Stereocontrolled Synthesis of a Steroid Side Chain

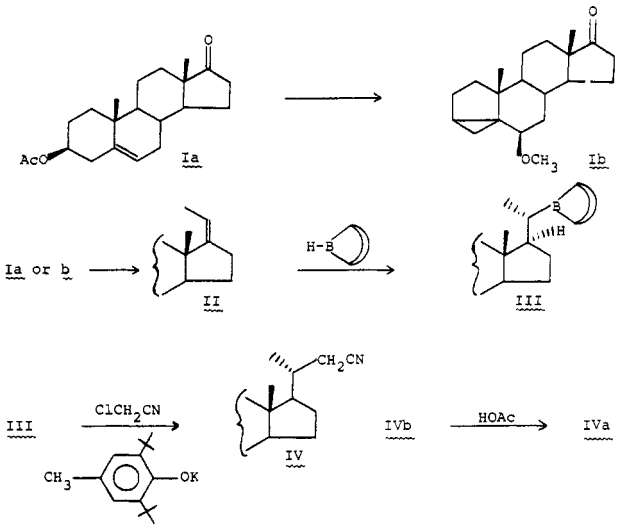
Summary: The hydroboration of 17(20)-(*Z*)-ethylidene steroids with 9-borabicyclo[3.3.1]nonane (9-BBN) proceeds in a highly selective manner from the α face of the steroid. Treatment of the resulting 9-BBN derivative with chloroacetonitrile and base produces a 21-cyano steroid possessing the correct natural configuration at C-17 and C-20.

Sir: The importance of steroids containing modified side chains, such as the ecdysones and the metabolites of vitamin D, has heightened interest in the synthesis of steroid side chains.[1] One approach to the synthesis of these compounds is to attach to a steroid nucleus a side chain which contains a functional group suitable for further elaboration. The ability to control stereochemistry in the acyclic chain, particularly at C-20, is crucial to this approach. Some recent solutions to this problem have employed palladium chemistry,[2] oxy-Cope or ene reactions,[3] catalytic hydrogenations,[4] and the use of optically active starting materials.[5] Herein we present a simple solution to this problem which uses the stereoselectivity of hydroboration to set the required chirality at C-20 (Scheme I).

The approach starts with the conversion of a 17-keto steroid (3β-acetoxy-5-androsten-17-one,[6] Ia, or the protected compound Ib) to a 17(20)-(*Z*)-ethylidene steroid (IIa or IIb) by the Wittig reaction[2,7] (ethyltriphenylphosphonium bromide/potassium *tert*-butoxide, 6 equiv, refluxing tetrahydrofuran, 12 h, 83% yield). It has been demonstrated that hydroboration of 17(20)-(*Z*)-ethylidene steroids with borane produces the required geometry at C-17 and C-20.[7a] Approach of borane from the β face is apparently blocked by the angular methyl group. Attempts to use this organoborane for carbon–carbon bond formations are futile since not all of the boron–carbon bonds are converted to product. Fortunately, we have found that this problem is circumvented by using 9-borabicyclo[3.3.1]nonane (9-BBN).[8] The hydroboration of II with 9-BBN (1 mol)[9] proceeds smoothly at room temperature. The reaction is generally over in a few hours although we usually stir the solution overnight. The chemoselectivity of 9-BBN[10] provides an additional bonus in that the 17(20) double bond preferentially reacts in the presence of the 5(6) double bond of IIa. Thus, it is not necessary to protect the 5(6) double bond as is customary in many other schemes.

A variety of stereospecific carbon–carbon bond forming reactions have been developed using organoboranes and

Scheme I



9-BBN as a blocking group.[11] Thus, hydroboration of the steroid with 9-BBN followed by a carbon–carbon bond forming reaction should be an efficient approach to the construction of steroid side chains. However, this approach is deceptively simple. Attempts to attach a cholesterol-type side chain directly through formation of an acetylene or allene[12] met with failure. Even two-carbon homologation to an ester by α alkylation of an ethyl haloacetate,[13] a reaction known to work with *B*-alkyl-9-BBN compounds, gave low yields under a variety of conditions.

With the assumption that steric factors could be causing the low yield, the reaction with the smaller chloroacetonitrile was investigated.[14] The organoborane (IIIa as the 3β acetate or alcohol or IIIb) solution (1.03 mmol in 2 mL of tetrahydrofuran (THF)) was cooled to 0 °C and 2.19 mL (1.03 mmol) of a 0.47 M slurry of potassium/2,6-di-*tert*-butyl-4-methylphenoxide[15] in THF was added to the flask followed by 65 μL (1.03 mmol) of chloroacetonitrile. After 1 h at 0 °C, 0.4 mL of ethanol was added and the solution stirred for 15 min at room temperature. Then 5 mL of hexane was added and the solution extracted with three 25-mL of portions of 1 N sodium hydroxide followed by two 20-mL portions of water. The organic phase was dried over magnesium sulfate and then chromatographed on silica gel. The product IV was isolated in 60–70% yield. The protected product IVb is readily converted to IVa by brief reflux in acetic acid. Compound IVa [3-acetate; mp 179–181 °C (lit.[16] mp 186–187 °C); NMR 0.70 (s, C-18 Me), 1.00 (s, C-19 Me), 1.16 (d, C-21 Me), 2.00 (s, acetate Me), 2.26 (m, CH_2CN)] was identical (^{13}C and ^1H NMR, melting point, TLC) with the nitrile prepared from conventional sources.[17]

A mixture of the two C-20 epimers was prepared to verify the purity of IV. Pregnenolone acetate[6] was treated with methylenetriphenylphosphorane (followed by acety-

(1) For a review on the construction of steroid side chains, see: Piatak, D. M.; Wicha, J. *Chem. Rev.* **1978**, *78*, 199.
(2) (a) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1978**, *100*, 3435. (b) Trost, B. M.; Matsumura, Y. *J. Org. Chem.* **1977**, *42*, 2036. (c) Temple, J. S.; Schwartz, J. *J. Am. Chem. Soc.* **1980**, *102*, 7381.
(3) Koreeda, M.; Tanaka, Y.; Schwartz, A. *J. Org. Chem.* **1980**, *45*, 1172. Tanabe, M.; Hayashi, K. *J. Am. Chem. Soc.* **1980**, *102*, 862. Dauben, W. G.; Brookhart, T. *Ibid.*, in press.
(4) Schow, S. R.; McMorris, T. C. *J. Org. Chem.* **1979**, *44*, 3760.
(5) Trost, B. M.; Bernstein, P. R.; Funfschilling, P. C. *J. Am. Chem. Soc.* **1979**, *101*, 4378. Grieco, P. A.; Takigawa, T.; Moore, D. R. *Ibid.* **1979**, *101*, 4380.
(6) Generously supplied by Syntex.
(7) (a) Krubiner, A. M.; Oliveto, E. P. *J. Org. Chem.* **1966**, *31*, 24. (b) Drefahl, G.; Ponsold, K.; Schick, H. *Chem. Ber.* **1965**, *98*, 604.
(8) Brown, H. C.; Knights, E. F.; Scouten, C. G. *J. Am. Chem. Soc.* **1974**, *96*, 7765. 9-BBN is available from Aldrich.
(9) During the formation of the ethylidene compound from I, the acetate group is lost. It may be replaced (acetic anhydride at reflux) or the alcohol used directly. In the latter case, 2 mol of 9-BBN must be used since the alcohol group reacts with 9-BBN.
(10) Brown, H. C.; Liotta, R.; Scouten, C. G. *J. Am. Chem. Soc.* **1976**, *98*, 5297.
(11) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. "Organic Syntheses via Organoboranes"; Wiley: New York, 1975.
(12) Midland, M. M. *J. Org. Chem.* **1977**, *42*, 2650.
(13) Brown, H. C.; Nambu, H.; Rogic, M. M. *J. Am. Chem. Soc.* **1969**, *91*, 6855. Brown, H. C.; Rogic, M. M. *Ibid.* **1969**, *91*, 2146. Brown, H. C.; Rogic, M. M.; Rathke, M. W.; Kabalka, G. W. *Ibid.* **1969**, *91*, 2150. We were able to reproduce the literature results using 9-BBN and 1-methylcyclopentene.
(14) Brown, H. C.; Nambu, H.; Rogic, M. M. *J. Am. Chem. Soc.* **1969**, *91*, 6854. The validity of the steric argument is speculative.
(15) Freshly prepared from the phenoxide and potassium metal.
(16) Herr, M. E.; Heyl, F. W. *J. Am. Chem. Soc.* **1950**, *72*, 1753.
(17) Johnson, R. L.; Carey, S. C.; Norman, A. W.; Okamura, W. H. *J. Med. Chem.* **1977**, *20*, 5.

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lation) to produce the 20(21)-methylene steroid. Hydroboration with borane·methyl sulfide produced a mixture of the 20*S*- and 20*R*-21-hydroxy steroids.[18,19] This mixture of hydroxy steroids was converted into the epimeric cyano compounds via the tosylate.[17] Comparison of the NMR spectra (^{1}H and ^{13}C) of the mixture to the spectra of IVa indicated that within the limits of detection, none of the C-20 epimer was present. The ^{13}C NMR spectrum was particularly informative. In the mixture a doubling of the resonances was observed for the C-18 methyl (11.8 and 12.0 ppm), C-19 methyl (19.1 and 19.6 ppm), and C-20 (33.4 and 32.1 ppm) as well as numerous other resonances. With the pure product single resonances were observed for C-18 (11.8 ppm), C-19 (19.1 ppm), and C-20 (33.4 ppm).

This process represents a short (essentially two step) method for attaching side chains to the readily available 17-keto steroids. The nitrile provides functionality which may be readily manipulated into more elaborate side chains. Furthermore, the 17(20)-(*E*)-ethylidene isomer is available and is reported to undergo hydroboration to produce the opposite configuration at C-20.[20] Thus, it should be feasible to prepare steroids with the unnatural configuration at C-20. Such compounds have recently been found in marine sources[21] and have also become important for biochemical studies.[22] We are continuing to explore these possibilities.

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Registry No. Ia, 853-23-6; Ib, 75917-53-2; IIa, 1167-33-5; IIb, 75863-82-0; IIIa 3β-acetate, 75863-83-1; IIIa 3β-alcohol, 75863-84-2; IIIb, 75863-85-3; IVa 3β-acetate, 75863-86-4; IVb, 75863-87-5; 9-BBN, 280-64-8; chloroacetonitrile, 107-14-2.

(18) Bottin, J.; Fetizon, M. *J. Chem. Soc. D* **1971**, 1087; *Bull. Soc. Chim. Fr.* **1972**, 2344.

(19) Hydroboration of the methylene compound with 9-BBN gave predominantly (14:1) the 20*S*-21-hydroxy steroid (natural configuration at C-20). Hydroboration with dicyclohexylborane produces a 25:1 mixture while borane·methyl sulfide gives a 1.1:1 ratio of 20*S*:20*R*. The availability of this alcohol from readily available 20-keto steroids offers an alternative route to steroid side chains.

(20) Bernassau, J. M.; Fetizon, M.; Hanna, I.; Rens, J.; Viger, A. *Tetrahedron* **1979**, *35*, 1657.

(21) Vanderah, D. J.; Djerassi, C. *J. Org. Chem.* **1978**, *43*, 1442.

(22) Koreeda, M.; Koizumi, N. *Tetrahedron Lett.* **1978**, 1641.

(23) Fellow of the Alfred P. Sloan Foundation.

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