Intramolecular sensitization within steroids: Excited-state interaction of C-17 α and β carbon–bromine bonds with a C-6 carbonyl group

Wen-Shan Li, Lokman Torun, and Harry Morrison

Abstract: The synthesis, photochemistry, and photophysics of 17α-bromo-3α-(triphenylsilyloxy)-5α-androstan-6-one (**1**) and 17β-bromo-3β-(triphenylsilyloxy)-5α-androstan-6-one (**2**) have been studied in aqueous tetrahydrofuran. The 17α-bromo isomer gives evidence (reduced ϕ_f, τ_1, and ϕ_{isc} for the ketone) for interaction between the ketone and C–Br moieties in the excited singlet state. Some photodehalogenation is also observed upon excitation of the ketone chromophore. This interaction seems to be absent or minimal for the 17β-bromo isomer.

Key words: photodehalogenation, bromosteroid, ketosteroid, intramolecular singlet–singlet energy transfer (ISSET).

Résumé : On a réalisé la synthèse et on a étudié la photochimie et la photophysique de la 17α-bromo-3α-(triphénylsilyloxy)-5α-androstan-6-one (**1**) et de la 17β-bromo-3β-(triphénylsilyloxy)-5α-androstan-6-one (**2**) dans le tétrahydrofurane. Avec l'isomère 17α-bromo, on a observé des résultats (valeurs réduites de ϕ_f, τ_1 et ϕ_{isc} pour la cétone) suggèrent l'existence d'une interaction entre les portions cétone et C–Br dans l'état singulet excité. On a aussi observé la présence de photodéshalogénation lors de l'excitation du chromophore de la cétone. Cette interaction semble être absente ou minimale dans l'isomère 17β-bromo.

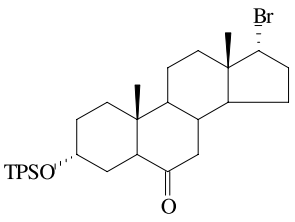
Mots clés : photodéshalogénation, bromostéroïde, cétostéroïde, transfert d'énergie singulet–singulet intramoléculaire (TESSI).

Introduction

For many years chemists have evinced interest in the use of rigid, well-defined hydrocarbon skeletons to study the photophysical and photochemical consequences of excited-state intramolecular energy transfer between distal functional groups. The most extensively studied frameworks have involved norbornylogous (1) and steroidal (2) backbones. The use of steroids to study intramolecular singlet–singlet and triplet–triplet energy transfer dates back to the 1960s (3). Though most efforts in the field have emphasized photophysics, we have had a particular interest in the capability of the steroid skeleton to facilitate the photochemical activation of a reactive, non-light absorbing, functional group (2). Both through-space and through-bond interactions can effect such a result. Given the interchromophore distances involved, chemistry resulting from triplet–triplet intramolecular energy transfer involving rings A and D of the steroid skeleton most convincingly makes the case for coupling through the hydrocarbon framework (4, 5).

In general, our program has explored the chemistry of unsaturated (e.g., ketone and olefin) acceptor groups resulting from the transfer of energy from an absorbing ("antenna") chromophore. However, in a preliminary communication, we recently presented evidence that a σ-bonded (e.g., C-Br) functionality attached to the steroid framework could be activated by interaction with a ketone antenna (2). Specifically, photonic excitation (directly or indirectly) of a 6-keto (i.e., ring B) functionality can effect the photochemical cleavage of an α C-17 (ring D) C—Br bond in the androstane **1**. We now present the details of this chemistry and extend the earlier study to include the β C-17 analogs (**2**). (Note that TPS and TBDMS in **2** are triphenylsilyl and *tert*-butyldimethylsilyl, respectively).

The somewhat surprising outcome of our most recent observations is that the interaction between the C-6 ketone and the C-17 C—Br bond appears to be specific to the 17α isomer.



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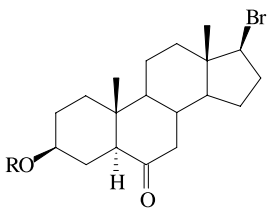

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(a) R = TPS
(b) R = TBDMS
(c) R = Me

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Dedicated to Professor Don Arnold for his contributions to chemistry.

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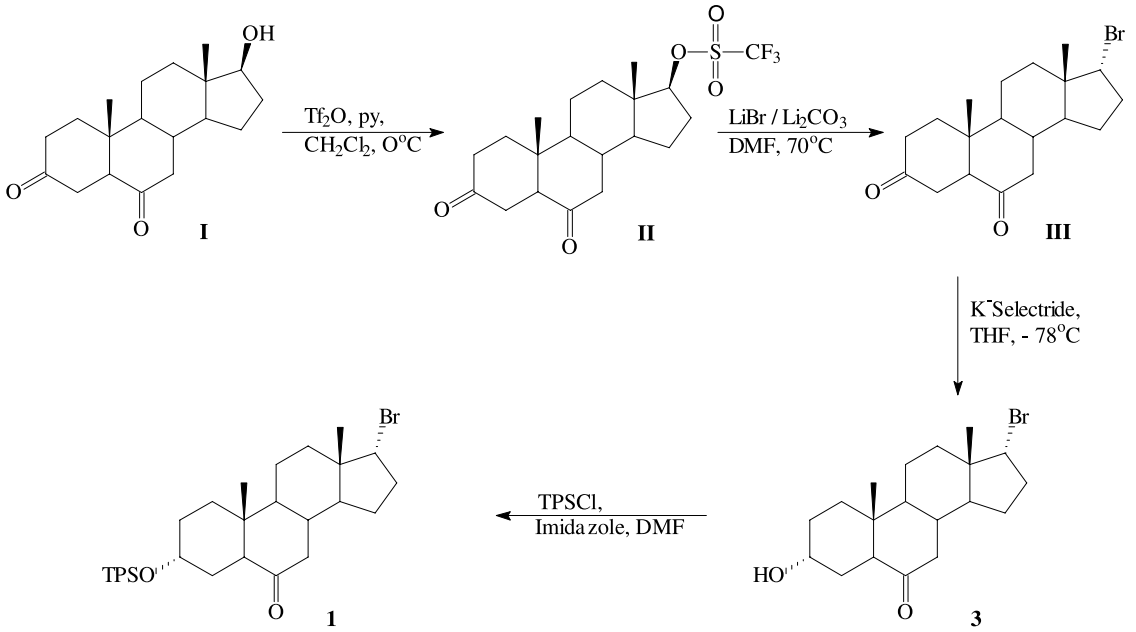
Scheme 1.



Results and discussion

Preparation of steroid substrates

17α-Bromo-3α-(triphenylsilyloxy)-5α-androstan-6-one (1; 3α-TPSO–6ketone–17α-Br)

This substrate was prepared as outlined in Scheme 1, starting with 17β-hydroxy-5α-androstane-3,6-dione that had itself been prepared from 17β-hydroxyandrost-4-en-3-one (6).

The assignment of structure to **1** was confirmed by X-ray analysis which clearly established the α orientations of both the 3-TPSO and 17-Br functionalities (2).

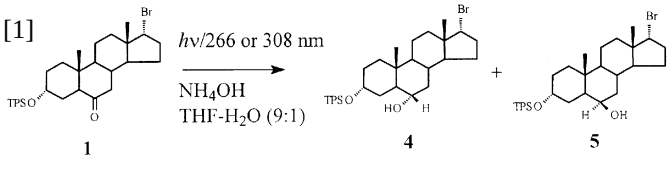
17β-Bromo-3β-(triphenylsilyloxy)-5α-androstan-6-one (2a; 3β-TPSO–6ketone–17β-Br)

The title compound was prepared in six steps from commercially available 5-androsten-3β-ol-17-one (dehydroisoandrosterone) as outlined in Scheme 2. The selective reduction of the vinylbromide in ring D in the presence of the cycloalkene in ring B is noteworthy. The conversion to the cycloalkyl bromide is virtually quantitative. An expanded discussion of this reaction as a synthetic tool will be presented elsewhere. As with compound **1**, X-ray analysis (Fig. 1) was employed to confirm the β bromide stereochemistry at C-17 as well as the β configuration of the 3-TPSO group. The latter was a matter of convenience in the availability of starting material. The stereochemistry in ring A is of no consequence to the photophysics discussed in this paper. The axial and pseudo-axial configurations of the methine protons at C-3 and C-17, respectively, were also evident in the chemical shifts of their resonances at 3.6–3.8 δ, characteristically upfield of the resonances for their equatorial and pseudo-equatorial counterparts in **1** that appear at 4.2–4.3 δ (7).

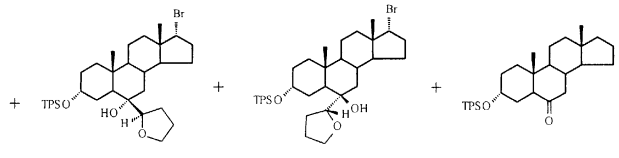
Two analogs of **2a** were also prepared. One was 17β-bromo-3β-(*tert*-butyldimethylsilyloxy)-5α-androstan-6-one (**2b**), using a route totally analogous to that used for **2a**. The other was 17β-bromo-3β-methoxy-5α-androstan-6-one (**2c**), wherein the 3-ol was methylated prior to the reduction of ring D and hydroboration–oxidation in ring B.

Photochemistry of compounds 1 and 2a–2c

The photolysis of **1** was studied using both 266 and 308 nm laser light. A mixture of THF and water was employed to facilitate solubility and ammonium hydroxide was present to neutralize released HBr. A summary of our observations, reproduced from our communication (2), is presented in eq. [1].

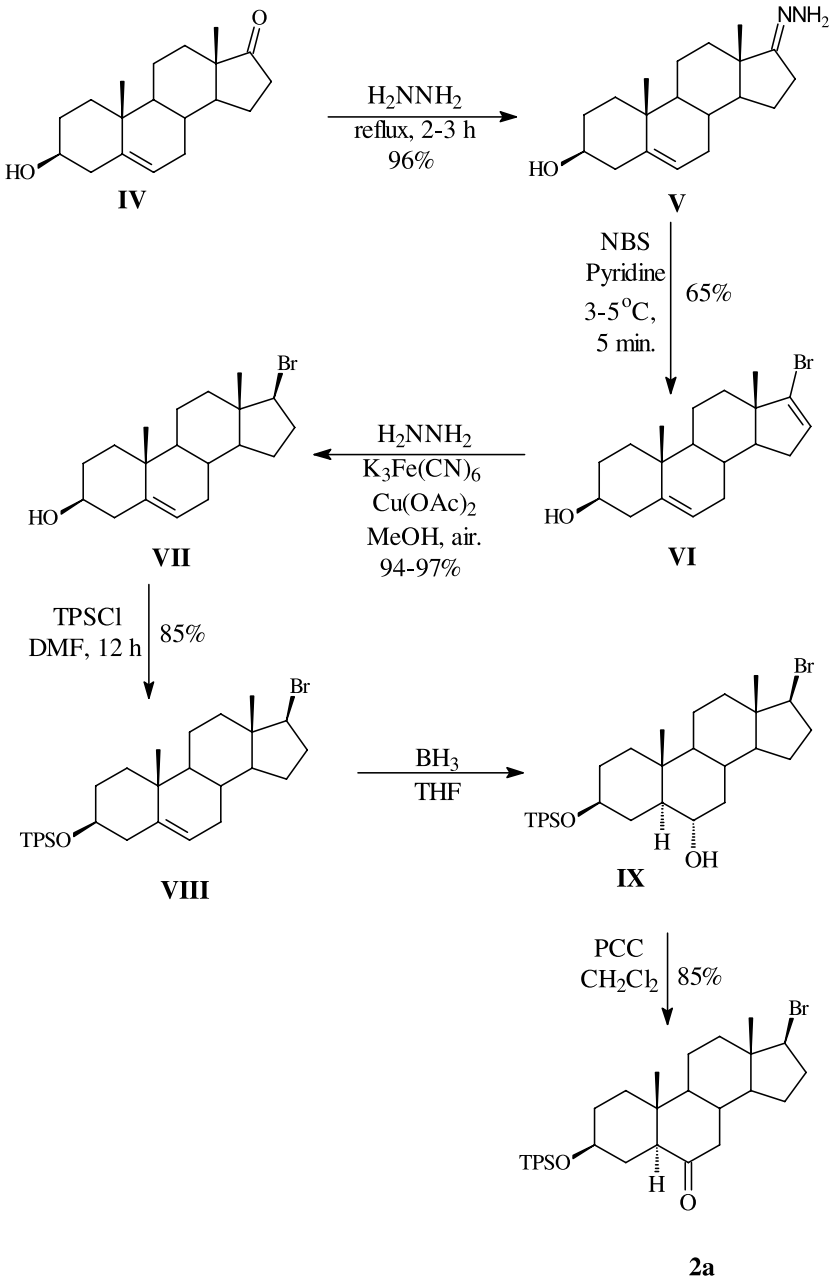


	ϕ_{-1}	ϕ_4	ϕ_5
266 nm	0.094	0.031	0.021
308 nm	0.086	0.025	0.017



	ϕ_{6+7}	ϕ_8
	0.029	0.0066
	0.036	0.0067

Scheme 2.

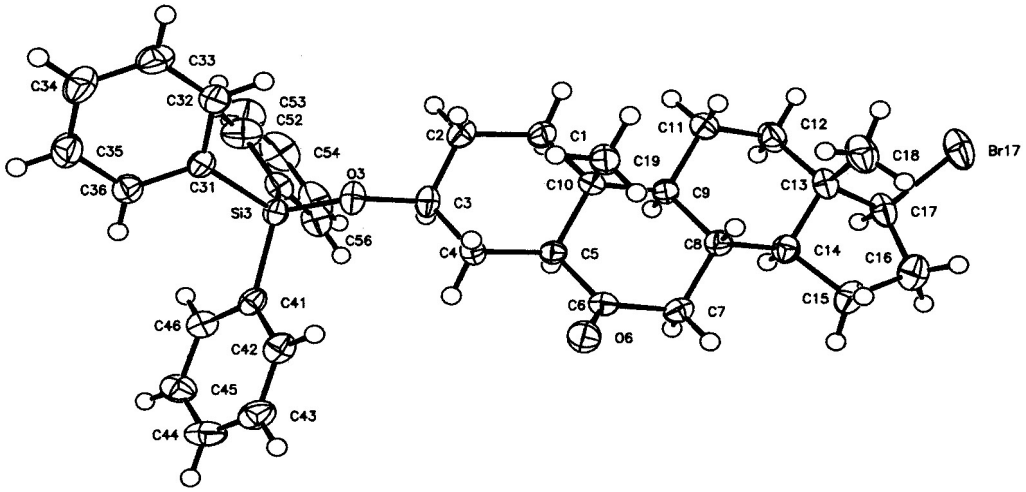


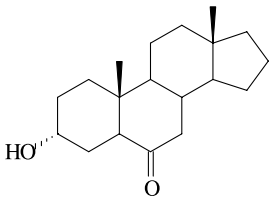
The assignment of **4** and **5** as the 6α and 6β alcohols, respectively, rests on the (axial) 6H resonance (3.14–3.28 δ) in **4** being located well upfield of the (equatorial) 6H resonance (3.54–3.60 δ) in **5** (7). The debromination characteristic of **8** was readily evident in the mass spectrum and in the disappearance of the downfield C-17 methine proton and C-17 carbon resonances characteristic of **1**. Compounds **4**, **5**, and **8** were independently synthesized, the alcohols by sodium borohydride reduction of **1**, and **8** by reduction of 5α-androstan-3,6-dione with K-Selectride followed by silylation. Compounds **6** and **7** were inseparable and handled as a mixture. The mass spectrum confirms the net addition of THF to **1** and the proton NMR is consistent with the assignment. These products are expected consequences of hydrogen abstraction from THF by the 6-keto group followed by bond formation by the radical pair. We cannot distinguish among the possible diastereomers that could result from such a mechanism.

Among the products shown in eq. [1], the most interesting is the debrominated steroid (**8**). To confirm that cleavage of the C-17 C—Br bond is occurring by intramolecular sensitization, we photolysed the 3α-OH–17α-Br steroid, both alone and in conjunction with **1**, using both 266 and 300 nm irradiation. No debromination was observed in any of these cases. Nor could debromination of this steroid be sensitized by the 3α-OH–6ketone (**9**) or by acetone (as solvent) using 300 nm irradiation.

Quantum efficiencies are included in eq. [1]. Note that the data for 266 vs. 308 nm irradiation are essentially identical within experimental error. The former deposits energy in the

Fig. 1. X-ray structure of **2a**.





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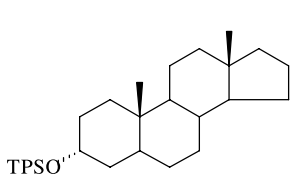
aryl chromophore while the latter selectively excites the carbonyl group. The lack of any significant dependence on the initial site of excitation is reasonable, since we have earlier demonstrated that singlet–singlet energy transfer from an α-arylsilyloxy group at C-3 to a ketone at C-6 is 90% efficient (8). (The efficiency drops to 77% when the arylsilyloxy group is β at C-3 (8)). These efficiencies are readily calculated from eq. [2] (or an analogous equation utilizing singlet lifetimes) (8). Inserting the TPSO fluorescence quantum efficiency for **1** of 9.5×10^{-4}, and using either that for **10** (1.0×10^{-2}) or **11** (9.3×10^{-3}) as the reference ("*r*"), likewise provides an efficiency of singlet energy transfer from C-3 to C-6 ($\phi^{\mathbf{1}}_{\text{intra3} \rightarrow 6}$) of 90%.



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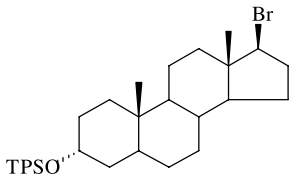

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[2] $$\phi^{\mathbf{1}}_{\text{intra3} \rightarrow 6} = [\phi_{f(r)} - \phi_{f(\mathbf{1})}]/\phi_{f(r)}$$

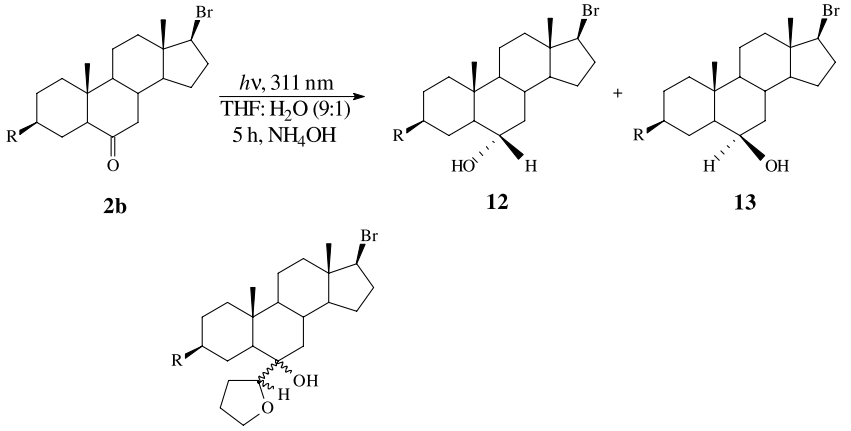
The highly efficient transfer of singlet energy to C-6 from the TPSO group, and the ability of the ketone, when directly excited, to initiate cleavage of the C-17 C—Br bond, argue for activation of the C—Br bond as involving the 6-keto group as the sensitizing chromophore. We return to this point, and address the question of the excited-state multiplicity of the ketone as sensitizer, later in the discussion.

The photochemistry of the β 17-Br series was studied in a manner identical to that outlined above for **1**. We began with the 3β-TPSO derivative (**2a**) but quickly found that the photolysis mixture was less readily resolved by the usual analytical techniques than had been the case with **1**. Recognizing that the aryl chromophore at C-3 was, in fact, superfluous for sensitization at C-17, we turned to the two analogs (**2b** and **2c**), which retained the requisite 6-keto functionality and proved more amenable to study by GLC. The photolysis of **2b** is outlined in eq. [3]. Note that only direct photolysis of the ketone with 311 nm light was employed since the TBDMSO functionality is transparent to 266 nm light.

The products proved to be analogous to those reported in eq. [1], with the exception that *no dehalogenated steroid could be detected*. The alcohols (**12** and **13**) were formed in a ca 1:1 ratio and together constituted 73% of the product mixture by area count. They were each identified by GC–MS spectrometry as a 6-ol but the spectral data in hand did not permit a specific assignment of stereochemistry to a specific peak. Three other peaks, totaling 27% of the product, were also resolvable by GLC. Each gave molecular ions by GC–MS corresponding to a THF adduct and are assigned as such, but again the data in hand did not allow one to differentiate among the possible diastereoisomers and they are grouped in eq. [3] as **14**.

Compound **2c** was likewise photolyzed with 311 nm light (see eq. [4]). Again, no dehalogenated steroid was detectable. In this case only a single peak, constituting 41% of the product area count, could be attributed to a 6 hydroxy product (**15**); the GC–MS spectrum did not allow us to distinguish between the two possible diastereomers. Four peaks at longer retention times, which together constituted 53% of the product, each gave mass spectra consistent with a THF adduct. They are grouped in eq. [4] as the mixture of isomers (**16**). Finally, a sixth peak (**17**, 6%) was detected with a retention time intermediate between the alcohols and the

[3]

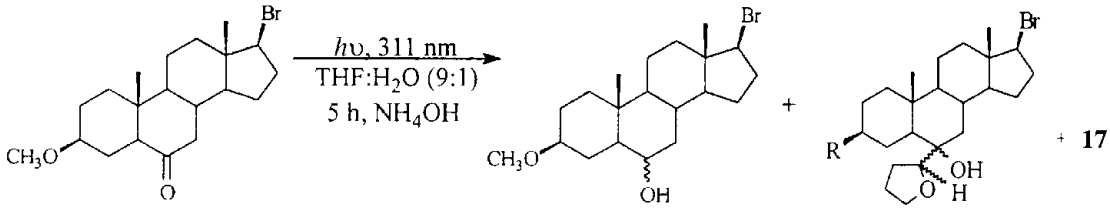


2b **12** **13**

14

R = TBDMSO-

[4]



2c **15** **16** + **17**

THF adducts that has not been identified. Its mass spectrum indicates that it still retains bromine.

In summary, much of the photochemistry of the two C-17 stereoisomers derives from reactions at C-6 that one would anticipate as resulting from initial hydrogen abstraction from the THF by the ketone exited state. Only in **1** do we see any indication of activation at C-17. Mechanistic and photophysical studies were conducted to further clarify the nature and extent of this interaction.

Mechanistic and photophysical studies

Our first concern was to establish the multiplicity of the ketone excited state(s) responsible for the chemistry depicted in eq. [1]. This was done using *cis*-piperylene (1.2 mM) as a potential triplet quencher for the 300 nm photolysis of 6 mM **1**. The contrasting effects on the products were striking; 50–70% of the alcohol and THF adduct (**4**–**7**) formation was quenched whereas there was no effect on the formation of the C-17 cleavage product (**8**). That the hydrogen abstraction chemistry should derive from the ketone triplet state is to be expected. What was not so obvious is that the C-17 cleavage chemistry would involve the ketone excited singlet state.

Nevertheless, this conclusion is supported by singlet lifetime data obtained for a pair of 3α-OH 6-keto steroids in which the C-6 ketone is the only emitting chromophore, i.e., compounds **3** (with Br at C-17) and **9** (no Br at C-17). Values of 2.5 ± 0.2 and 3.6 ± 0.1 ns were measured for these two compounds, respectively. We attribute the ca 31% reduction in ketone singlet lifetime in **3** to interaction between the carbonyl singlet excited state and the C-Br functionality. The reduction in singlet lifetime should also be manifested in the relative quantum efficiencies for intersystem crossing at C-6 (ϕ_{isc}) in these two steroids. Knowing that the reduction products at C-6 derive from the triplet state, and assuming that the ketone ϕ_{isc} would be ca 1.0 in the model (**9**), the relative conversions to C-6 reduction products (at identical photon flux) should provide the ϕ_{isc} for C-6 in **3**. In the event, we observed a 37% diminution (by GLC) of alcohols and THF adducts from photolysis of the halogen-containing steroid (**3**) relative to that observed with the model (**9**), thus leading us to estimate that ϕ_{isc} for **3** is 0.63. The ratio of 1.6 for the relative ϕ_{isc}s for **9**:**3** compares well with the ratio of 1.4 for their respective singlet lifetimes. The two sets of data, taken together, lead to the conclusion that there is an additional mode of singlet decay present in **3** that causes a reduction in this compound's singlet lifetime and ϕ_{isc}.

Perhaps most notable in this series of studies is that the measured singlet lifetime for the C-6 ketone in the 17β C-Br steroid (**2c**) is 3.2 ± 0.2 ns. It is debatable as to whether the 11% reduction relative to **9** is statistically significant, but it seems clear that the α C-17 C-Br functionality in **3** has a much great effect on the C-6 ketone singlet state than does a β C—Br bond in the same location. This conclusion is supported by a comparison of the photoreactivity of **2c** relative to the non-brominated model (**9**) as was done for the ϕ_{isc} study for **3** described above. We found that the relative photoreactivities of compounds **2c** vs. **9** was 1.06, essentially identical within experimental error. It is also interest-

ing to note that the C-6 ketone triplet seems to be ineffective in sensitizing cleavage of the C-17 C—Br bond, despite the fact that its estimated (using cyclohexanone) energy of ca 78 kcal mol^{-1} (9) should be well in excess of the estimated (using isopropyl bromide) bond energy for the C—Br bond of ca 68 kcal mol^{-1} (10). Additional studies in a solvent less capable of intercepting the carbonyl triplet state are necessary to confirm that triplet energy remains totally localized at the ketone. The challenge, of course, will be to do this while simultaneously efficiently trapping the C-17 radical generated by C-Br homolysis.

Further consideration of the interaction between the C-6 carbonyl group and the C-17 C—Br bond in 1

Given that the singlet lifetime of the C-6 ketone has been shortened from 3.6 to 2.5 ns by the presence of an α C-17 C—Br bond (see above), if one assumes that this shortening is entirely due to new decay involving an interaction between the two moieties, one calculates a rate constant for this decay mode of 1.2×10^8 s^{-1}. An analogous calculation using the 37% reduction in ϕ_{isc} yields a rate of singlet decay because of interaction of 1.5×10^8 s^{-1}. We have already estimated that ca 37% of the ketone singlets are diverted from intersystem crossing by this interaction. Only 0.0066 (the quantum by efficiency for formation of **8** (eq. [1])) is accounted for by product formation resulting from C-Br cleavage. Clearly, a very small fraction (ca 2%) of the diverted singlets surface as product, either because cleavage of the interacting C—Br bond is minimal or because there is efficient cleavage but also efficient radical-pair recombination.

As to the specific nature of the ketone–C-Br interaction, we suggest that this may occur through TBI coupling of the ketone n,π* singlet state with the C-Br n,σ* state, by analogy with the proposed explanation for the sensitized photoactivation of a β C—Cl bond in chloronorbornenes (11) and chlorobenzobicyclics (12). The strong stereoelectronic dependence of the interaction is not surprising, there being ample precedent in systems having fewer σ bonds between the two moieties (13). However, the apparent preference for interaction with the α, pseudo-axial C—Br bond at C-17 was unexpected, since the "all trans" rule is generally accepted as leading to enhanced coupling of σ-bonded equatorial vs. axial substituents with the steroid framework (14). Nevertheless, though we have likewise observed a greater rate of intramolecular triplet–triplet energy transfer (intraTTET) from an equatorial (DPSO) donor at C-3 to an olefin at C-17, relative to its axial C-3 counterpart (4), the inverse was observed when the donor was σ-bonded to C-17. In that event, intraTTET from C-17 to C-3 was found to be almost 10-fold faster from the α-DPSO group (15). Thus, the evaluation of additional steroidal ketobromides, both by experiment and by theory, is needed to determine whether the stereoelectronics associated with the C-6–C-17 interaction studied here is prototypical or peculiar to the specific placement of the C—Br bond at C-17 in ring D.

Experimental

General

A considerable amount of the experimental details is available in the doctoral dissertation of L. Torun (16) or as supplemental material for the preliminary communication (2). Thus, only the most salient features are presented below or as supplemental material.[2]

^{13}C NMR spectra were obtained in $CDCl_3$ with a Varian spectrometer operating at 50 MHz with chemical shifts relative to the residual chloroform peak at 77 ppm unless otherwise noted. ^1H NMR spectra were obtained in $CDCl_3$ with a Varian spectrometer operating at 200 MHz with chemical shifts relative to the residual chloroform peak at 7.24 ppm. In the case of two synthetic intermediates, the proton count in the steroid aliphatic region read ca 5–10% high relative to the downfield protons; this is indicated in the listing of the proton spectra. Mass spectrometry utilized a Finnigan 4000 mass spectrometer operating at a source temperature of 250°C. Electron impact (EI) mass spectra and chemical ionization (CI) mass spectra were recorded at an ionization energy of 70 eV, with the latter utilizing isobutane at a pressure of 0.30 torr (1 torr = 133.322 Pa). Elemental analysis was done by HR-MS using either FAB or EI ionization on samples analytically pure by GLC. Ultraviolet absorption spectra were recorded using 1-cm quartz cells on a dual beam Cary model 100 UV–vis spectrophotometer interfaced to a computer using Cary software. Steady-state fluorescence spectra were obtained with 1 cm square fluorescence cells on a SLM Aminco SPF-500 spectrophotometer using a 250 W xenon arc lamp operating in the A/B mode. Fluorescence quantum efficiencies were obtained using toluene as the reference. The fluorescence lifetime measurements were obtained using a PTI model 100 spectrophotometer at room temperature. All the fluorescence samples were purged with argon for 20 min prior to analysis. For the X-ray structural analysis, crystals of 17α-bromo-3α-(triphenylsilyloxy)-5α-androstan-6-one (**1**) were prepared by recrystallization of column-purified material from hexane–CH_2Cl_2. A colorless plate with dimensions of $0.41 \times 0.35 \times 0.22$ mm was placed on a glass fiber in a random orientation. X-ray data were collected with MO Kα radiation (λ = 0.71073 Å) on a Nonius Kappa CCD computer-controlled diffractometer equipped with a graphite crystal, incident beam monochromator. Cell constants and an orientation matrix for data collection were obtained from least-squares refinement, using the setting angle of 17 224 reflections in the range $4 < \theta < 27°$. Data were collected at a temperature of 173 ± 1°C to a maximum of 2θ of 55.8°. Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Laser irradiations were conducted at 266 nm using a Continuum NY-61 Nd:YAG laser equipped with a frequency quadrupler (10 Hz, ca 3.0 mJ/pulse). Samples (3 mL, 10.0 mM) were degassed with argon for at least 25 min prior to irradiation

[2] Supplementary data may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0S2, Canada (http://www.nrc.ca/cisti/irm/unpub_e.shtml for information on ordering electronically). These data can be obtained, free of charge, via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax +44 1223 336033; or deposit@ccdc.cam.ac.uk).

and kept closed with septa. They were photolyzed in square vycor photolysis cells with continuous stirring using a 2 mm stirring bar. The power of the laser was measured with an OPHIR power meter, model AN/2. Data were corrected for scatter and reflectance of light from the cell walls. For 311 nm irradiations, a reactor was equipped with 8 × 311 nm Phillips TL01 (20 W) lamps and a merry-go-round turntable apparatus that positioned 8 cylindrical quartz tubes (10 mm i.d.) approximately 2 cm from the lamps. The 300 nm irradiation employed a Rayonet Reactor (New England Ultraviolet Co.) equipped with lamps having maximal output at 300 nm. All solutions were deoxygenated with a stream of argon prior to photolysis. Uranyl oxalate actinometry was used for the quantum efficiency determinations. 4-Androsten-3,17-dione, 3β-hydroxy-5α-androstan-17-one, 17β-hydroxy-5α-androtan-3-one, 3β-hydroxy-5-androsten-17-one, 5-androsten-3β-ol-17-one (dehydroisoandrosterone), and testosterone were purchased from Sigma.

17-Bromo-3β-hydroxy-androsta-5,16-diene (VI)

3β-Hydroxy-5-androsten-17-hydrazone (**V**) (2.0 g, 6.57 mmol), prepared from commercially available 3β-hydroxy-5-androsten-17-one (**IV**), was dissolved in pyridine (30 mL) and the solution cooled in an ice bath. NBS (2.0 g, 16.85 mmol) dissolved in 15 mL of pyridine was added dropwise to the solution over 5 min. After stirring the yellow-colored solution at ice bath temperature for 5 min, the solution was poured into 50 mL of ice water and the mixture extracted with ether. The combined ether layers were washed with 10% HCl (3 × 20 mL), $NaHCO_3$ solution (3 × 20 mL), and water (2 × 20 mL) and dried over Na_2SO_4. The crude product was chromatographed on silica gel with 2% EtOAc in hexane to give a white solid product in 48–65% yield; mp: 163 to 164°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 5.90–5.80 (dd, 1H), 5.4–5.3 (m, 1H), 3.6–3.4 (m, 1H), 2.4–0.85 (m, ca 24 H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 141.2, 135.6, 129.0, 121.1, 71.6, 55.5, 50.4, 48.5, 42.2, 37.1, 36.7, 34.5, 31.8, 31.5, 31.3, 30.7, 20.6, 19.3, 15.0. CI (*m*/*z*): $(M + H)^+$: 351/353 (base peak). EI: 350/352 $(M)^+$; 91 (base peak).

17β-Bromo-5-androsten-3β-ol (VII)

Hydrazine monohydrate (3.0 mL) was added to a flask containing 17-bromo-3β-hydroxy-androsta-5,16-diene (**VI**) (0.7 g, 1.99 mmol) dissolved in 30 mL of methanol. To this solution was added $K_3Fe(CN)_6$ (1.2 g, 3.64 mmol) and a catalytic amount of $Cu(OAc)_2$ (~10 mg). The resulting solution was stirred at room temperature with continuous monitoring by GC. Hydrazine monohydrate (3.0 mL each time) was added as needed to eliminate all starting material in the solution. A total of 9 to 10 mL was added over 3 days. The milky white solution was filtered and MeOH was removed in vacuo. The resulting aqueous residue was partitioned between dichloromethane and water and extracted with dichloromethane. The solvent was dried over Na_2SO_4, concentrated, and purified by column chromatography on silica gel using 15% EtOAc in hexane to afford a white solid in 85–92% yield; mp: 145–147°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 5.4–5.2 (d, 1H), 3.85–3.65 (t, 1H), 3.65–3.40 (m, 1H), 2.40–0.75 (m, 26H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 140.88, 121.10, 71.59, 61.94, 51.34, 50.01, 43.82, 37.21, 36.54, 36.19, 32.82, 32.44, 31.50, 24.53, 20.63, 19.38, 13.96. EI (*m*/*z*): 352/354 $(M)^+$.

17β-Bromo-3β-(triphenylsilyloxy)-5-androsten (VIII)

17β-Bromo-5-androsten-3β-ol (**VII**) (52 mg, 0.14 mmol) was added to a round-bottomed flask containing DMF (2.0 mL). To this solution was added triphenylsilyl chloride (0.65 mg, 0.22 mmol), imidazole (20 mg, 0.28 mmol), and a catalytic amount of 4(dimethylamino)pyridine, and the solution was stirred under argon for 12 h. Water (10 mL) was added and the solution was extracted with ether. The organic extracts were washed with water. After drying and concentrating, the crude product was chromatographed on a Chromatotron plate prepared with silica gel using hexane to obtain 0.27 g (80%) as an oily product. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.65–7.58 (m, 6H), 7.48–7.32 (m 9H), 5.25–5.10 (bs, 1H), 3.85–3.65 (m, 2H), 2.60–0.80 (m, ca 25H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 141.24, 135.40, 134.94, 134.89, 130.10, 129.97, 127.90, 127.76, 73.31, 62.03, 51.34, 49.96, 43.82, 42.30, 37.16, 36.56, 36.19, 32.80, 32.45, 31.77, 31.53, 24.53, 20.59, 19.40, 13.97. EI (*m*/*z*): 610/612 (M^+), 259 $(Ph_3Si)^+$ base peak. HR-MS (EI) calcd. for $C_{37}H_{43}BrOSi$: 610.2267; found: 610.2250.

17β-Bromo-3β-triphenylsilyoxy-5α-androstan-6α-ol (IX)

The general procedure used for hydroboration was to add the silylated bromoandrostene (ca 0.5 to 0.6 mmol) to a flask containing 10 mL of dry THF, cool to ice bath temperature, and then add a borane solution (1 M) in THF (0.8 mL) under argon. After stirring in an ice bath for 1 h, and then at room temperature for 12 h, the excess borane was destroyed with water. A 2 N solution of NaOH (1.5 mL) and 30% H_2O_2 (1.5 mL) was added and the resulting mixture stirred at 50°C for 1 h. After cooling to room temperature, the crude product was extracted with ether (3 × 15 mL). The combined organic layers were washed with water and dried over Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on a column using CH_2Cl_2:hexanes (1:2) to obtain the products as white solids in >90% yield. For 17β-bromo-3β-triphenylsilyoxy-5α-androstan-6α-ol: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.72–7.6 (m, 6H), 7.50–7.30 (m, 9H), 3.85–3.65 (t, 2H), 3.45–3.3 (m, 1H), 2.40–0.50 (m, 27 H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 135.38, 134.85, 129.85, 127.74, 72.88, 69.14, 61.83, 53.60, 51.81, 50.79, 44.04, 40.90, 37.22, 36.18, 35.06, 32.39, 32.10, 31.34, 24.30, 20.58, 14.09, 13.38. CI (*m*/*z*): 353/355 $(M - Ph_3SiO)^+$. HR-MS (FAB) calcd. for $C_{37}H_{45}BrO_2Si$: 628.2372; found: 628.2352.

17β-Bromo-3β-(triphenylsilyloxy)-5α-androstan-6-one (2a)

17β-Bromo-3β-triphenylsilyoxy-5α-androstan-6α-ol (**IX**) (0.24 g, 0.38 mmol) was dissolved in 5 mL of dichloromethane and added to a stirred suspension of pyridinium chlorochromate (0.123 g, 0.58 mmol) and sodium acetate (0.031 g, 0.44 mmol). The solution was stirred at room temperature for 3 h, filtered, concentrated, and chromatographed on a silica gel column using hexane to afford 0.16 g (85% yield) of an oily product that solidified over several days; mp 186–190°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.70–7.55 (m, 6 H), 7.50–7.30 (m, 9H), 3.80–3.60 (m, 2H), 2.40–2.17 (m, 2H), 2.15–1.50 (m, 12H), 1.50–0.96 (m, 6H), 0.89 (s,

3H), 0.84 (s, 3H). ^{13}C NMR ($CDCL_3$, 50 MHz) δ: 210.14, 135.40, 129.92, 127.79, 72.21 61.17, 56.75, 53.77, 51.45, 48.25, 44.44, 40.73, 38.58, 36.88, 35.96, 32.28, 30.97, 28.91, 24.25, 20.99, 14.11, 13.15. CI (*m*/*z*): 627/629 (M^+), 351/353 (base peak). HR-MS (FAB) calcd. for $C_{37}H_{43}BrO_2Si$: 627.2294; found: 627.22267.

17β-Bromo-3β-(tert-butyldimethylsilyloxy)-5α-androstan-6-one (2b)

The methods used for this preparation were analogous to those described above for **2a**. It was obtained as a white crystalline material, mp 172 to 173°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.83–3.67 (t, 1H), 3.59–3.40 (m, 1H), 2.40–0.95 (m, 20H), 0.85 (s, 9H), 0.80 (s, 3H), 0.74 (s, 3H), 0.01 (s, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 210.31, 71.26, 61.21, 56.95, 53.91, 51.48, 46.27, 44.46, 40.78, 38.58, 36.83, 36.01, 32.30, 31.24, 30.18, 25.84, 24.27, 21.04, 18.18, 14.13, 13.18, –4.63, –4.71. HR-MS (CI) calcd. for $C_{25}H_{43}BrO_2Si$ $(M + H)^+$: 483.2294; found: 483.2309.

17β-Bromo-3β-methoxy-5α-androstan-6-one (2c)

The methods used for this preparation were analogous to those described above for **2a**. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.85–3.65 (t, 1H), 3.32 (s, 3H), 3.20–2.90 (m, 1H), 2.40–1.50 (m, 11 H), 1.50–0.95 (m, 7 H), 0.81 (s, 3H), 0.74 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 210.05, 78.92, 61.14, 56.62, 55.60, 53.80, 51.39, 46.18, 44.41, 40.98, 38.50, 36.57, 35.92, 32.25, 27.44, 25.80, 24.22, 21.00, 14.10, 13.06. CI (*m*/*z*): 383/385 $(M + H)^+$. EI: 382/384 (M^+), 353/355 (base peak). HR-MS calcd. for $C_{20}H_{29}BrO_2$: 382.1507; found: 382.1507.

Photolyses

The details for the preparative photolysis of compound **1** have been presented (2). For the study of 17β-bromo-3β-(*tert*-butyldimethylsilyloxy)-5α-androstan-6-one (**2b**), 5.0 mM solutions in THF:H_2O (9:1) containing ca 5 mM of NH_4OH were degassed with argon for 20 min and irradiated in quartz tubes with 311 nm light for 5 h. The reactions were analyzed by GLC using a 30 m DB-5 column at 280°C under isocratic conditions. The starting material, with a retention time of 11.9 min, was the major component of the reaction mixtures and constituted 65% of the total area counts. Five photoproducts were also observed in the chromatograms. Two major photoproducts appeared with retention times of 11.1 and 11.2 min in a 12.1:13.6 relative ratio. There were three other peaks with retention times of 20.5, 21.5, and 21.9, with relative ratios of 6.0:1.51:1.5. The five products were characterized by GC–MS analyses. The two major photoproducts had very similar EI and CI mass spectra, with a $(M + H)^+$ molecular ion evident in the CI mass spectrum at *m*/*z* 485/487. Loss of water was evident at 467/469. There were three additional photoproducts with retention times of 20.5, 21.5, and 21.9 min. One (20.5 min) exhibited a small molecular ion peak in the CI spectrum at *m*/*z* = 555/557 corresponding to the addition of THF to **2b**. The spectrum also contained a fragment ion peak at *m*/*z* = 537/539 as the base peak, corresponding to the loss of water. The other two products had very similar EI and CI mass spectra but lacked the small molecular ion peak.

Photolysis of 17β-bromo-3β-methoxy-5α-androstan-6-one (**2c**) was conducted in a similar manner. Five photoproducts were detectable by GLC in addition to unreacted starting material (6.3 min) that made up 69% of the total GLC area count. The first photoproduct had a retention time at 6.2 min and constituted 10% of the total area count. The EI mass spectrum showed a molecular ion peak at *m*/*z* = 384/386 corresponding to reduction of the ketone. Fragment ions were observable at 366/368 $(M - H_2O)^+$ and 353/355 (base peak; $M - OCH_3)^+$. The other four photoproducts had relatively long GLC retention times (11.9, 12.2, 12.4, and 12.7 min), were formed in a ratio of 4.5:4.9:1.7:1.6, respectively, and had a combined area count constituting 13% of the total area. All four products had identical EI mass spectra and very similar CI mass spectra. The former contained the THF fragment ion (*m*/*z* = 71) as the base peak, and included fragment ion peaks at *m*/*z* = 383/385 $(M - THF)^+$ and *m*/*z* = 351/353 $(M - THF - CH_3OH)^+$. The base peak in the CI spectra appeared at *m*/*z* = 437/439 $[(M + H) - H_2O)^+$. A sixth photoproduct (9.0 min) constituted 1.3% of the total area count. Its CI mass spectrum exhibited a fragment ion at *m*/*z* = 368/370 as the base peak.

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References

1. T.A. Smith, N. Lokan, N. Cabral, S.R. Davies, M.N. Paddon-Row, and K.P. Ghiggino. J. Photochem. Photobiol. A, **149**, 55 (2002), and refs. therein.
2. W.-S. Li and H. Morrison. Org. Lett. **2**, 15 (2000), and refs. therein.
3. (*a*) D.E. Breen and R.A. Keller. J. Am. Chem. Soc. **90**, 1935 (1968); (*b*) R.A. Keller. J. Am. Chem. Soc. **90**, 1940 (1968); (*c*) R.A. Keller and L.J. Dolby. J. Am. Chem. Soc. **91**, 1293 (1969).
4. L.D. Timberlake and H. Morrison. J. Am. Chem. Soc. **121**, 3618 (1999).
5. (*a*) C.-H. Tung, L.-P. Zhang, Y. Li, H. Cao, and Y. Tanimoto. J. Phys. Chem. **100**, 4480 (1996); (*b*) C.-H. Tung, L.-P. Zhang, Y. Li, H. Cao, and Y. Tanimoto. J. Am. Chem. Soc. **119**, 5348 (1997).
6. J.H. Fried, A.N. Nutile, and G.E. Arth. J. Am. Chem. Soc. **82**, 5704 (1960).
7. J.E. Bridgeman, P.C. Cherry, A.S. Clegg, J.M. Evans, E.R.H. Jones, A. Kasal, V. Kumar, G.D. Meakins, Y. Morisawa, E.E. Richards, and P.D. Woodgate. J. Chem. Soc. C, 250 (1970).
8. J.K. Agyin, L.D. Timberlake, and H. Morrison. J. Am. Chem. Soc. **119**, 7945 (1997).
9. N.J. Turro. Modern molecular photochemistry. Benjamin/Cummings, Menlo Park, Calif. 1978. p. 290.
10. S.W. Benson. Thermochemical kinetics. Wiley, New York. 1968.
11. D.M. Pearl, P.D. Burrow, J.J. Nash, H. Morrison, and K.D. Jordan. J. Am. Chem. Soc. **115**, 9876 (1993); J.J. Nash, D.V. Carlson, A.M. Kaspar, D.E. Love, K.D. Jordan, and H. Morrison. J. Am. Chem. Soc. **115**, 8969 (1993); B.D. Maxwell, J.J.

Nash, H.A. Morrison, M.L. Falcetta, and K.D. Jordan. J. Am. Chem. Soc. **111**, 7914 (1989).
12. A.J. Post, J.J. Nash, D.E. Love, K.D. Jordan, and H. Morrison. J. Am. Chem. Soc. **117,** 4930 (1995), and other papers in this series.
13. H. Morrison, T.-V. Singh, L. De Cardenas, D. Severance, K. Jordan, and W. Shaefer. J. Am. Chem. Soc. **108**, 3862 (1986).
14. N. Liang, J.R. Miller, and G.L. Closs. J. Am. Chem. Soc. **112**, 5353 (1990), and preceding papers in this series.
15. L. Timberlake. Doctoral Dissertation, Purdue University, W. Lafayette, Indiana, December 1998.
16. L. Torun. Doctoral Dissertation, Purdue University, W. Lafayette, Indiana, December 2001.