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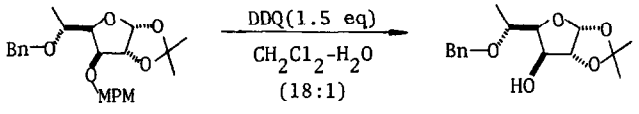
SELECTIVE HYDROGENOLYSIS OF THE BENZYL PROTECTING GROUP FOR HYDROXY FUNCTION WITH RANEY NICKEL IN THE PRESENCE OF THE MPM (4-METHOXYBENZYL) AND DMPM (3,4-DIMETHOXYBENZYL) PROTECTING GROUPS

Yuji Oikawa, Tatsuyoshi Tanaka, Kiyoshi Horita, and Osamu Yonemitsu*
Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

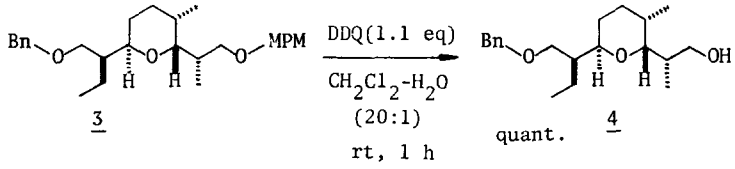
Summary. The benzyl protecting group for hydroxy function was selectively removed by catalytic hydrogenolysis with Raney nickel in the presence of the MPM (4-methoxybenzyl) and DMPM (3,4-dimethoxybenzyl) protecting groups, and applied to the synthesis of some synthons to macrolide and polyether antibiotics.

Discrimination among reactive sites of the same class by selective reactions is intensively required for the current synthesis of complex natural products such as macrolide and polyether antibiotics. Recently, we reported a highly selective removal of the MPM (4-methoxybenzyl) protecting group for hydroxy function by DDQ oxidation[1] and its extensions including the kinetic acetalization[2] and DMPM (3,4-dimethoxybenzyl) protection.[3] For example, the MPM group of 1 was removed selectively with DDQ to give 2, in which a benzyl protecting group remained unaffected. Synthetic intermediates of salinomycin (3) and tylosin (5) gave similarly the corresponding de-MPM alcohols, 4 and 6, respectively.

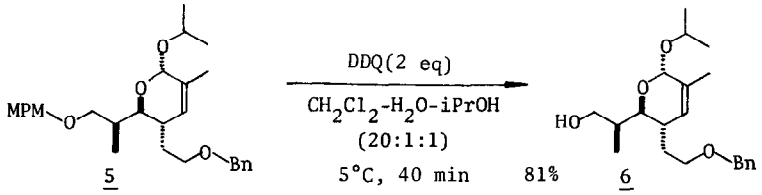


1 2

Bn: $C_6H_5CH_2$
MPM: 4-$CH_3OC_6H_4CH_2$



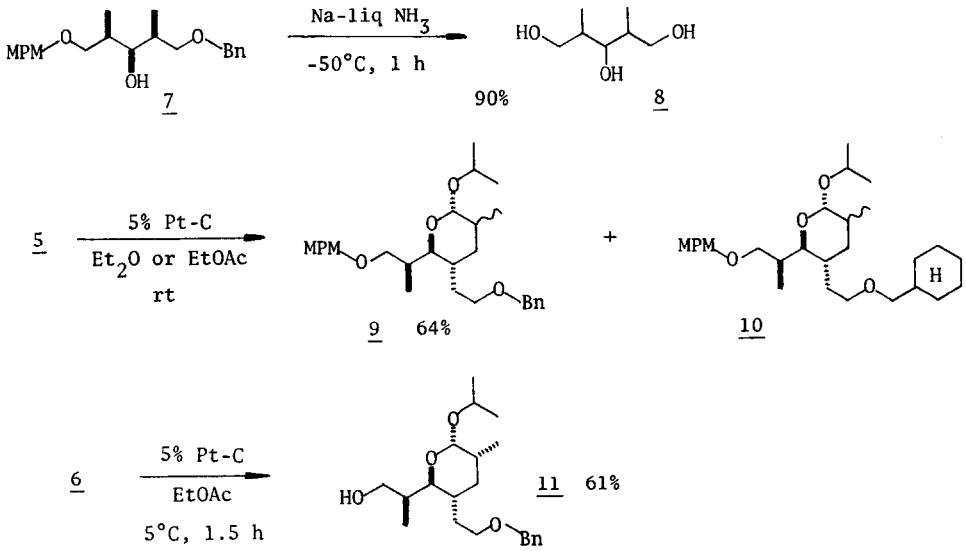
3 4



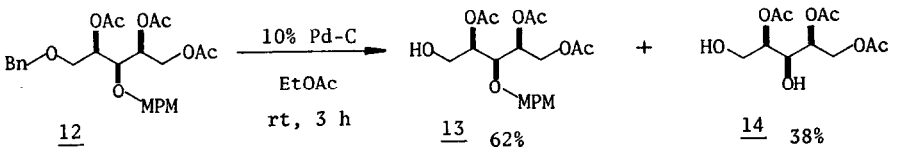
5 6

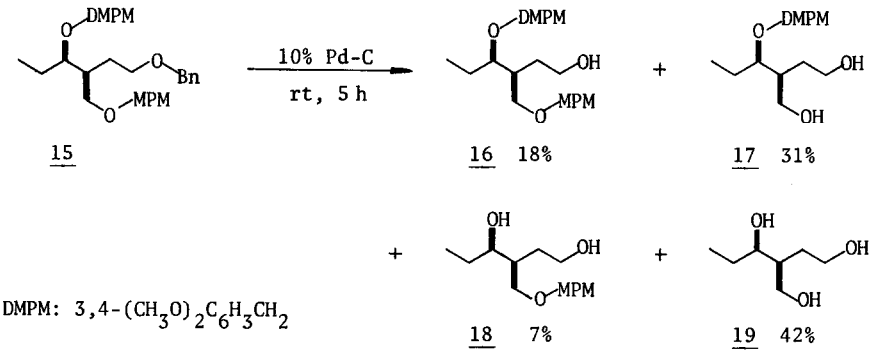
On the contrary, if the benzyl (Bn) group can be selectively removed from these compounds, the usefulness of the MPM protection will be further extended. The most common way for debenzylation is the reductive cleavage by catalytic hydrogenation and alkali metal-liquid ammonia reduction. Because the latter has no selectivity as exemplified in 7 → 8, the former with platinum, rhodium, palladium, and nickel catalysts under various conditions was next examined and applied to the synthesis of some synthons to macrolide and polyether antibiotics.

When 5 was hydrogenated in the presence of 5% platinum-charcoal (Pt-C) at ordinary pressure and temperature, the isolated double bond was first reduced to give mainly 9 with a small amount of an aromatic ring reduced product (10) and very small amounts of hydrogenolysis products. A similar result was obtained in the reduction of the de-MPM compound (6). No improvement was observed by the use of 5% rhodium-alumina ($Rh-Al_2O_3$) catalyst.

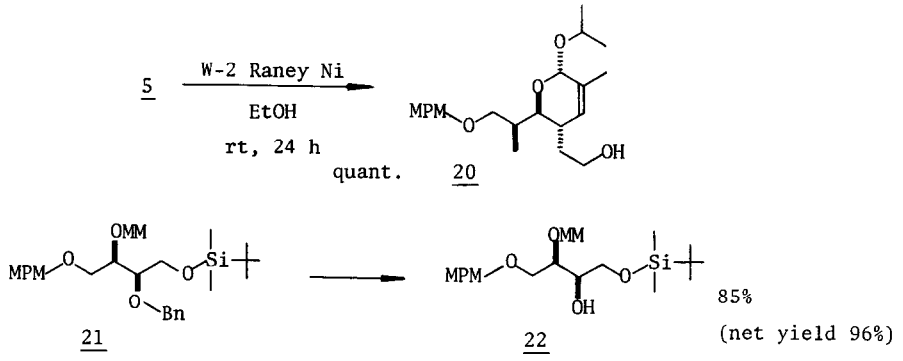


Palladium-charcoal (Pd-C) gave better results. When 12 was hydrogenated in the presence of 10% Pd-C until 12 completely disappeared, the debenzylated alcohol (13) was isolated as the main product, but simultaneous formation of a considerable amount of the diol (14) was unavoidable. Careful examination of the reduction products (16 - 19) from 15 containing Bn, MPM, and DMPM groups gave a more clear result, which shows the order of reactivity to be Bn > MPM > DMPM, but the selectivity of this reduction was far from practical use. In order to decrease the reactivity and to increase the selectivity of the palladium catalyst, various amounts of pyridine were added, but no improvement was observed.



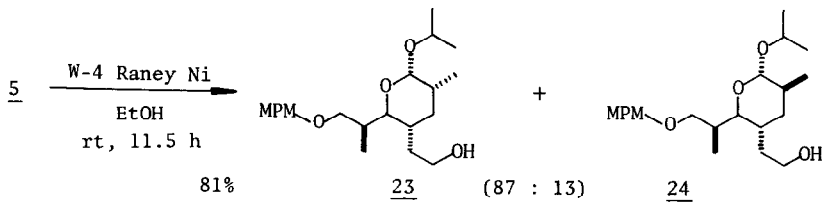


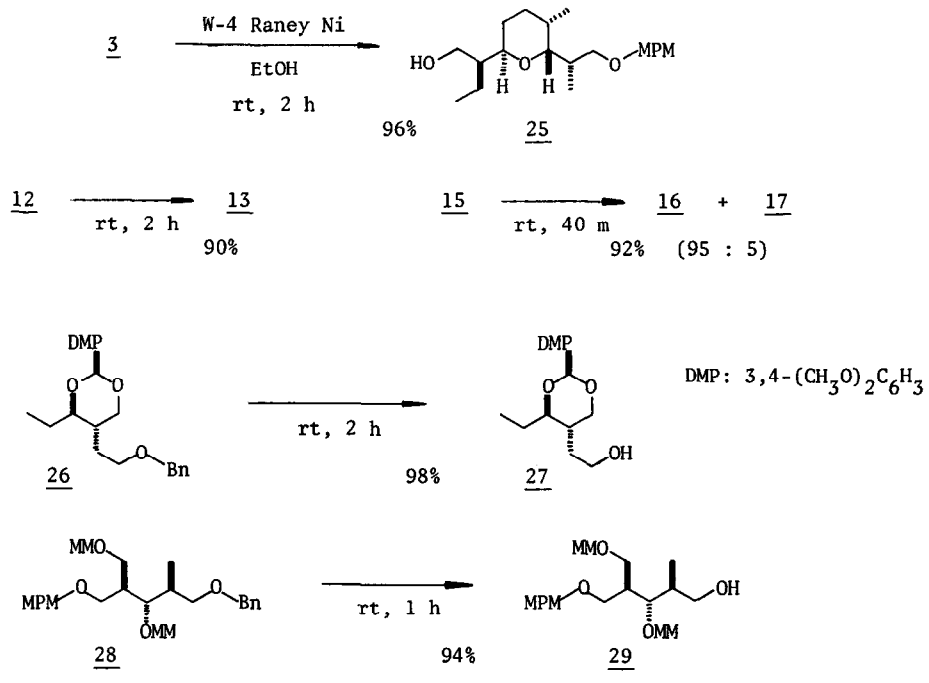
Raney nickel (Ni) catalyst showed, however, an excellent selectivity. When 5 was hydrogenated with W-2 Raney Ni,[4] the hydrogenolysis of only the benzyl group proceeded, though required 24 hours, to give 20 in a quantitative yield. Compound 21 was also hydrogenated with W-2 Raney Ni to give selectively 22, whose net yield after 24 hours was 96%, but 12% of the starting compound (21) was still recovered.



More reactive W-4 Raney Ni[5] significantly accelerated the reduction. In the case of 5, simultaneous reduction of the double bond occurred to give a mixture of stereoisomers, 23 and 24, in 81% yield. Cleavage of the isopropyl protecting group, not of the MPM group, was observed as a side reaction.

Compound 3 containing no reducible double bond gave the corresponding debenzylated alcohol (25) within 2 hours in an excellent yield. Similarly, 12 gave only 13, but in the case of 15 the reduction proceeded more rapidly, and 16 together with a small amount of 17 was isolated. Again, 26 containing a DMP (3,4-dimethoxyphenyl) acetal group and 28 gave excellent results.





On the mechanism of catalytic hydrogenolysis of benzyl alcohols and benzyl ethers with substituents at their benzylic positions in the presence of Raney Ni and Pd catalysts, a extensive study mainly based on the stereochemistry at the benzylic position by Mitsui revealed that S_Ni- and S_N2-type mechanisms were operative.[6] Benzyl alcohols with substituents on the benzene ring, not at the benzylic position, were hydrogenated in the presence of Pd-C through the S_N2 mechanism with a negative ρ value (-0.37) derived from the Hammett-Yukawa relation.[7,8] Although our precise mechanistic study is still lacking, the above mechanisms seem difficult to explain the data presented here, which will be nevertheless very useful in synthetic organic chemistry especially for complex natural products.

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