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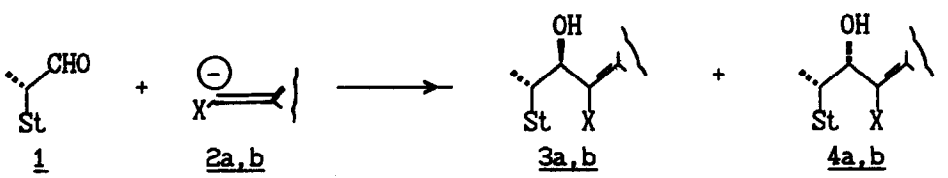
HIGHLY STEREOSELECTIVE SYNTHESIS OF STEROIDAL 22α-ALLYLIC ALCOHOLS VIA 22-ALDEHYDES AND 1-SILYL-1-IODO-1-ALKENES: A NEW EFFICIENT ROUTE TO THE SIDE CHAIN CONSTRUCTION OF BRASSINOLIDE

V. A. Khripach*, V. N. Zhabinskiy, V. K. Olkhovick

Institute of Bioorganic Chemistry, Byelorussian Academy of Sciences,
Zhodinskaya 5/2, 220045 MINSK, USSR

Summary: *1-Lithium-1-(trimethylsilyl)-3-methyl-1-butene 9 undergoes smooth addition with aldehyde 10 to give 22α-alcohol 11 as a major product. Desilylation of 11 and further oxidation of 14 by MCPBA leads to epoxyalcohol 16 suitable for brassinolide synthesis.*

One of the most important and complicated problems for the synthesis of brassinosteroids is the stereoselective construction of the side chain possessing four chiral centres. For its solving several side chain formation methods have been elaborated[1]. Many of them are based on the reactions of steroidal 22-aldehydes 1 with various kinds of vinyl carbanions 2a and further transformations of allylic alcohol intermediates 3a. However these stereoselectivities were not high[2] and gave relatively low yields of the desired 22α-alcohols 3a along with substancial amounts of their 22β-isomers 4a. We proposed that the reaction could be more stereoselective if the



1 2a,b 3a,b 4a,b

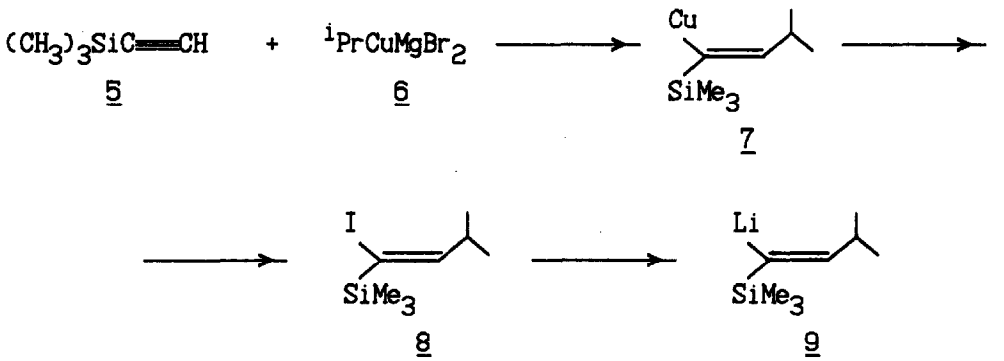
a: X=H; b: X=$SiMe_3$

anionic centre of nucleophile was directly connected to some group other

than H. The most suitable for this purpose it seemed us to be trimethylsilyl group because it can be easily removed on the next stages[3] and furthermore it facilitates[4] the formation of carbanion 2b.

That is why, we have tested here the stereoselectivity of addition of 1-lithium-1-(trimethylsilyl)-3-methyl-1-butene 9 with aldehyde 10 obtained by usual method from stigmasterol[5].

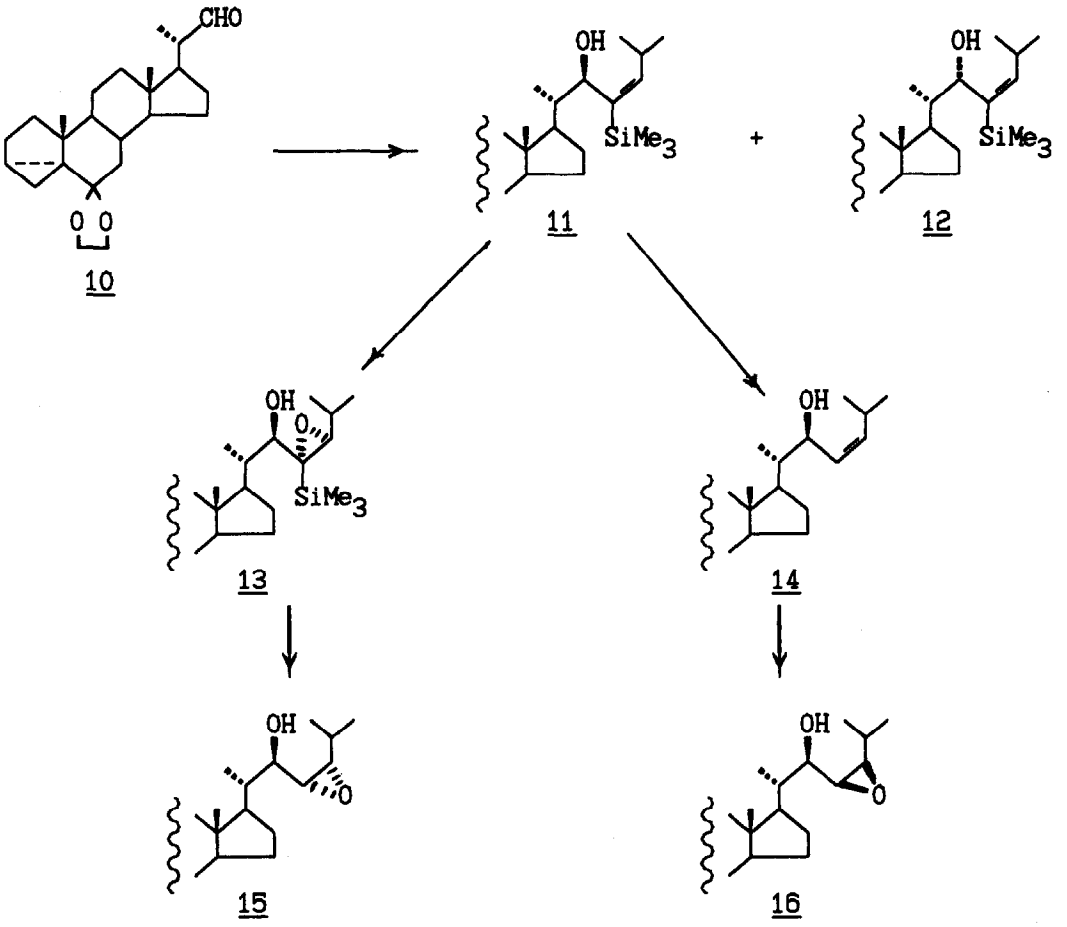
The synthesis of iodovinylsilane 8, a starting material for lithium



derivative 9, was achieved as depicted in the scheme. Trimethylsilylacetylene 5 was transformed into 7 by the addition[6] of isopropylcuprate 6. Further substitution of Cu-atom in 7 by iodine gave[7] 8. Structure of 8 corresponds with spectral and literature data of the reactions of alkylcuprates with ethynylsilanes[8].

The reaction of the aldehyde 10 with the lithium derivative 9, obtained from 8 under the action of BuLi, proceeded smoothly at -78°C to give a 10:1 mixture of the epimeric alcohols 22α(R)-OH 11[7] and 22β(S)-OH 12[7] in 97% total yield. For example, one of the most selective synthesis based on the employing of vinyl carbanions[2c] gave a 3:1 epimeric mixture of the 22α- and 22β-alcohols in 64% total yield. The structure 11 was assigned to an isomer whose ^{1}H-NMR spectrum showed J_{20}-J_{22}=0 Hz. Such value is characteristic of 22α-alcohols[2d]. An additional proof is conversion of 11 to compounds 14 and 16 with known structures of the side chains[2b,d].

Epoxidation of 11 with MCPBA followed by nucleophilic cleavage of Si-C- bond in 13[7] gave epoxide 15[7] as a main product. On the other hand, an initial Si-C-bond cleavage in 11 followed by epoxidation of alkene 14[7] with MCPBA afforded the brassinosteroid intermediate 16[7] in almost quantitative yield. The further construction of the side chain of brassinolide from 16 is known[2b,d].



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7. All compounds were characterized by ^{1}H NMR, IR and mass-spectroscopy. Selected spectral data are as follows.

Compound 8: ^{1}H-NMR (360 MHz, $CDCl_3$) 0.16(s, 9H), 1.01(d, 6H), 2.69(m, 1H), 5.84(d, 1H). MS(m/e) 268(M), 194, 139.

Compound 11: ^{1}H-NMR (360 MHz, $CDCl_3$) 0.1(s, 9H), 0.33(t, 1H), 0.70(s, 3H), 0.89(d, 3H), 0.92(d,3H), 0.93(d, 3H), 1.00(s,3H), 2.62(m, 1H), 3.69-4.04 (m, 4H), 4.72(s, 1H), 5.40(d, 1H). IR(cm^{-1}) 3520, 2960, 2870, 840.
MS(m/e) 514(M), 496, 441, 423, 342.

Compound 12: ^{1}H-NMR (360 MHz, $CDCl_3$) 0.1(s, 9H), 0.3(t, 1H), 0.74(s, 3H), 0.77(d, 3H), 0.89(d, 3H), 0.91(d, 3H), 0.98(s, 3H), 2.65(m, 1H), 3.68-4.04(m, 4H), 4.44(d, 1H), 5.54(d, 1H). IR(cm^{-1}) 3500, 1600, 835.
MS(m/e) 514(M), 499, 481, 343.

Compound 14: ^{1}H-NMR (360 MHz, $CDCl_3$) 0.33(t, 1H), 0.72(s, 3H), 0.95(d, 3H), 0.96(d, 3H), 0.97(s, 3H), 0.99(d, 3H), 2.59(m, 1H), 3.71-4.06(m, 4H), 4.55(d, 1H), 5.25(dt, 1H), 5.40(dd, 1H). MS(m/e) 442(M), 427, 424, 343.

Compound 15: ^{1}H-NMR (360 MHz, $CDCl_3$) 0.33(t, 1H), 0.75(s, 3H), 1.00(s, 3H), 1.01(d, 3H), 1.06 (d, 3H), 1.10(d, 3H), 2.69(dd, 1H), 3.00(dd, 1H), 3.49(dd, 1H), 3.69-4.03 (m, 4H). MS(m/e) 458(M), 443.

Compound 16: ^{1}H-NMR (360 MHz, $CDCl_3$) 0.32(t, 1H), 0.72(s, 3H), 0.97(d, 3H), 1.00 (s, 3H), 1.06(d, 3H), 1.10 (d, 3H), 2.67 (dd, 1H), 3.04(dd, 1H), 3.62(d, 1H), 3.70-4.05(m, 4H). MS(m/e) 458(M), 443, 402.

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