Tetrahedron Letters No.47, pp. 4155-4158, 1969. Pergamon Press. Printed in Great Britain.

NOVEL USE OF BORATE PROTECTIVE GROUPS IN ORGANIC SYNTHESIS. A FACILE SYNTHESIS OF DIHYDRO-β-SANTALOL

Wayne I. Fanta and William F. Erman

The Procter & Gamble Company, Miami Valley Laboratories, Cincinnati, Ohio 45239

(Received in USA 16 July 1969; received in UK for publication 9 September 1969)

Although methods for preparing boric acid esters have been known for many years (1), this means of protecting hydroxyl groups has found very limited practical use particularly in the field of organic synthesis.* We wish to communicate here the conversion of several complex alcohols to borates and subsequent utilization of these borates in hydrobromination, alkylation, and Wittig reactions where protection of a hydroxyl group was required. More specifically, we have applied these reactions to the synthesis of dihydro-β-santalol (I), a material with the powerful, woody fragrance of East Indian sandalwood oil (2). We also record here a novel Meerwein-Pondorf reduction discovered during these synthetic studies.

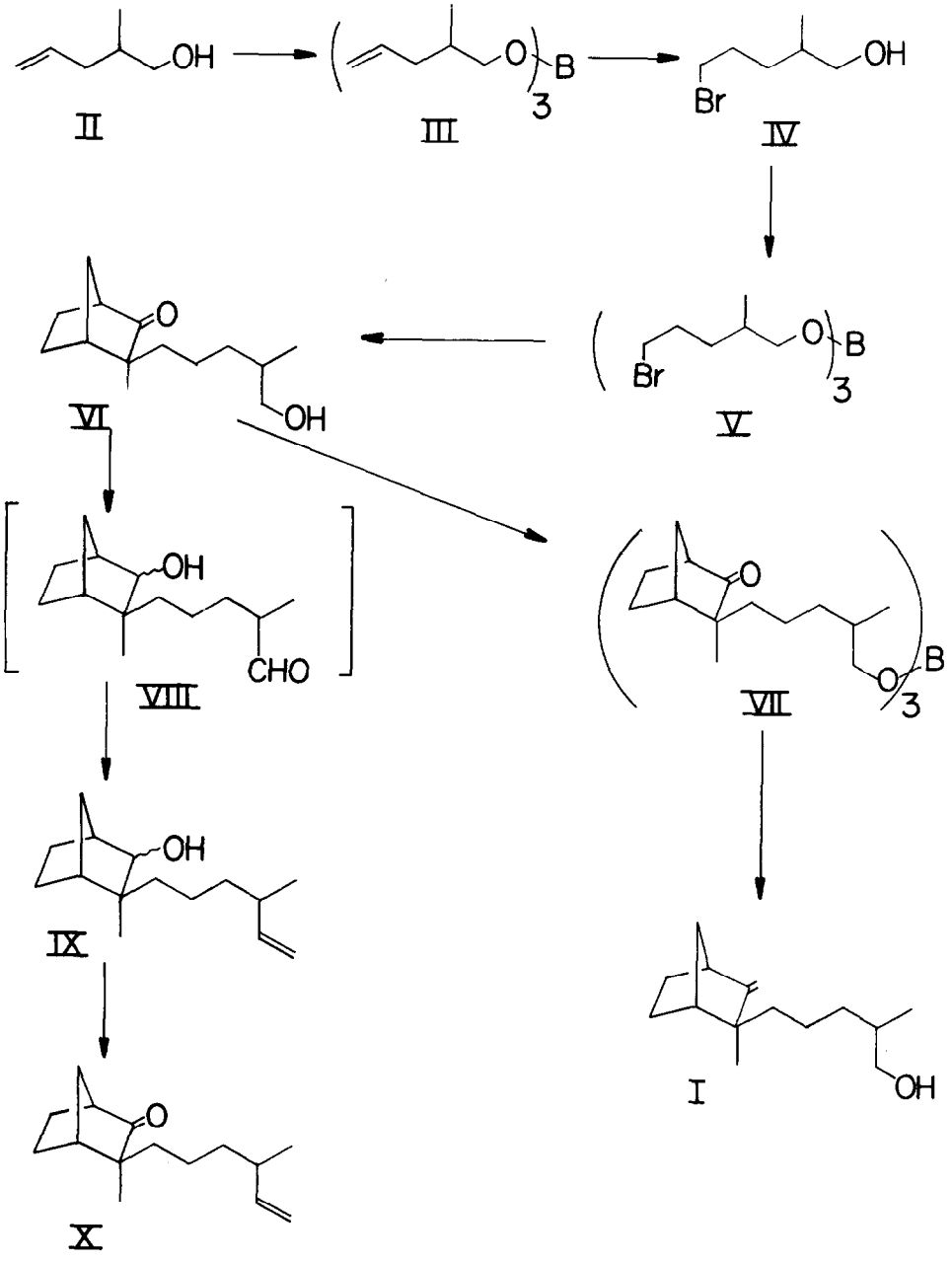
The basic system of santalol I can be constructed by alkylating methyl norcamphor with the appropriate six carbon side chain. The required alkylation agent seemed most easily obtained from alcohol II (3) by protection of the hydroxyl group and subsequent anti-Markownikoff hydrobromination of the terminal unsaturation. Chart I depicts the stepwise sequence required to construct dihydro-β-santalol. Although several standard blocking groups (acetate, tetrahydropyranyl ether) did find a place in this work,** we found protection of the alcohol as the boric

---

* See J. Staněk, M. Černý, J. Kocourek, and J. Pacák, The Monosaccharides, Academic Press, New York (1963), pp. 40, 254 and references therein for applications in carbohydrate chemistry. L. F. Fieser and M. Fieser, Reagents for Organic Synthesis, J. Wiley and Sons, Inc., New York, (1967), pp. 64-66, and references therein describe limited applications in hydroxylation and condensation reactions and in monoglyceride chemistry.

** These groups had several deficiencies which prevented their general usage in this synthetic scheme. These limitations will be elaborated in the full paper.

CHART I


OH
II
O
B
3
III
Br
OH
IV
O
B
Br
3
V
O
OH
VI
OH
CHO
VIII
O
B
O
3
VII
OH
IX
O
X
OH
I

acid ester to be far more versatile and convenient. The borates were formed in quantitative yield and were decomposed during product isolation by aqueous workup.*

Refluxing a benzene solution of alcohol II, bp 57-58° (12 mm), and one third of a molar equivalent of boric acid with constant removal of generated water afforded a quantitative yield of crude borate III: ir**(neat) 3.30, 6.11, 6.78, 7.08, 7.51, 9.61, 10.06, 10.94 μ; nmr (CCl_4) τ 3.95-4.42 (multiplet, 1, -C$\underline{H}$=), 4.85-5.15 (multiplet, 2, CH=C$\underline{H}_2$), 6.35 (doublet, 2, $\underline{J}$ = 6 Hz, C$\underline{H}_2$O), 7.65-8.50 (multiplet, 3, -C$\underline{H}_2$C$\underline{H}$(CH_3)-), 9.08 (doublet, 3, $\underline{J}$ = 6 Hz, CHC$\underline{H}_3$). Hydrobromination of an ice-cooled, hexane solution of crude borate III in the presence of benzoyl peroxide followed by dilute aqueous base isolation afforded bromohydrin IV (86%): bp 62° (0.02 mm); ir (neat) 2.99, 9.68 μ; nmr (CCl_4) τ 4.30 (singlet, 1, O$\underline{H}$), 6.61 (doublet, 2, $\underline{J}$ = 6 Hz, C$\underline{H}_2$OH), 6.63 (triplet, 2, $\underline{J}$ = 6 Hz, C$\underline{H}_2$Br), 9.07 (doublet, 3, $\underline{J}$ = 6 Hz, CHC$\underline{H}_3$) (4). Subsequent interaction of IV with boric acid as previously described afforded a quantitative crude yield of the required alkylating agent V: ir (neat) 6.75, 7.05, 7.48, 9.68 μ; nmr (CCl_4) τ 6.38 (doublet, 2, $\underline{J}$ = 5.5 Hz, C$\underline{H}_2$OB), 6.63 (triplet, 2, $\underline{J}$ = 6.5 Hz, C$\underline{H}_2$Br), 9.10 (doublet, 3, $\underline{J}$ = 6 Hz, C$\underline{H}$C$\underline{H}_3$).

Treatment of the sodium enolate of 3-methylnorcamphor (5) with bromide V in refluxing toluene for 68 hr afforded ketol VI (62%): bp 127-130° (0.07 mm); ir (neat) 2.90, 5.73, 7.30, 9.60, 10.92, 13.02 μ; nmr (CCl_4) τ 6.72 (doublet, 2, $\underline{J}$ = 6 Hz, C$\underline{H}_2$OH), 7.06 (singlet, 1, O$\underline{H}$), 9.07 (singlet, 3, C$\underline{H}_3$), 9.16 (doublet, 3, $\underline{J}$ = 6.5 Hz, CHC$\underline{H}_3$) (4,6). The ketol VI on condensation with excess methylenetriphenylphosphorane in dimethyl sulfoxide afforded, in addition to dihydro-β-santalol, substantial amounts of the isomeric hydroxy olefin IX. A sample of the material collected by preparative glpc showed the following spectral data: ir (neat) 2.96, 3.28, 6.10, 9.42, 10.03, 10.96 μ; nmr (CCl_4) τ 4.45 (multiplet, AA'BX, 1, $\underline{J}_{AB}$ = 17 Hz, $\underline{J}_{A'B}$ = 10 Hz, $\underline{J}_{BX}$ = 7 Hz, $\rangle CH_X\underline{C}\underline{H}_B{=}CH_A\underline{H}_{A'}$), 5.18 (doublet, 1, $\underline{J}_{AB}$ = 17 Hz, ${=}C\underline{H}_A\underline{H}_{A'}$), 5.21 (doublet, 1, $\underline{J}_{A'B}$ = 10 Hz, ${=}CH_A\underline{H}_{A'}$), 6.50 (doublet, 1, $\underline{J}$ = 4 Hz, C$\underline{H}$OH), 9.02 (doublet, 3, J = 7 Hz, CHC$\underline{H}_3$), 9.21 (singlet, 3, CH_3). The combination of a highly hindered ketone and a labile alcohol in a strongly basic medium apparently sets the stage for an unusually facile Meerwein-Pondorf reaction. This process can be visualized as proceeding through an intramolecular eight membered

---

* Although quite stable to anhydrous base or acid conditions, the borates are smoothly hydrolyzed by shaking for a few minutes in aqueous media whether neutral, acidic or basic.

** Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer.

transition state to the intermediate hydroxy aldehyde VIII which subsequently reacts with Wittig reagent. Oxidation of the resulting hydroxy olefin afforded keto olefin X: ir (neat) 3.30, 5.73, 6.11, 10.03, 10.95 μ; nmr (CCl_4) 4.46 (multiplet, AA'BX, 1, J_{AB} = 17 Hz, $J_{A'B}$ = 10 Hz, J_{BX} = 7 Hz, $\rangle CH_X\underline{C}H_B{=}CH_AH_{A'}$), 5.19 (doublet, 1, J_{AB} = 17 Hz, $=CH_A\underline{H}_{A'}$), 5.22 (doublet, 1, $J_{A'B}$ = 10 Hz, $=CH_A\underline{H}_{A'}$), 9.05 (doublet, 3, J = 7 Hz, $CHC\underline{H}_3$), 9.09 (singlet, 3, $C\underline{H}_3$) (4).

A high yield of dihydro-β-santalol (I) could be realized by prior conversion of ketol VI to keto borate VII: ir (neat) 5.72, 7.08, 7.50, 9.69, 10.59, 10.98 μ. Subsequent treatment with excess methylenetriphenylphosphorane in dimethyl sulfoxide for 24 hr at 70° afforded, on hydrolysis, 90% pure dihydro-β-santalol (90% from ketol VI). A sample of the alcohol purified by glpc showed the following spectral data: bp 106-107° (0.1 mm); $n_D^{26°}$ 1.4920; ir (neat) 3.00, 3.29, 6.03, 9.64, 11.35 μ; nmr (CCl_4) 5.31, 5.57 (singlets, 2, $=C\underline{H}_2$), 5.87 (singlet, 1, O$\underline{H}$), 6.65 (quartet, 2, J_1 = 6 Hz, J_2 = 4 Hz, $C\underline{H}_2OH$), 7.35, 7.89 (broad singlets, 2, bridgehead $\underline{H}$'s), 8.96 (singlet, 3, $C\underline{H}_3$), 9.09 (doublet, 3, J = 6 Hz, $CHC\underline{H}_3$); mass spectrum parent ion, m/e 222 (4).

A priori, one may be surprised by the apparent stability of these borates to nucleophilic reagents. However, this phenomenon is not entirely unexpected if one considers the fact that in this instance rather bulky nucleophiles would be required to react with highly substituted borates. Regardless of the reason for the stability, it would appear from the representative cases studied above that protection of alcohol groups as borates should find broad utility in organic synthesis.

Acknowledgments. The authors gratefully acknowledge the helpful suggestions of Prof. E. Wenkert and Prof. E. C. Taylor and the technical assistance of Mr. Kerry Fitzpatrick.

REFERENCES

1. M. F. Lappert, Chem. Rev., 56, 959 (1956).
2. E. Guenther, The Essential Oils, Vol. V, D. Van Nostrand Co., Inc., New York (1952), pp. 173-187.
3. M. Chérest, H. Felkin, C. Frajerman, C. Lion, G. Roussi and G. Swierczewski, Tetrahedron Letters, 875 (1966).
4. Satisfactory analytical data were also obtained.
5. E. J. Corey, R. Hartmann, and P. A. Vatekencherry, J. Amer. Chem. Soc., 84, 2611 (1962).
6. The stereochemistry of the product is consistent with the observation that alkylation of methyl norcamphor occurs from the exo-side of the molecule (5).