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A highly chemoselective and diastereoselective trifluoromethane sulfonic acid catalyzed addition of allyltributylstannanes to a steroidal aldehyde in aqueous media

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Abstract

Trifluoromethane sulfonic acid catalyzes the addition of allylic tributylstannanes to steroidal aldehyde **1** in aqueous media to give the corresponding homoallylic alcohols in high yields and high diastereoselectivities.

1. Introduction

Steroids play an important role in the biological systems of animals and plants. In recent years, the isolation of new steroids possessing functionalized side chains, such as vitamin D metabolites, insect moulting hormones, the plant growth promoters brassinolide, castasterone and dolicholide, and sex stimulating steroids has highlighted that the stereochemistry of the side chain is important for the biological activity.[1–5] Furthermore, findings by Janowski have shown that oxysterols are potential ligands for orphan nuclear liver X receptor (LXRα), which transcriptionally regulates three crucial metabolic pathways: steroid hormone biosynthesis, bile acid synthesis, and the conversion of lanosterol to cholesterol.[6,7] Further research by Corey suggested that the introduction of a hydrogen bonding acceptor on the steroid side chain may result in higher-affinity ligands.[8–10] Therefore the development of new methods which allow easy access to various oxysterols has attracted a good deal of interest among organic chemists.

2. Results and discussion

Our interest in the application of organic reactions in aqueous media[11] for the construction of steroidal side chains has encouraged us to investigate the allylation reaction of steroidal aldehyde **1**, a commercially available steroid, with tributylallylic stannanes **2** in aqueous media[12–17] (Scheme 1).

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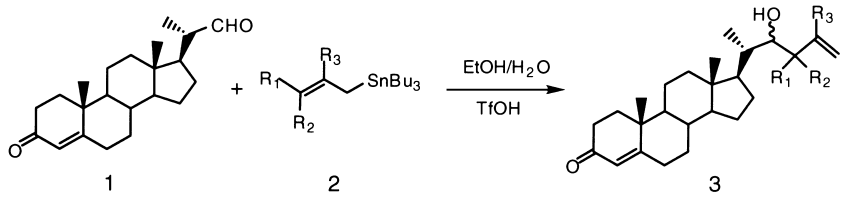
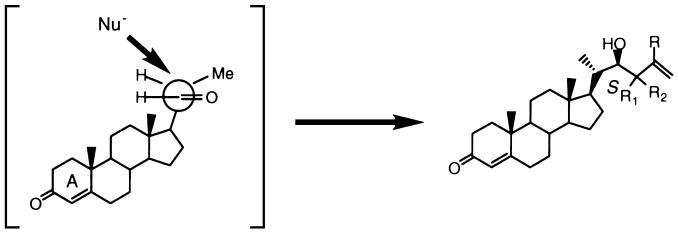


Scheme 1.

Initially, we carried out the reaction of allyltributyltin with steroidal aldehyde **1** in a pure aqueous environment (entry 1). Unfortunately, the desired product was not obtained even when the reaction was stirred for 36 h. This is probably due to the low solubility of the steroidal aldehyde in water. However, when the reaction was carried out in a mixed solvent of EtOH:H_2O (1:1) (entry 3), the reaction proceeded smoothly to afford the desired homoallylic alcohol in good yield and high selectivity, which is even better than the reaction in pure EtOH (entry 2). We have also investigated the reaction with several Brönsted acids (entries 3–5). Results show that, comparing with TfOH, most of the Brönsted acids were not effective enough in catalyzing the formation of the allylation product and lower diastereoselectivities were noted (entries 3–5). After discovering EtOH/H_2O as the good solvent system and TfOH as the best catalyst for the reaction, reactions using various allylic stannanes were carried out (entries 6–9).

The special features of this methodology are: (1) in all cases, the reactions proceeded smoothly at ambient temperature to give the desired homoallylic alcohols in good yields, with the (22*S*) isomer predominating over the (22*R*) isomer after usual workup. Especially noteworthy is the high 22*S* diastereoselectivity observed in some cases (entries 3 and 8); (2) the reactions are highly chemoselective, reacting only with the aldehyde functionality. No reaction was observed with the enone functionality in the A ring; and (3) this reaction proceeded in aqueous media and allylic stannanes containing acidic proton can also be used directly without the need for protection (entry 7).

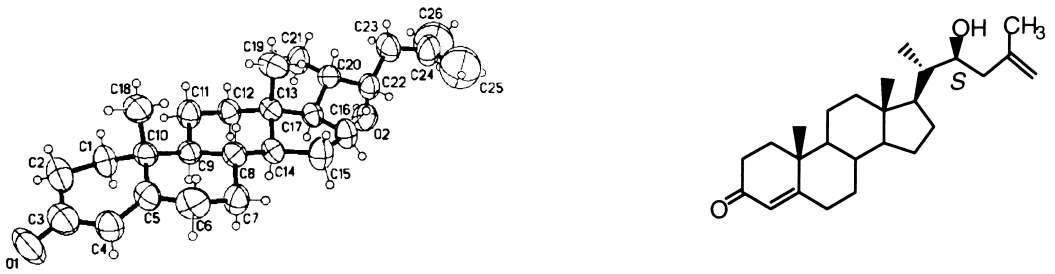
The high 22*S* selectivity observed can be explained using the Felkin–Ahn model as shown in Scheme 2.



Scheme 2.

The structure of one of the allylation products was confirmed by a single crystal X-ray† diffraction analysis (Scheme 3). All the other product isomers were confirmed based on the similarities of the polarity, and ^1H and ^{13}C NMR chemical shifts.

† X-Ray data for major isomer of entry 6: $C_{26}H_{40}O_2$; monoclinic; *P*2(1); $a = 13.165(1)$ Å; $b = 9.8978(8)$ Å; $c = 17.855(1)$ Å; $\alpha = 90°$; $\beta = 100.226(1)°$; $\gamma = 90°$; $Z = 4$; $R_1[I > 2\alpha(I)] = 0.0830$.



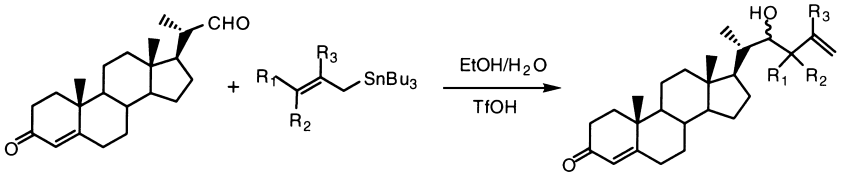
Scheme 3.

In conclusion, this work demonstrates that trifluoromethane sulfonic acid-catalyzed addition of allylstannanes to a steroidal aldehyde in aqueous media [EtOH:H_2O (1:1)] affords the corresponding products in good yields and high diastereoselectivities. The use of this methodology for the synthesis of other steroid side chains is in progress.[18]

3. Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker ACF 300 (^1H, 300 MHz and ^{13}C, 75.4 MHz) nuclear magnetic resonance spectrometer in $CDCl_3$.

3.1. General procedure of allylation reaction 20-(1′-hydroxy-3′-buten-1′-yl)-3-oxopregn-4-ene (Table 1, entry 3)

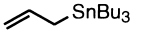
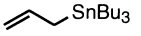
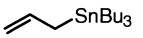
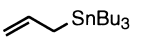
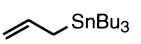
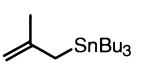
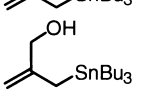
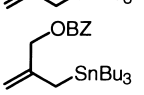
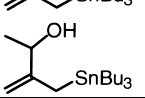


A typical procedure is as follows: to a solution of allyltributylstannane (0.2 mmol, 0.062 ml) and steroid **1** (0.1 mmol, 0.033 g) in EtOH (0.2 ml) and water (0.2 ml), commercially available trifluoromethane sulfonic acid (0.1 mmol, 0.009 ml) was added. The reaction mixture was stirred vigorously at room temperature overnight and finally extracted by ethyl acatate (50 ml). The organic extract was dried over anhydrous magnesium sulfate, concentrated under vacuum and purified by flash silica gel column chromatography to afford the desired homoallylic alcohol as a white solid (0.0352 g, 0.095 mmol) in 95% yield.

3.2. 20-(1′-Hydroxy-3′-buten-1′-yl)-3-oxopregn-4-ene (Table 1, entry 3)

White solid, m.p. 178–180°C. FTIR (NaCl) ν 3368, 2939, 1674, 1432, 1229, 886 cm^{-1}; H NMR (300 MHz) δ 0.72 (s, 3H, **C(19)H$_3$**), 0.92 (d, J 6.03 Hz, 3H, **C(21)H$_3$**), 1.18 (s, 3H, **C(18)H$_3$**), 3.68–3.72 (m, 1H, **CH**OH), 5.08–5.14 (2H, =**CH$_2$**), 5.72 (s, 1H, **CH**=C), 5.75–5.81 (m, 1H, **CH**=CH$_2$); ^{13}C NMR δ 11.53,11.75, 17.27, 20.96, 23.99, 27.53, 31.88, 32.79, 33.84, 35.58, 38.48, 39.54, 39.93, 40.02, 42.23, 52.48, 53.65, 55.66, 72.26, 117.28, 123.67, 135.55, 171.35, 199.41 ppm; HREIMS

Table 1
Reactions of steroidal aldehyde **1** with various allyltributylstannanes in the presence of CF_3SO_3H[a]

Entry	Allylic Stannane	Conditions	Yield%[b]	Selectivity (22*S*:22*R*)
1		TfOH (1eq), H_2O, rt, 36 h	0	-
2		TfOH (1eq), EtOH, rt, 12 h	90	86:14
3		TfOH (1eq), EtOH-H_2O (1:1), rt, 12 h	95	92:8
4		HCl (1M) (1eq), EtOH-H_2O (1:1), rt, 12 h	50	74:26
5		CF_3COOH (1eq), EtOH-H_2O (1:1), rt, 12 h	80	79:21
6		TfOH (1eq), EtOH-H_2O (1:1), rt, 36 h	97	86:14
7		TfOH (1eq), EtOH-H_2O (1:1), rt, 48 h	99	87:13
8		TfOH (1eq), EtOH-H_2O (1:1), rt, 72 h	80	92:8
9		TfOH (1eq), EtOH-H_2O (1:1), rt, 48 h	99	87:13[c]

[a] All reactions were carried out on 0.05-0.2 mmol scale. [b] Isolated yield. [c] 1:1 mixture at C-25 (racemic mixture of allylstannane was used)

(M^+) calcd for $C_{25}H_{38}O_2$ 370.2888, found 370.2872. Minor (22*R*) isomer, ^1H NMR (300 MHz, $CDCl_3$) δ 0.74 (**C(19)H$_3$**).

3.3. 20-(1′-Hydroxy-3′-methyl-3′-buten-1′-yl)-3-oxopregn-4-ene (Table 1, entry 6)

White solid, m.p. 186–188°C. ν 3433, 2939, 1661, 1231, 983 cm^{-1}; ^1H NMR (300 MHz) δ 0.72 (s, 3H, **C(19)H$_3$**), 0.92 (d, *J* 6.03 Hz, 3H, **C(21)H$_3$**), 1.18 (s, 3H, **C(18)H$_3$**), 1.75 (s, 3H, **CH$_3$**C=), 3.82–3.84 (m, 1H, **CH**OH), 4.78 (s, 1H, =**CH$_2$**), 4.84 (s, 1H, =**CH$_2$**), 5.72 (s, 1H, **CH**=C); ^{13}C NMR δ 11.67, 13.47, 17.26, 20.94, 22.34, 23.99, 26.71, 27.58, 31.88, 32.79, 33.84, 35.56, 38.47, 39.51, 40.11, 42.23, 43.96, 52.59, 53.63, 55.63, 70.05, 112.88, 123.66, 142.99, 171.43, 199.46 ppm; HREIMS (M^+) calcd for $C_{26}H_{40}O_2$ 384.2985, found 384.3028. Minor (22*R*) isomer, ^1H NMR (300 MHz, $CDCl_3$) δ 0.75 (**C(19)H$_3$**).

3.4. 20-(1′-Hydroxy-3′-(hydroxymethyl)-3′-buten-1′-yl)-3-oxopregn-4-ene (Table 1, entry 7)

White solid, m.p. 192–194°C. FTIR (NaCl) ν 3326, 2943, 1664, 1561, 1378, 1071, 989 cm^{-1}; ^1H NMR (300 MHz) δ 0.72 (s, 3H, **C(19)H$_3$**), 0.92 (d, *J* 6.03 Hz, 3H, **C(21)H$_3$**), 1.18 (s, 3H, **C(18)H$_3$**), 3.79–3.83 (m, 1H, **CH**OH), 4.04–4.18 (m, 2H, **CH$_2$**OH), 4.95 (s, 1H, =**CH$_2$**), 5.11 (s, 1H, =**CH$_2$**), 5.72 (s, 1H, **CH**=C); ^{13}C NMR δ 11.75, 13.48, 17.26, 20.94, 23.99, 26.72, 27.55, 31.87, 32.79, 33.84, 35.56, 38.48, 39.53, 40.15, 40.93, 42.25, 52.53, 53.63, 55.65, 66.30, 72.44, 113.33, 123.67, 142.99, 171.40, 199.55 ppm; HREIMS (M^+–H_2O) calcd for $C_{26}H_{38}O_2$ 382.2880, found 382.2872. Minor (22*R*) isomer, ^1H NMR (300 MHz, $CDCl_3$) δ 0.74 (**C(19)H$_3$**).

3.5. 20-(1′-Hydroxy-3′-((phenylmethoxy)methyl)-3′-buten-1′-yl)-3-oxopregn-4-ene (Table 1, entry 8)

Colorless oil. FTIR (NaCl) ν 3434, 2931, 1684, 1490, 1269 cm^{-1}; ^1H NMR (300 MHz) δ 0.71 (s, 3H, **C(19)H$_3$**), 0.94 (d, J 6.03 Hz, 3H, **C(21)H$_3$**), 1.18 (s, 3H, **C(18)H$_3$**), 3.83–3.92 (m, 1H, **CH**OH), 4.72–4.92 (m, 2H, **CH$_2$**OBz), 5.09 (s, 1H, =**CH$_2$**), 5.25 (s, 1H, =**CH$_2$**), 5.72 (s, 1H, **CH**=C), 7.42–8.08 (m, 5H, **phenyl-H**); ^{13}C NMR δ 11.66, 11.77, 17.27, 20.94, 23.98, 27.10, 27.58, 31.86, 32.79, 33.85, 35.57, 38.47, 39.52, 39.76, 40.44, 40.60, 42.24, 52.54, 53.61, 55.62, 67.06, 71.04, 115.02, 123.69, 128.33, 129.55, 130.10, 133.02, 141.46, 166.10, 171.39, 199.48 ppm; HREIMS (M^+) calcd for $C_{33}H_{44}O_4$ 504.3267, found 504.3251. Minor (22R) isomer, ^1H NMR (300 MHz, $CDCl_3$) δ 0.73 (**C(19)H$_3$**).

3.6. 20-(1′-Hydroxy-3′-((1″-hydroxy)etheyl)-buten-1′-yl)-3-oxopregn-4-ene (Table 1, entry 9)

White solid, m.p. 176–178C. FTIR (NaCl) ν 3460, 2945, 1670, 1257, 1117, 838, 776 cm^{-1}; ^1H NMR (300 MHz) δ 0.72 (s, 3H, **C(19)H$_3$**), 0.92 (d, J 7.22 Hz, 3H, **C(21)H$_3$**), 1.18 (s, 3H, **C(18)H$_3$**), 1.29 (d, J 6.86 Hz, 3H, **CH$_3$**CHOH), 3.76–3.89 (m, 1H, **CH**OH), 4.27–4.35 (m, 1H, **CH**=CH$_2$), 4.93 (s, 1H, =**CH$_2$**), 5.13 (s, 1H, =**CH$_2$**), 5.72 (s, 1H, **CH**=C); ^{13}C NMR δ 11.85, 13.53, 17.34, 21.89, 22.63, 24.07, 26.81, 27.83, 31.95, 32.86, 33.91, 35.66, 37.65, 38.54, 39.61, 40.94, 42.33, 52.66, 53.80, 55.72, 70.60, 72.69, 111.80, 123.76, 150.49, 171.43, 199.51 ppm; HREIMS (M^+) calcd for $C_{27}H_{42}O_3$ 414.3110, found 414.3134. Minor (22R) isomer, ^1H NMR (300 MHz, $CDCl_3$) δ 0.74 (**C(19)H$_3$**).

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18. This research was assisted financially by grants from the National University of Singapore.