction proceeded but yielded a mixture of 3α and 3β azides. This lack of stereoselectivity presumably reflects the intervention of the cyclopropanyl intermediates commonly invoked for substitutions at this centre.[13]



Scheme 3

In conclusion, the use of methanesulfonic acid in the Mitsunobu reaction provides an effective and high-yielding method for converting a hydroxyl into a leaving group with inversion of configuration, at least for the equatorial cycloalkanols discussed in this paper. The preparation of **8b** *via* this method provides convenient access to a range of asymmetrically functionalised cholic acid derivatives, and is likely to play an important rôle in our programme on steroid-based receptors.

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9. A second literature method, employing MeOTs as source of TsO^-, had been applied just to 3β-cholestanol (**4a**). See: Loibner, H.; Zbiral, E. *Helv. Chim. Acta* **1976**, *59*, 2100. This procedure was not investigated in the present work due to the modest yield reported (60%), and the success of the mesylation described herein.
10. **Typical Procedure** (Preparation of **8b**): Methanesulfonic acid (1.6 ml, 24.7 mmol, 2.1 equiv) was added to a solution of methyl cholate (**8a**) (5 g, 11.8 mmol) and triphenylphosphine (9.4 g, 36 mmol, 3 equiv) in dry THF (38 ml) under argon. The temperature was raised to 40 °C and DEAD (5.7 ml, 36 mmol, 3 equiv) was added dropwise over a 12 minute period with vigorous stirring, and with careful exclusion of moisture. The characteristic yellow colour of DEAD persisted in the reaction flask after *ca.* 90 % addition. After 15 minutes the reaction mixture became white and viscous. The mixture was stirred vigorously for 24 hours at 40 °C under argon. The volatiles were then removed under reduced pressure and the residue redissolved in chloroform. The crude product was purified by flash chromatography on silica gel (200 g), eluting with ethyl acetate-hexane-dichloromethane (7:1:0.05) to give mesylate **9** as an off-white solid (5.3 g, *ca.* 90%): TLC R_f 0.6 (ethyl acetate) (minor impurities also detectable); δ_H (300 MHz, $CDCl_3$) 0.67 (3 H, s, 18-Me), 0.89 (3 H, s, 19-Me), 0.94 (3 H, d, 21-Me), 2.96 (3 H, s, OSO_2Me), 3.64 (3 H, s, CO_2Me), 3.85 (1 H, m, 7β-H), 3.99 (1 H, m, 12β-H), 4.92 (1 H, br m, 3α-H). This material was dissolved in dry DMPU (35 ml) and sodium azide (5 g, 75.8 mmol) was added. The mixture was stirred vigorously at 40-45 °C for 48 hours then partitioned between water (150ml) and ether (100ml). The aqueous layer was extracted with ether (4 x 100 ml), and the combined organic phases were dried ($MgSO_4$), filtered and concentrated in vacuo to gave an off-white solid. The crude product was purified by flash chromatography on silica gel (200 g), eluting with hexane-ethyl acetate (3:2) to give **8b** as a white solid, (3.95 g, 75 % overall from **8a**): TLC R_f 0.83 (hexane-ethyl acetate, 1:1); ν_{max} (film from $CHCl_3$) 2094 (N_3), 1748 (ester) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.66 (3 H, s, 18-Me), 0.88 (3 H, s, 19-Me), 0.96 (3 H, d, 21-Me), 2.82 (1 H, d, -OH), 3.13 (1 H, br m, 3β-H), 3.64 (3 H, s, CO_2Me), 3.83 (1 H, m, 7β-H), 3.96(1 H, m, 12β-H); δ_C (75.46 MHz, $CDCl_3$) 12.42, 17.28, 22.50, 23.17, 26.50, 26.81, 27.48, 28.16, 30.81, 31.03, 34.60, 34.76, 35.29, 35.35, 35.46, 39.36, 41.84, 41.85, 46.53, 47.20, 51.45, 61.31, 68.24, 73.02, 174.78.
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12. For other examples of convergence through stereodifferentiating inversion, see: Harada, T.; Shintani, T.; Oku, A. *J. Am. Chem. Soc.* **1995**, *117*, 12346, refs. cited therein, and discussion in Davis, A. P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 591.
13. The method of Galynker and Still (ref. 5a) is reported to give tosylation with retention of configuration when applied to cholesterol.

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