CHEMISTRY LETTERS, pp. 1389 - 1392, 1984.

COMBINATION OF BORANE-DIMETHYL SULFIDE COMPLEX WITH CATALYTIC SODIUM TETRAHYDROBORATE AS A SELECTIVE REDUCING AGENT FOR α-HYDROXY ESTERS. VERSATILE CHIRAL BUILDING BLOCK FROM (*S*)-(−)-MALIC ACID

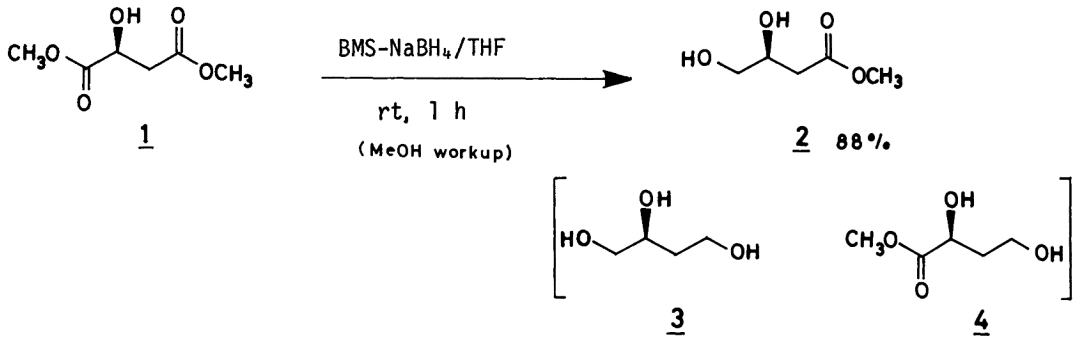
Seiki SAITO, Takashi HASEGAWA, Masami INABA, Ryosuke NISHIDA, Toshikazu FUJII, Seiya NOMIZU, and Toshio MORIWAKE*
Department of Synthetic Chemistry, School of Engineering, Okayama University, Tsushima, Okayama 700

Borane-dimethyl sulfide complex has proven to be an efficient and selective reducing agent in the presence of catalytic sodium tetrahydroborate for α-hydroxy esters as exemplified in the reduction of dimethyl (*S*)-(−)-malate, providing the versatile chiral building block of four-carbon backbone.

The selective reduction of carbonyl functional groups is frequently and inevitably required in organic synthesis and, in this connection, a variety of selective reducing agents have been developed so far, playing an important role in current functional group transformations.[1] It still remains challenging task, however, to achieve the selective reduction of an ester group at one site while keeping the same one at other site intact.[2] In our effort to develop synthetic approach to structures related to versatile chiral synthetic blocks of four-carbon framework, we have envisioned the selective reduction of the ester group α to the hydroxyl group of dimethyl (*S*)-(−)-malate (1).[3] Disclosed herein is a realization of this goal by means of the combination of borane-dimethyl sulfide complex (BMS) with catalytic amount of sodium tetrahydroborate ($NaBH_4$).

The reduction of esters to alcohols with BMS is known to be relatively slow.[4] In order to remedy this drawback, some efforts have been done for BMS to be met the demands for practical use.[5] Apart from the reduction of esters, an early report has indicated that a reducing power of borane can be remarkably increased by the aid of a small amount of $NaBH_4$ in tetrahydrofuran (THF) at 25 °C.[6] Being encouraged by these informations, the reduction of 1 with BMS (one-mole equivalent) in the presence of $NaBH_4$ (5 mol%) in THF at 20 °C (room temperature) has been carried out. Fortunately the reduction proceeded very efficiently and was completed after one hour. To our satisfaction, the product of this experiment has been confirmed to be methyl (3*S*)-3,4-dihydroxybutanoate (2) (88% yield),[7] neither triol (3) nor another possible diol (4) being detected. There emerges an important corollary that the reduction occurred definitely at the ester group α to the hydroxyl group of 1, leaving the other unchanged. The crucial role of the present reducing system has become immediately apparent when the reduction of 1 has been attempted solely with BMS or $NaBH_4$. Thus, the reduction of 1 with BMS (THF, 20 °C) was extremely

sluggish and, even after three days, 1 still remained partly unchanged (34% recovered), though the reduction has exhibited the selective feature, giving rise to 2 in 50% yield. On the other hand, $NaBH_4$ reduced 1 within two hours (THF, 20 °C) but the products in this case consisted of multiple components which refused to be separated for structural diagnosis.

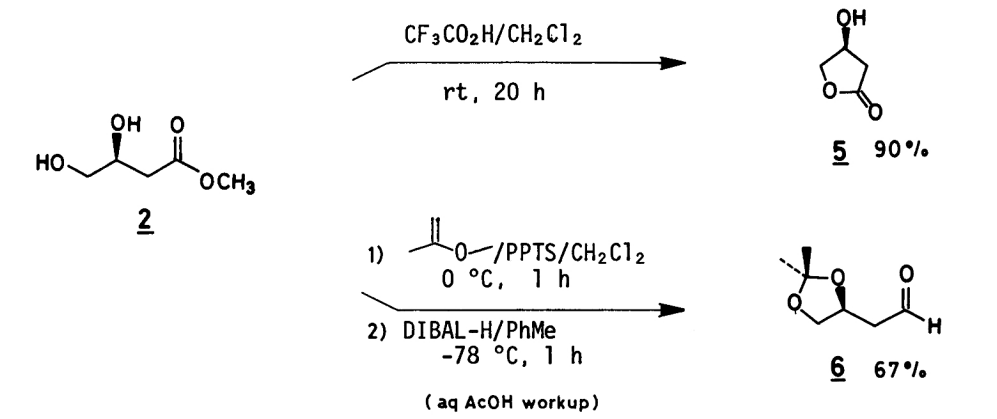


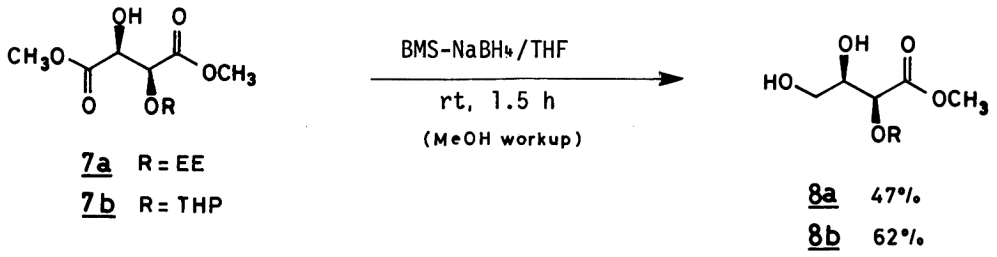
1 2 3 4

The following description of the experimental procedure is illustrative. To a solution of 1 (19.4 g, 0.12 mol) in dry THF (250 ml) was added BMS (12.2 ml, 0.122 mol)[8] and the mixture was stirred at 20 °C for 0.5 h. Then, $NaBH_4$ (0.2 g, 6 mmol) was thrown into the mixture and the resulting mixture was stirred for an additional 0.5 h, followed by the addition of dry methanol (77 ml), stirring being continued for 0.5 h. The solvent was removed by using rotary evaporator to give a colorless oil which was purified by means of column chromatography on silica gel (EtOAc), affording 2 in 88% yield (14.1 g). The volume of hydrogen evolved until the reaction was quenched by methanol, reached to that equivalent to the molar quantity of 1 employed. If the hydroxyl group of 1 is blocked as 1'-ethoxyethyl derivative, the reduction was no more effected under the given conditions.

There are no decisive proofs for the mechanism related to the emergences of both the satisfactory reducing power and exceptionally high selectivity highlighted by BMS–$NaBH_4$ system for 1. However, the regiocontrol in the ester reduction of 1 is of considerable synthetic utility. For instance, a promising chiral building block, (3*S*)-3-hydroxy-4-butanolide (5),[9] becomes available via two steps from 1, involving trifluoroacetic acid-catalyzed lactonization as the second step, for the antipode of which the previous route required seven steps.[3] In addition, a short-cut access to a useful chiral building block, (3*S*)-3,4-*O*-isopropylidene-3,4-dihydroxybutanal (6),[3] can be executed relying on the present method and involves three steps.[10]

An expected regiocontrol has been observed again in the reduction of monoprotected dimethyl L-tartrate (7a or 7b) with BMS–$NaBH_4$ system. Thus, 7a or 7b was converted to the derivatives of methyl (2*S*,3*S*)-2,3,4-trihydroxybutanoate[11] (8a or 8b) although the yields were somewhat low because the reactions were accompanied by an unforeseen splitting off of the hydroxy-protecting groups. Nevertheless, 8 should be versatile chiral building block of potential utility because each terminus as well as internal hydroxyl functions are unequally functionalized, which may be individually elaborated.





The method explored in this study for the selective reduction of the ester group located specifically as in 1 or 7 may serve as a beneficial device in organic synthesis, although its generalization, including the reducing mechanism in terms of the selectivity or parlayed reducing power,[12] and its scope and applicability in organic synthesis, must await future explorations in this field, which are currently in progress.

References

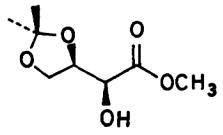
1) a) A. Hajós, "Complex Hydrides," Elsevier Scientific Publishing Co., Amsterdam, 1979; b) H. C. Brown and S. Krishnamurphy, Aldrichimica Acta, 12, 3 (1979); c) E. Winterfeldt, Synthesis, 1975, 617: see also references cited therein.

2) For example, DIBAL-H sometimes reduces ester groups selectively (Ref. 1c) and $NaBH_4$ reduces $-COOCH_3$ group attached to the γ-position of γ-butyrolactone, selectively (K. Koga, M. Taniguchi, and S. Yamada, Tetrahedron Lett., 1971, 263). To the best of our knowledge, however, no articles have ever described the selective reduction of one of the two identical ester groups located differently.

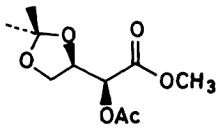
3) K. Mori, T. Tanigawa, and T. Matsuo, Tetrahedron, 35, 436 (1979).

4) L. M. Braun, R. A. Braun, H. R. Crissman, M. Opperman, and R. M. Adams, J. Org. Chem., 36, 2388 (1971); C. F. Lane, Aldrichimica Acta, 8, 20 (1975).

5) H. C. Brown and Y. M. Choi, Synthesis, 1981, 439.
6) H. C. Brown and N. M. Yoon, J. Am. Chem. Soc., 90, 2687 (1968).
7) Structure determination, performed on the corresponding 3,4-*O*-isopropylidene derivative: NMR ($CDCl_3$, 100 MHz) δ 1.36 (s, 3H), 1.41 (s, 3H), 2.52 (dd, 1H, *J*=15.7, 6.8 Hz), 2.71 (dd, 1H, *J*=15.7, 6.4 Hz), 3.65 (dd, 1H, *J*=8.3, 6.3 Hz), 3.70 (s, 3H), 4.16 (dd, 1H, *J*=8.3, 5.9 Hz), and 4.45 ppm (m, 1H); IR (film) 1745, 1421, 1385, 1375, 1215, and 1070 cm^{-1}; Mass m/z (EI, 70 eV) 159 ($M-CH_3$); $[\alpha]_D^{12}$ +8.62° (c 5.01, EtOH).
8) Commercial product from Aldrich Chemical Co.; one-mole equivalent or slight excess of BMS was strictly required for the completion of the reduction.
9) Spectral data (NMR and IR) and physical constants (bp and n_D) are fully consistent with those reported for the antipode (Ref. 3): $[\alpha]_D^{9}$ -85.9° (c 2.2, EtOH).
10) Previous route involved five steps (Ref. 3): recent report by S. Hanessian, A. Ugolini, and M. Therien (J. Org. Chem., 48, 4430 (1984)) has described shorter route to 6 by one-step than that of ours, involving BMS reduction–alcohol acetalization–PCC oxidation sequence starting from (*S*)-(−)-malic acid, the yields of the second and third steps being not mentioned.
11) Structure determination, performed on the corresponding deprotected 3,4-*O*-isopropylidene derivative (9) or 2-acetoxy-3,4-*O*-isopropylidene derivative (10): NMR for 10 ($CDCl_3$, 100 MHz) δ 1.36 (s, 3H), 1.43 (s, 3H), 2.18 (s, 3H), 3.78 (s, 3H), 3.93 (dd, 1H, *J*=8.8, 5.9 Hz), 4.10 (dd, 1H, *J*=8.8, 6.3 Hz), 4.52 (m, 1H), and 5.09 ppm (d, 1H, *J*=5.1 Hz); IR for 9 (film) 3500, 1745, 1440, 1380, 1370, 1260, 1210, and 1065 cm^{-1}; Mass for 9 m/z (EI, 70 eV) 175 ($M-CH_3$); $[\alpha]_D^{2}$ +18.4° (c 1.44, $CHCl_3$) for 9.

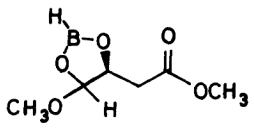


9

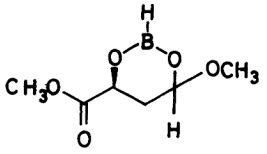


10

12) We are tentatively speculating that boroxolane-type intermediate (11) could be produced as an essentially final product before being decomposed with MeOH (see text). The simplest explanation for the selectivity observed in the present reduction might be that relatively short B–O bond length or entropy factor, or both of them can be responsible for more feasible formation of 11 than that of boroxane-type intermediate (12).



11



12

(Received May 31, 1984)