

## STEREOCHEMISTRY OF CUPRATE-MEDIATED CONJUGATE ADDITIONS OF A 17-IODOANDROST-16-ENE TO *E*- AND *Z*-6-METHYLHEPT-2-EN-4-ONE

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Dedicated to the memory of Dr Václav Černý, DrSc., a pioneer of steroid chemistry.

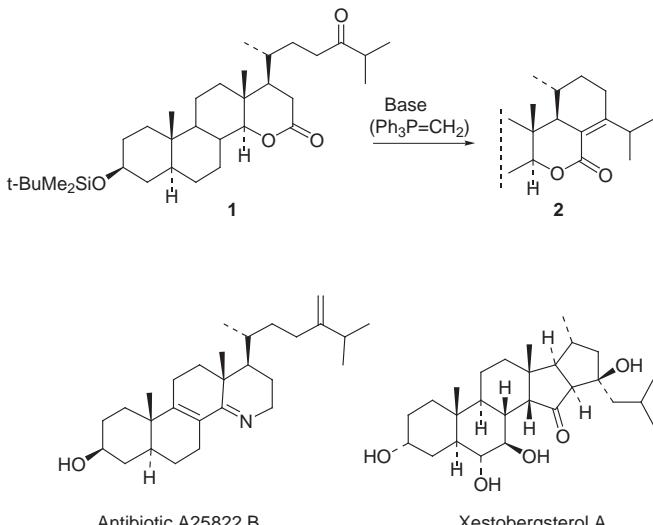
(*3S,15R*)-15-(Benzylxy)-3-[(*tert*-butyldimethylsilyl)oxy]-17-iodoandrosta-5,16-diene (**3**) was prepared from the corresponding 17-hydrazone **9** with iodine in the presence of tetramethylguanidine. The vinyl iodide **3** was converted into the corresponding organocuprate and conjugate additions of the latter were performed with both (*E*)- and (*Z*)-6-methylhept-2-en-4-one (**4a** and **4b**, respectively). In each case, the resulting adduct **5a** was obtained exclusively with the unnatural *20S* configuration. (*3S,15R*)-15-(Benzylxy)-3-[(*tert*-butyldimethylsilyl)oxy]androsta-5,16-diene (**13**) and the corresponding 17,17' homocoupling product **14** were obtained as byproducts. When the addition to the *E*-enone was repeated in the presence of chloro(trimethyl)silane, the yield of the conjugate addition product improved, but the stereochemistry at C-20 remained the same.

**Keywords:** Vinyl iodides; Cuprates; Conjugate additions; Steroids; Total syntheses; Antibiotics; A25822 B.

Steroids containing a wide range of side chains at C-17 have been reported and the nature of the side chain plays an important role in determining biological activity<sup>1</sup>. Consequently, considerable effort has been expended in devising new methods for the elaboration of steroid side chains from a variety of precursors<sup>2</sup>. The majority of strategies reported to date involve transformations or extensions of existing side chains, or the use of 17-oxo derivatives for the installation of new ones. Although several 17-iodo- $\Delta^{16}$ -steroids have been prepared in the androstan<sup>3</sup>, estrane<sup>3g-3i,4</sup> and 4-azaandrostan<sup>3h,3i</sup> series, only a few examples of their use in the construction of steroid side chains have been reported, usually employing palladium-catalyzed coupling reactions<sup>3f-3i,4c</sup>. In general, vinyl iodides can be conveniently prepared from the corresponding ketones by treatment of

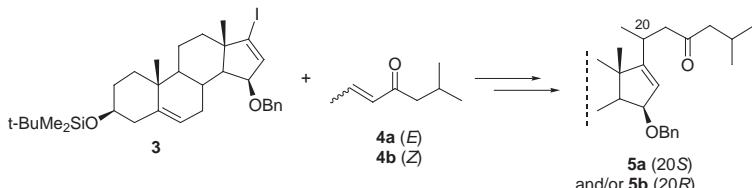
their hydrazones with iodine and a base such as tetramethylguanidine *via* the procedure of Barton and coworkers<sup>5</sup>.

In the course of our work directed toward the synthesis<sup>6</sup> of the antimycotic agent antibiotic A25822 B (ref.<sup>7</sup>), we observed the inadvertent cyclization of the keto lactone **1** to **2** *via* an intramolecular aldol condensation during an attempted Wittig reaction (Scheme 1). Similar aldol cond-



SCHEME 1

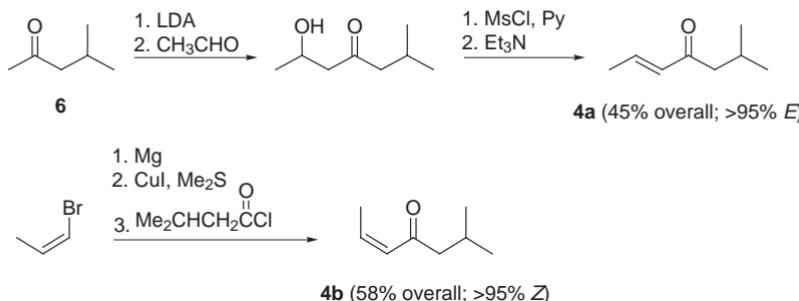
sations of 15,23-dioxo steroids were recently employed by Jung<sup>8</sup> and Krafft<sup>9</sup> and their coworkers in syntheses of the complex marine sterol xestobergsterol A (ref.<sup>10</sup>) and related compounds. Prompted by these precedents, we wished to investigate the possibility of using a 17-iodo- $\Delta^{16}$  sterol containing an appropriate oxygen function at C-15 for the purpose of introducing a suitably functionalized side chain at C-17. We now report the preparation of the novel steroidal vinyl iodide **3** and our first attempts at its cuprate-mediated conjugate addition to enone **4** to afford adduct **5** *via* Scheme 2. Of particular interest was the determination of the effect of the *E,Z* geometry of the enone upon the stereochemistry at C-20 in the product.



SCHEME 2

## RESULTS AND DISCUSSION

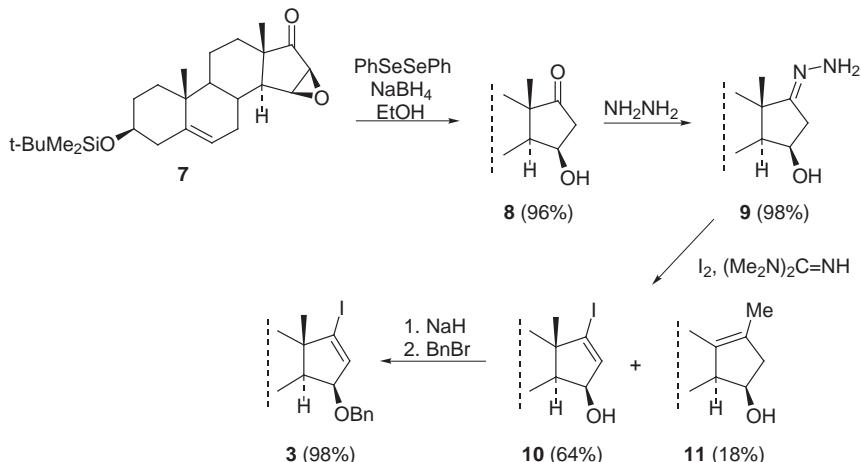
The *E*-isomer **4a** was conveniently obtained by a literature method from the aldol condensation of ketone **6** with acetaldehyde, followed by dehydration<sup>11</sup> (Scheme 3). Since an earlier synthesis of the *Z*-isomer **4b** required the separation of an *E,Z*-mixture by preparative gas chromatography<sup>12</sup>, we developed a stereoselective method for its preparation (Scheme 3). Thus, **4b** was obtained by the copper(I)-catalyzed coupling of (*Z*)-prop-1-enyl-1-magnesium bromide with 3-methylbutanoyl chloride by means of the general procedure of Kochetkov *et al.*<sup>13</sup>. Both products were obtained as essentially pure (>95%) geometrical isomers.



SCHEME 3

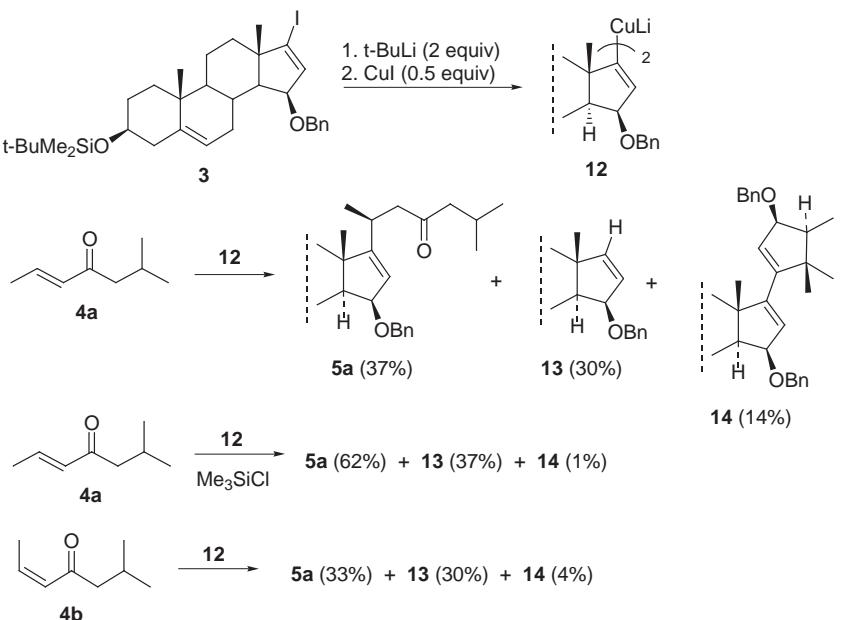
The vinyl iodide **3** was prepared by the general method of Barton *et al.*<sup>5b</sup>. Thus, the known epoxy ketone **7** (ref.<sup>14</sup>) was first reduced to the corresponding 15 $\beta$ -hydroxy derivative **8** with diphenyl diselenide and sodium borohydride in ethanol<sup>15</sup>. The latter steroid was converted to its hydrazone **9** and subjected to the Barton protocol, thereby providing **10** and a small amount of the rearranged product **11** (ref.<sup>16</sup>). Finally, the *O*-benzylation of **10** afforded the desired 15 $\beta$ -benzyloxy vinyl iodide **3** (Scheme 4).

The vinyl iodide **3** was then converted to the corresponding cuprate **12** by lithiation with *tert*-butyllithium and addition to copper(I) iodide-tributylphosphine complex<sup>17</sup>. When the cuprate was added to the (*E*)-enone **4a**, the conjugate addition product **5a** was obtained in relatively poor yield, along with the alkene **13** and the dimer **14**, the latter two products resulting from hydrolysis and homocoupling of the cuprate, respectively. Since chloro(trimethyl)silane is known to affect the rate and the stereochemistry of conjugate additions of cuprates<sup>18,19</sup>, the reaction was repeated in the presence of the chlorosilane. This resulted in a significant improvement in the yield of adduct **5a**, but had no effect on the stereochemistry at C-20. We then performed the cuprate addition to the *Z*-isomer **4b** in order to de-



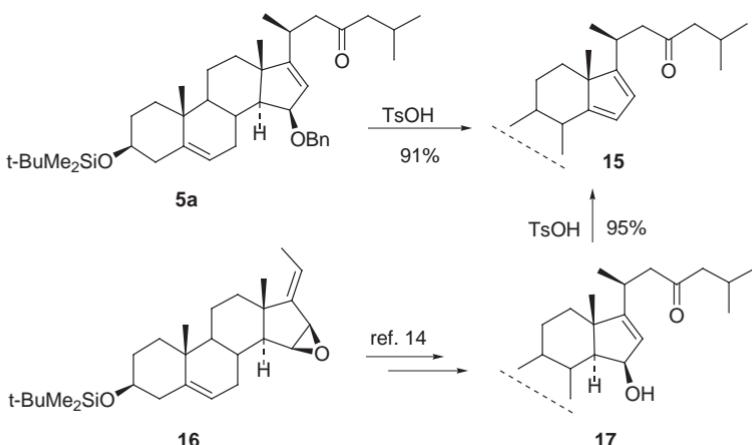
SCHEME 4

termine whether the complementary epimer at C-20 would be produced. However, the same adduct **5a** was obtained as in the reaction of cuprate **12** with enone **4a**. We were unable to detect any significant amount of the C-20 epimer **5b** in any of these experiments. These results are summarized in Scheme 5.



SCHEME 5

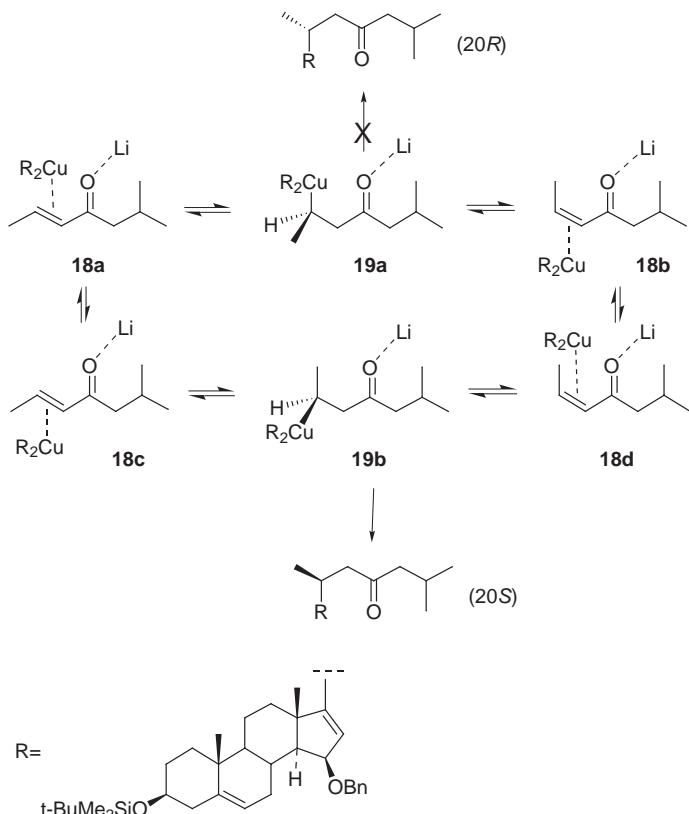
In order to confirm the C-20 configuration of the adduct **5a**, it was subjected to acid-catalyzed elimination of the benzyloxy group to afford triene **15**. The latter compound was identical to the product of dehydration of the known allylic alcohol **17**, in turn produced from the epoxy alkene **16** by the method of Tsuji *et al.*<sup>14</sup> (Scheme 6). Thus, it was established that the



SCHEME 6

product of cuprate addition to either geometrical isomer of the enone (**4a** or **4b**) contained the “unnatural” 20*S* configuration. Attempts to convert **5a** to the known allylic alcohol **17** by hydrogenolysis or Birch reduction of the benzyl group resulted in simultaneous hydrogenation at  $\Delta^5$  and reduction of the 23 oxo group, respectively. The observed formation of the same C-20 epimer from both enone isomers can be explained (Scheme 7) by assuming that the four possible initial d- $\pi^*$  complexes **18a–18d** (formed respectively from attack of the cuprate upon either face of either enone isomer) are in equilibrium and that product formation ensues from the preferential irreversible reductive elimination of the copper(III) intermediate **19b** instead of **19a** (refs<sup>19,20</sup>).

In conclusion, a simple procedure for the preparation of the vinyl iodide **3** was developed, along with one for obtaining the (*Z*)-enone **4b** stereoselectively. Surprisingly, the conjugate additions of cuprate **12**, derived from iodide **3**, to either geometrical isomer of enone **4** afforded the same adduct **5a**, possessing the 20*S* configuration. Thus, while the method provides access to unnatural 20*S* sterols, it is not viable as a new approach to xestobergsterol A and related compounds.



SCHEME 7

## EXPERIMENTAL

Melting points were obtained on an A. H. Thomas hot-stage apparatus and are uncorrected. IR spectra (wavenumbers in  $\text{cm}^{-1}$ ) were recorded on a Mattson 4030 spectrometer. Proton and carbon spectra were obtained on a Bruker ACE 200 ( $^1\text{H}$ , 200 MHz;  $^{13}\text{C}$ , 50 MHz), a Bruker AM 400 ( $^1\text{H}$ , 400 MHz;  $^{13}\text{C}$ , 100 MHz) or a Bruker DRX 400 ( $^1\text{H}$ , 400 MHz;  $^{13}\text{C}$ , 100 MHz) spectrometer. Chemical shifts are given in ppm ( $\delta$ -scale), coupling constants ( $J$ ) in Hz. Deuterochloroform was used as the solvent and residual chloroform or tetramethylsilane were used as the internal standards, unless otherwise noted.  $^{13}\text{C}$  NMR signals were assigned as C, CH,  $\text{CH}_2$  or  $\text{CH}_3$  by DEPT experiments<sup>21</sup>. Low- and high-resolution mass spectra were obtained on a VG 7070 or a Kratos MS80 mass spectrometer. All mass spectra were obtained by electron impact at 70 eV with direct probe sample introduction. Chromatography refers to flash chromatography<sup>22</sup> performed on Merck 230–400 mesh silica gel.

(Z)-Prop-1-enyl-1-magnesium bromide<sup>23</sup>, epoxide 7 (ref.<sup>14</sup>) and (E)-6-methylhept-2-en-4-one<sup>11</sup> (**4a**) were prepared according to literature methods. (Z)-Prop-1-enyl-1-magnesium bromide and *tert*-butyllithium were titrated using 1 M *sec*-butyl alcohol in xylenes and 1,10-phenanthroline as the indicator<sup>24</sup>.

**(Z)-6-Methylhept-2-en-4-one (4b)**

A precooled (*ca* -45 °C) solution of (*Z*)-prop-1-enyl-1-magnesium bromide (10 ml of a 1.0 M solution in THF, 10 mmol) was added to copper(I) bromide-dimethyl sulfide complex (10 mmol) in 10 ml of THF and 10 ml of dimethyl sulfide at -45 °C. The black solution was stirred for 10 min, and 2 ml of hexamethylphosphoramide was added. The mixture was stirred for an additional 10 min, 3-methylbutanoyl chloride (830 mg, 6.91 mmol) in 2 ml of THF was added, and the mixture was stirred for 4 h at -25 °C. The reaction was quenched with NH<sub>4</sub>Cl solution and partitioned between 10% aqueous NH<sub>4</sub>OH solution and ether. The resulting heterogeneous solution was filtered through Celite and extracted with ether. The ether layer was washed with 10% aqueous NH<sub>4</sub>OH solution, water, NaCl solution, dried (anhydrous MgSO<sub>4</sub>), and evaporated at reduced pressure. This gave 500 mg (58%) of **4b** as a colourless oil. IR (neat): 1 697, 1 673, 1 633, 1 058, 972. <sup>1</sup>H NMR (400 MHz): 6.19–6.12 (m, 2 H); 2.32 (d, *J* = 7.0, 2 H); 2.12 (m, 1 H); 2.11 (dd, *J* = 5.5, 0.5, 3 H); 0.94 (d, *J* = 6.6, 6 H). <sup>13</sup>C NMR (100 MHz): 202.3, 142.7, 128.4, 53.7, 25.3, 23.1, 16.2. MS, *m/z* (rel.%): 126 (M<sup>+</sup>, 11), 111 (12), 84 (14), 69 (100). Exact mass calculated for C<sub>8</sub>H<sub>14</sub>O: 126.1045; found: 126.1054.

**(3*S*,15*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-15-hydroxyandrost-5-en-17-one (8)**

Sodium borohydride (582 mg, 15.4 mmol) was slowly added to a solution of diphenyl diselenide (2.4 g, 7.7 mmol) in 70 ml of absolute ethanol. The initial yellow color faded and the mixture was stirred for 5 min. Acetic acid (60  $\mu$ l, 1.0 mmol) was added, followed by epoxy ketone **7** (2.07 g, 4.97 mmol) and the solution was stirred for 2 h. The reaction was diluted with NH<sub>4</sub>Cl solution and extracted several times with ether. The combined ether extracts were washed with 10% HCl solution, NaHCO<sub>3</sub> and NaCl solutions, dried (anhydrous MgSO<sub>4</sub>), and the solvent was evaporated. The residue was purified by chromatography (elution with 0–20% ethyl acetate–hexanes) to afford 1.45 g (60%) of recovered diphenyl diselenide and 2.00 g (96%) of hydroxy ketone **8** as a white solid, m.p. 180–182 °C (chloroform–hexanes). IR (KBr): 3 499, 1 734, 1 254, 1 166, 1 156, 1 130, 1 098. <sup>1</sup>H NMR (200 MHz): 5.35 (m, 1 H); 4.55 (m, 1 H); 3.49 (m, 1 H); 1.19 (s, 3 H); 1.07 (s, 3 H); 0.89 (s, 9 H); 0.067 (s, 3 H); 0.065 (s, 3 H). <sup>13</sup>C NMR (100 MHz): 220.0 (C), 142.1 (C), 119.9 (CH), 72.4 (CH), 67.3 (CH), 56.0 (CH), 50.6 (CH), 47.0 (C), 46.7 (CH<sub>2</sub>), 42.7 (CH<sub>2</sub>), 37.3 (CH<sub>2</sub>), 36.8 (C), 32.8 (CH<sub>2</sub>), 32.0 (CH<sub>2</sub>), 30.4 (CH<sub>2</sub>), 27.6 (CH), 25.9 (CH<sub>3</sub>), 20.3 (CH<sub>2</sub>), 19.3 (CH<sub>3</sub>), 18.2 (C), 17.4 (CH<sub>3</sub>), -4.6 (CH<sub>3</sub>). MS, *m/z* (rel.%): 361 (M<sup>+</sup> - *t*-Bu, 1), 251 (28), 75 (100). For C<sub>25</sub>H<sub>42</sub>O<sub>3</sub>Si calculated: 71.72% C, 10.11% H; found: 71.63% C, 9.98% H.

**(3*S*,15*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-15-hydroxy-17-iodoandrosta-5,16-diene (10) and (3*S*,15*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-15-hydroxy-17-homo-18-norandrosta-5,17-diene (11)**

Hydroxy ketone **8** (9.03 g, 21.6 mmol), hydrazine hydrate (6.5 ml of a 55% aqueous solution, 0.12 mol), and triethylamine (6.5 ml, 47 mmol) were stirred in 70 ml of absolute ethanol for 12 h. The solvent was evaporated to give 9.17 g (98%) of the corresponding hydrazone **9**, which was used directly in the next step.

A solution of 1,1,3,3-tetramethylguanidine (6.9 ml, 55 mmol) in 160 ml of THF was added over 15 min to iodine (4.2 g, 17 mmol) dissolved in 100 ml of THF. The solution was cooled to 0 °C, and the above hydrazone (3.40 g, 7.86 mmol) in 60 ml of THF was added dropwise. The mixture was stirred for 30 min and then the THF was evaporated *in vacuo*.

The residue was diluted with ether, washed with 10% aqueous HCl solution,  $\text{NaHCO}_3$ ,  $\text{Na}_2\text{S}_2\text{O}_3$  and NaCl solutions, dried (anhydrous  $\text{MgSO}_4$ ), and the solvent was evaporated. Chromatography with 0–3% ether–benzene gave two fractions. The first contained 2.67 g (64%) of the desired vinyl iodide **10** as a white solid, m.p. 140–141 °C (methanol). IR (KBr): 3 420, 1 575, 1 256, 1 101, 1 012, 1 001, 836.  $^1\text{H}$  NMR (200 MHz): 6.34 (d,  $J$  = 2.9, 1 H); 5.35 (m, 1 H); 4.47 (dd,  $J$  = 4.9, 3.0, 1 H); 3.50 (m, 1 H); 1.10 (s, 3 H); 1.08 (s, 3 H); 0.90 (s, 9 H); 0.07 (s, 6 H).  $^{13}\text{C}$  NMR (50 MHz): 142.0 (C), 139.0 (CH), 121.2 (C), 120.3 (CH), 74.6 (CH), 72.5 (CH), 58.2 (CH), 50.9 (CH), 50.6 (C), 42.7 ( $\text{CH}_2$ ), 37.2 ( $\text{CH}_2$ ), 36.9 (C), 36.3 ( $\text{CH}_2$ ), 32.0 ( $\text{CH}_2$ ), 30.7 ( $\text{CH}_2$ ), 28.1 (CH), 25.9 ( $\text{CH}_3$ ), 22.0 ( $\text{CH}_3$ ), 20.7 ( $\text{CH}_2$ ), 19.2 ( $\text{CH}_3$ ), 18.2 (C), –4.6 ( $\text{CH}_3$ ). MS,  $m/z$  (rel.%): 513 ( $\text{M}^+ - \text{CH}_3$ , 2), 510 ( $\text{M}^+ - \text{H}_2\text{O}$ , 2), 471 ( $\text{M}^+ - t\text{-Bu}$ , 51), 453 (15), 252 (25), 75 (100). For  $\text{C}_{25}\text{H}_{41}\text{IO}_2\text{Si}$  calculated: 56.81% C, 7.82% H; found: 57.01% C, 7.96% H.

The second fraction contained 560 mg (18%) of the rearranged product **11** as a solid foam. IR (KBr): 3 557, 1 252, 1 223, 1 195, 1 086, 838.  $^1\text{H}$  NMR (400 MHz): 5.34 (m, 1 H); 4.30 (t,  $J$  = 5.4, 1 H); 3.51 (m, 1 H); 1.64 (s, 3 H); 0.95 (s, 3 H); 0.90 (s, 9 H); 0.07 (s, 6 H).  $^{13}\text{C}$  NMR (100 MHz): 140.8 (C), 133.4 (C), 125.3 (C), 120.8 (CH), 72.6 (CH), 70.2 (CH), 58.4 (CH), 48.3 (CH), 47.7 ( $\text{CH}_2$ ), 42.7 ( $\text{CH}_2$ ), 37.4 (CH<sub>2</sub>), 36.7 (C), 32.7 ( $\text{CH}_2$ ), 32.0 ( $\text{CH}_2$ ), 30.6 (CH), 25.9 ( $\text{CH}_3$ ), 25.5 ( $\text{CH}_2$ ), 25.2 ( $\text{CH}_2$ ), 19.3 ( $\text{CH}_3$ ), 18.2 (C), 13.3 ( $\text{CH}_3$ ), –4.6 ( $\text{CH}_3$ ). MS,  $m/z$  (rel.%): 345 ( $\text{M}^+ - t\text{-Bu}$ , 23), 327 (78), 312 (25), 253 (100). Exact mass calculated for  $\text{C}_{21}\text{H}_{33}\text{O}_2\text{Si}$  ( $\text{M}^+ - t\text{-Bu}$ ): 345.2250; found: 345.2255.

(3*S*,15*R*)-15-(Benzylxyloxy)-3-[(*tert*-butyldimethylsilyl)oxy]-17-iodoandrosta-5,16-diene (**3**)

Alcohol **10** (452 mg, 0.854 mmol) was dissolved in 25 ml of THF. Sodium hydride (170 mg of a 60% dispersion in mineral oil, 4.27 mmol) was added slowly and the solution was stirred for 1 h at room temperature. Benzyl bromide (0.51 ml, 4.3 mmol) and tetrabutylammonium iodide (16 mg, 0.043 mmol) were added and the mixture was stirred for a further 17 h before water was added. The mixture was extracted several times with ether, dried (anhydrous  $\text{MgSO}_4$ ), and the solvent was evaporated. The crude product was subjected to kugelrohr distillation, 100 °C at 13 Pa, to remove the excess benzyl bromide. The residue contained 516 mg (98%) of benzyl ether **3** as a white solid, m.p. 112–113 °C (ether). IR (KBr): 1 572, 1 248, 1 096, 1 070, 838.  $^1\text{H}$  NMR (200 MHz): 7.37–7.22 (m, 5 H); 6.42 (d,  $J$  = 2.6, 1 H); 5.31 (m, 1 H); 4.54 (d,  $J$  = 11.8, 1 H); 4.38 (d,  $J$  = 11.8, 1 H); 4.11 (dd,  $J$  = 5.1, 2.6, 1 H); 3.48 (m, 1 H); 1.09 (s, 3 H); 1.06 (s, 3 H); 0.89 (s, 9 H); 0.06 (s, 6 H).  $^{13}\text{C}$  NMR (50 MHz): 141.8 (C), 138.8 (C), 137.3 (CH), 128.2 (CH), 127.4 (2 CH), 121.9 (C), 120.7 (CH), 80.7 (CH), 72.5 (CH), 71.0 ( $\text{CH}_2$ ), 58.3 (CH), 50.9 (CH), 50.8 (C), 42.7 ( $\text{CH}_2$ ), 37.3 ( $\text{CH}_2$ ), 36.9 (C), 36.3 ( $\text{CH}_2$ ), 32.0 ( $\text{CH}_2$ ), 30.6 (CH<sub>2</sub>), 28.3 (CH), 25.9 ( $\text{CH}_3$ ), 20.8 (CH<sub>3</sub>), 20.7 ( $\text{CH}_2$ ), 19.2 (CH<sub>3</sub>), 18.2 (C), –4.6 (CH<sub>3</sub>). MS,  $m/z$  (rel.%): 618 ( $\text{M}^+$ , 0.2), 603 ( $\text{M}^+ - \text{CH}_3$ , 1), 561 ( $\text{M}^+ - t\text{-Bu}$ , 78), 453 (14), 379 (9), 252 (19), 91 (100). For  $\text{C}_{32}\text{H}_{47}\text{IO}_2\text{Si}$ : 62.12% C, 7.66% H; found: 61.77% C, 8.06% H.

Conjugate Addition of Cuprate **12** to Enone **4a**

*tert*-Butyllithium (0.45 ml of a 1.8 M solution in pentane, 0.80 mmol) was added to a solution of iodide **3** (233 mg, 0.377 mmol) in 2 ml of ether at –78 °C, and the mixture was stirred for 1 h. This solution was added to copper(I) iodide–tributylphosphine complex<sup>17,25</sup> (74 mg, 0.19 mmol) in 2 ml of ether. The solution was stirred for 1 h at –78 °C, followed by the addition of enone **4a** (24 mg, 0.19 mmol) in 1 ml of ether, and the mixture was warmed

from -78 to 0 °C over 3 h. It was quenched with  $(\text{NH}_4)_2\text{SO}_4$  solution, extracted several times with ether, washed with NaCl solution, dried (anhydrous  $\text{MgSO}_4$ ), and the solvent was evaporated. Chromatography with 50% benzene–hexanes afforded three fractions.

The first fraction contained 55 mg (30%) of *(3S,15R)-15-(benzyloxy)-3-[(tert-butyl-dimethylsilyl)oxy]androsta-5,16-diene* (**13**) as a white solid, m.p. 109–111 °C (methanol–petroleum ether). IR (KBr): 1 601, 1 589, 1 141, 1 119, 1 094, 1 058.  $^1\text{H}$  NMR (200 MHz): 7.38–7.23 (m, 5 H); 6.20 (d,  $J$  = 5.8, 1 H); 5.98 (dd,  $J$  = 5.6, 2.2, 1 H); 5.33 (m, 1 H); 4.57 (d,  $J$  = 12.0, 1 H); 4.42 (d,  $J$  = 12.0, 1 H); 4.21 (dd,  $J$  = 5.2, 2.1, 1 H); 3.48 (m, 1 H); 1.14 (s, 3 H); 1.09 (s, 3 H); 0.91 (s, 9 H); 0.08 (s, 6 H).  $^{13}\text{C}$  NMR (50 MHz): 149.1 (CH), 141.6 (C), 139.4 (C), 128.8 (CH), 128.1 (CH), 127.3 (CH), 127.1 (CH), 121.0 (CH), 80.8 (CH), 72.6 (CH), 70.8 (CH<sub>2</sub>), 59.2 (CH), 51.4 (CH), 46.0 (C), 42.8 (CH<sub>2</sub>), 37.3 (CH<sub>2</sub>), 36.9 (C), 35.7 (CH<sub>2</sub>), 32.0 (CH<sub>2</sub>), 30.9 (CH<sub>2</sub>), 27.7 (CH), 25.9 (CH<sub>3</sub>), 22.1 (CH<sub>3</sub>), 20.7 (CH<sub>2</sub>), 19.3 (CH<sub>3</sub>), 18.2 (C), -4.6 (CH<sub>3</sub>). MS,  $m/z$  (rel.%): 492 (M<sup>+</sup>, 3), 477 (M<sup>+</sup> - CH<sub>3</sub>, 15), 435 (M<sup>+</sup> - *t*-Bu, 75), 91 (100). For  $\text{C}_{32}\text{H}_{48}\text{O}_2\text{Si}$  calculated: 77.99% C, 9.82% H; found: 77.80% C, 10.06% H.

The second fraction contained 25 mg (14%) of *17,17-bis{(2S,15R)-15-(benzyloxy)-3-[(tert-butyl-dimethylsilyl)oxy]androsta-5,16-diene}* (**14**) as a white solid, m.p. 116–117 °C (methanol–petroleum ether). IR (KBr): 1 560, 1 254, 1 149, 1 096.  $^1\text{H}$  NMR (400 MHz): 7.36–7.23 (m, 5 H); 5.99 (m, 1 H); 5.34 (m, 1 H); 4.54 (d,  $J$  = 12.0, 1 H); 4.46 (d,  $J$  = 12.0, 1 H); 4.20 (dd,  $J$  = 5.1, 2.4, 1 H); 3.49 (m, 1 H); 1.30 (s, 3 H); 1.08 (s, 3 H); 0.89 (s, 9 H); 0.06 (s, 6 H).  $^{13}\text{C}$  NMR (100 MHz): 153.9 (C), 141.7 (C), 139.6 (C), 128.2 (CH), 127.4 (CH), 127.2 (CH), 126.5 (CH), 121.1 (CH), 79.9 (CH), 72.6 (CH), 71.0 (CH<sub>2</sub>), 59.9 (CH), 51.0 (CH), 48.0 (C), 42.9 (CH<sub>2</sub>), 39.3 (CH<sub>2</sub>), 36.8 (C), 35.9 (CH<sub>2</sub>), 32.1 (CH<sub>2</sub>), 30.8 (CH<sub>2</sub>), 27.5 (CH), 25.9 (CH<sub>3</sub>), 22.2 (CH<sub>3</sub>), 21.0 (CH<sub>2</sub>), 19.2 (CH<sub>3</sub>), 18.2 (C), -4.6 (CH<sub>3</sub>). MS,  $m/z$  (rel.%): 759 (39), 108 (89), 69 (100). For  $\text{C}_{64}\text{H}_{94}\text{O}_4\text{Si}_2$  calculated: 78.09% C, 9.63% H; found: 77.95% C, 9.78% H.

The third fraction contained 43 mg (37%) of *(3S,15R,20S)-15-(benzyloxy)-3-[(tert-butyl-dimethylsilyl)oxy]cholesta-5,16-dien-23-one* (**5a**) as a gum: IR (KBr): 1 713, 1 616, 1 291, 1 252, 1 090, 1 067.  $^1\text{H}$  NMR (400 MHz): 7.37–7.21 (m, 5 H); 5.62 (d,  $J$  = 1.8, 1 H); 5.33 (m, 1 H); 4.51 (d,  $J$  = 12.1, 1 H); 4.41 (d,  $J$  = 12.1, 1 H); 4.13 (dd,  $J$  = 5.1, 2.4, 1 H); 3.48 (m, 1 H); 2.81 (m, 1 H); 2.53 (dd,  $J$  = 16.0, 5.0, 1 H); 1.17 (s, 3 H); 1.09 (d,  $J$  = 6.8, 3 H); 1.08 (s, 3 H); 0.90 (d,  $J$  = 7.1, 6 H); 0.89 (s, 9 H); 0.06 (s, 6 H).  $^{13}\text{C}$  NMR (100 MHz): 209.8 (C), 166.2 (C), 141.7 (C), 139.7 (C), 128.1 (CH), 127.3 (CH), 127.1 (CH), 121.9 (CH), 121.1 (CH), 79.6 (CH), 72.6 (CH), 70.6 (CH<sub>2</sub>), 60.1 (CH), 52.4 (CH<sub>2</sub>), 51.2 (CH), 50.5 (CH<sub>2</sub>), 47.6 (C), 42.8 (CH<sub>2</sub>), 37.3 (CH<sub>2</sub>), 36.9 (C), 34.9 (CH<sub>2</sub>), 32.1 (CH<sub>2</sub>), 30.8 (CH<sub>2</sub>), 27.6 (CH), 27.4 (CH), 25.9 (CH<sub>3</sub>), 24.5 (CH), 22.59 (CH<sub>3</sub>), 22.56 (CH<sub>3</sub>), 21.1 (CH<sub>3</sub>), 21.2 (CH<sub>3</sub>), 20.6 (CH<sub>2</sub>), 19.2 (CH<sub>3</sub>), 18.2 (C), -4.6 (CH<sub>3</sub>). MS,  $m/z$  (rel.%): 618 (M<sup>+</sup>, 0.4), 603 (M<sup>+</sup> - CH<sub>3</sub>, 0.8), 561 (M<sup>+</sup> - *t*-Bu, 21), 510 (16), 453 (22), 279 (26), 91 (100). Exact mass calculated for  $\text{C}_{36}\text{H}_{53}\text{O}_3\text{Si}$  (M<sup>+</sup> - *t*-Bu): 561.3764; found: 561.3763.

### Conjugate Addition of Cuprate **12** to Enone **4a** in the Presence of Chloro(trimethyl)silane

*tert*-Butyllithium (0.38 ml of a 1.78 M solution in pentane, 0.68 mmol) was added to iodide **3** (211 mg, 0.341 mmol) in 2 ml of ether at -78 °C, and the mixture was stirred for 1 h. A homogeneous solution of copper(I) iodide–tributylphosphine complex<sup>25</sup> (67 mg, 0.17 mmol) in 2 ml of ether was added, the mixture was stirred for 1 h at -78 °C, and a solution of enone **4a** (22 mg, 0.17 mmol) and chloro(trimethyl)silane (43  $\mu$ l, 0.34 mmol) in 1 ml of ether was added. The mixture was warmed from -78 to 0 °C over 4 h. The reaction was quenched with  $(\text{NH}_4)_2\text{SO}_4$  solution, extracted several times with ether, washed with NaCl

solution, dried (anhydrous  $MgSO_4$ ), evaporated, and purified by chromatography (elution with 50% benzene–hexanes). This gave three fractions. The first contained 62 mg (37%) of **13**, the second contained 2 mg (1%) of dimer **14**, and the third fraction contained 66 mg (62%) of **5a**. These products were identical (TLC and  $^1H$  NMR) with those obtained in the absence of chloro(trimethyl)silane.

### Conjugate Addition of Cuprate **12** to Enone **4b**

Iodide **3** (275 mg, 0.444 mmol) in 2 ml of ether at  $-78^\circ C$  was reacted with *tert*-butyllithium (0.66 ml of a 1.35 M solution in pentane, 0.89 mmol) for 15 min. A homogeneous mixture of copper(I) iodide (43 mg, 0.23 mmol) and dimethyl sulfide<sup>25</sup> (65  $\mu$ l, 0.88 mmol) in 2 ml of THF was added, and the solution was stirred for 30 min at  $-40^\circ C$ . Enone **4b** (28 mg, 0.22 mmol) in 1 ml of THF was added and the mixture was stirred for 2 h, during which the reaction mixture was warmed from  $-78^\circ C$  to room temperature. The reaction was quenched with  $NH_4Cl$  solution, diluted with ether, washed with NaCl solution, dried ( $MgSO_4$ ), and the solvent was removed *in vacuo*. Chromatography with 50% benzene–hexanes gave three fractions: 64 mg (30%) of **13**, 10 mg (4%) of dimer **14**, and 45 mg (33%) of **5a**. The  $^1H$  NMR spectra of these compounds were identical to those obtained from enone **4a**.

### (*3S,20S*)-3-[(*tert*-Butyldimethylsilyl)oxy]cholesta-5,14,16-trien-23-one (**15**)

The epoxide **16** was prepared and converted into the allylic alcohol **17** by the method of Tsuji *et al.*<sup>14</sup>. The latter compound was refluxed in methylene chloride in the presence of a catalytic amount of 4-methylbenzene-1-sulfonic acid for 3 h to afford triene **15** in 95% yield, after chromatography (elution with 50% benzene–hexanes). The same product was obtained in 91% yield when **5a** was subjected to similar conditions. Product **15** was a white solid, m.p. 97–98  $^\circ C$  (methanol–petroleum ether). IR (KBr): 1 712, 1 256, 1 079, 1 018, 889.  $^1H$  NMR (400 MHz): 6.04 (d,  $J$  = 1.9, 1 H); 5.82 (d,  $J$  = 1.9, 1 H); 5.41 (m, 1 H); 3.49 (m, 1 H); 2.97 (m, 1 H); 2.61 (dd,  $J$  = 16.1, 5.5, 1 H); 2.44 (dd,  $J$  = 16.4, 8.5, 1 H); 1.12 (d,  $J$  = 7.2, 3 H); 1.11 (s, 3 H); 1.05 (s, 3 H); 0.91 (d,  $J$  = 6.9, 6 H); 0.90 (s, 9 H); 0.07 (s, 6 H).  $^{13}C$  NMR (100 MHz): 210.1 (C), 162.7 (C), 158.4 (C), 140.9 (C), 122.2 (CH), 120.9 (CH), 118.5 (CH), 72.6 (CH), 53.8 (CH), 53.7 (C), 52.7 (CH<sub>2</sub>), 51.5 (CH<sub>2</sub>), 42.8 (CH<sub>2</sub>), 37.7 (CH<sub>2</sub>), 37.3 (C), 35.7 (CH<sub>2</sub>), 32.0 (CH<sub>2</sub>), 31.7 (CH), 29.1 (CH<sub>2</sub>), 27.1 (CH), 25.9 (CH<sub>3</sub>), 24.5 (CH), 22.62 (CH<sub>3</sub>), 22.59 (CH<sub>3</sub>), 22.4 (CH<sub>2</sub>), 21.1 (CH<sub>3</sub>), 19.5 (CH<sub>3</sub>), 18.2 (C), -4.6 (CH<sub>3</sub>). MS, *m/z* (rel. %): 510 (M<sup>+</sup>, 15), 411 (17), 353 (11), 279 (23), 207 (100), 158 (51), 75 (85). Exact mass calculated for  $C_{33}H_{54}O_2Si$ : 510.3893; found: 510.3872.

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25. When the cuprate in the conjugate addition to **4a** was prepared from CuI and dimethyl sulfide, with or without chlorotrimethylsilane, a poorer yield of **5a** was obtained than with the tributylphosphine complex. Attempts at utilizing mixed cuprates failed to produce significant amounts of conjugate addition products and returned **13** as the principal product. However, we did not observe the formation of the 20*R* epimer **5b** in any of these experiments.