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Dialkyl Sulfide Stabilisation in a Catalytic Dicuprate 1,6-Dienone Addition Process

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Abstract:

The catalytic dicuprate addition of 1,9-dibromononane to a sterol 1,6-dienone is strongly enhanced by the presence of dimethylsulfide. Dimethylsulfide appears to have an important stabilising effect on the active organo-dicuprate species formed by reaction of Cu(I)Cl with di(bromomagnesio)nonane. In the absence of dimethlysulfide, 1,2-addition of the Grignard and loss of acetate from the sterol are the dominant processes. The overall reaction yield is also very sensitive to the order of addition of various reagents, with controlled addition of the preformed Grignard reagent to a dienone/Cu(I)Cl/dimethyl sulfide mixture leading to high yields of the desired alkylated bis-enone.

Introduction

7α-[9-(4,4,5,5,5-Pentafluoropentylsulfinyl)-nonyl]estra-1,3,5-(10)-triene-3,17*β*-diol (Fulvestrant, Faslodex) is a steroidal antiestrogen targeted towards cancers of the breast. The synthesis of the active ingredient is well documented[1−3] (Scheme 1), and a key step is the introduction of the side chain *via* carbon−carbon bond formation at C-7 on the steroid nucleus. This key bond formation is achieved *via* an organocuprate addition process involving the bromo-substituted side chain **1** (Scheme 1, step (a)).

Syntheses of certain key impurities relating to fulvestrant were required to assist in analytical method development, drug registration, and confirmation of impurity identity. A structurally interesting impurity **2** (referred to trivially within our group as the "sterol dimer", Figure 1) in fulvestrant was required in gram quantities. It is formed during the organocuprate addition process and results from reaction of the steroid with 1,9-dibromononane, present as a low level impurity in the alkyl bromide, **1**.

Our first attempts to synthesise gram quantities of the sterol dimer were *via* the seemingly straightforward α-alkylation of 6-oxo-estradiol derivatives with 1,9-dibromononane (Scheme 2). Our planned approach was to doubly alkylate two steroid nuclei α to the ketone functionality. Deprotection and subsequent reduction of the ketone groups would thus afford the desired sterol dimer product.

In the case of **3**, introduction of a ketone at position 6 of estradiol diacetate was successfully achieved using CrO_3 and 3,5-dimethylpyrazole.[4] Hydrolysis and reprotection (using standard procedures[5]) of the resulting 6-oxo estradiol diacetate gave the di-THP and di-Et_3Si analogues (**4** and **5** respectively) of the phenol and hydroxyl functionalities at positions 3 and 17. Bis-alkylation of these 6-oxo-estradiol derivatives with 1,9-dibromononane was, however, unsuccessful, despite repeated attempts using a variety of base and solvent conditions; in all cases, starting materials were recovered.

Our thoughts turned to synthesis of the required sterol dimer via a copper-catalysed 1,6-addition of the Grignard reagent to the dienone substrate **6**, Scheme 3, analogous to that utilised in the commercial synthesis of fulvestrant[3] (Scheme 1).

The 1,4-Michael addition of a Grignard reagent to a conjugated enone or nitrile in the presence of a copper(I) salt is well established methodology, as is that of copper-mediated 1,6-addition to a conjugated dienone.[6,7] Copper-catalysed Michael additions of Grignard reagents derived from α,ω-dibromides are comparatively rare but appeared to be a promising approach. Schisla[8] and Rabjohn[9] reported the formation of Grignard reagents derived from a wide variety of α,ω-dibromides, and the derived reagents were utilised in copper-catalysed addition to unsaturated nitriles for the synthesis of several long-chain hydrocarbons.

Initial investigations showed that formation of 1,9-di(bromomagnesio)nonane from 1,9-dibromononane was fairly straightforward in either diethyl ether or THF. 1,9-Dibromononane was added portionwise to magnesium and catalytic quantities of iodine in dry THF at 45 °C. Titration of the resulting reagent[10] indicated a high conversion (∼85%) to the desired di-Grignard. The resulting Grignard solution was cooled to −30 °C, and catalytic quantities of dried Cu(I)Cl were added. The dienone **6** (Scheme 3) was then added slowly as a solution in THF maintaining a temperature of around −30 °C. However, no new products were observed by TLC at −30 °C and the reaction was allowed to warm slowly to 20 °C. Further reaction monitoring revealed a complex mixture of components all of which were more polar than the starting dienone (Scheme 4).

Analysis by ^1H and ^{13}C NMR of the mixture confirmed both significant loss of the acetate at position 17 (resulting in 17-hydroxyenone, **7**) and 1,2-addition to the carbonyl group at position 3 (affording quantities of tertiary alcohol, **8**); no 1,6-addition products were observed. These results are typical of uncatalysed Grignard reagents and suggest that the required cuprate had not been formed.

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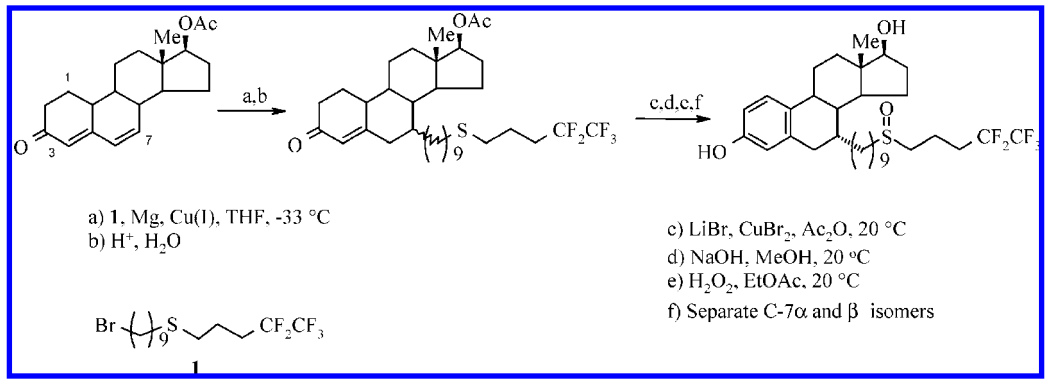
Scheme 1. **Synthesis of fulvestrant**



Further consideration of the reaction suggested that transient formation of the cuprate prior to reaction with the substrate would be facilitated by solubilization of CuCl and stabilization of the cuprate by a dialkyl sulfide.[11,12] Indeed, we postulated that coordination by the sulphur atom present within the alkyl bromide, **1**, utilised in the fulvestrant synthesis (or the fulvestrant cuprate addition product itself) could be contributing to the formation and subsequent reaction of the cuprate derived from 1,9-dibromononane leading to alkylated bis-enone **9**, as an impurity (Figure 2). In view of this, the synthesis of the alkylated ketone was attempted in the presence of added dimethylsulfide.

Formation of 1,9-di(bromomagnesio)nonane was repeated in dry, inhibitor-free THF, and the solution was cooled to −30 °C. Dimethylsulfide (2.0 mol equiv) and catalytic quantities of Cu(I)Cl were then added. The dienone was then added slowly as a solution in dry THF maintaining a reaction temperature of −30 °C. After a 1 h hold at −30 °C, small quantities of water and glacial acetic acid were added. THF solvent was removed by distillation *in vacuo*, and the resulting oil was chromatographed on silica gel to afford small quantities of the desired bis-alkylated enone **9** as a mixture of diastereomers in 15% isolated yield. Again, significant quantities of 1,2-addition products were obtained.

This result, although promising, suggested that, in contrast with the fulvestrant synthesis,[3] the rate of turnover of the catalytic cycle leading to cuprate formation was insufficient to compete effectively with direct reaction of the Grignard (in excess for the majority of the reaction) with the dienone. We therefore tried an alternative addition profile, in which the preformed Grignard reagent was added to the dienone, copper(I) chloride, and dimethylsulfide mixture, thus lowering the concentration of the Grignard reagent relative to that of the copper catalyst. This methodology (see Experimental Section) proved to be very effective, leading to the desired bis-alkylated enone **9** (Figure 2) as a mixture of diastereomers in 75% isolated yield.

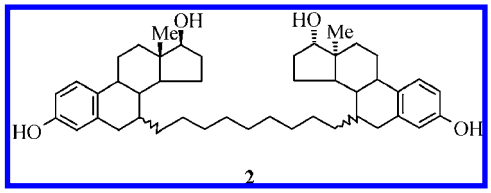
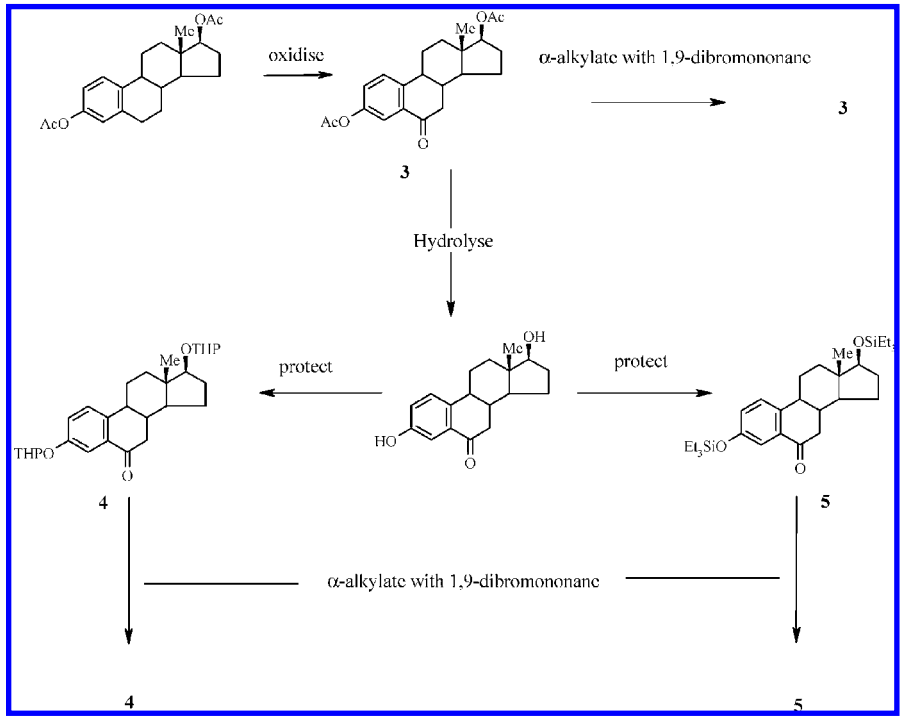
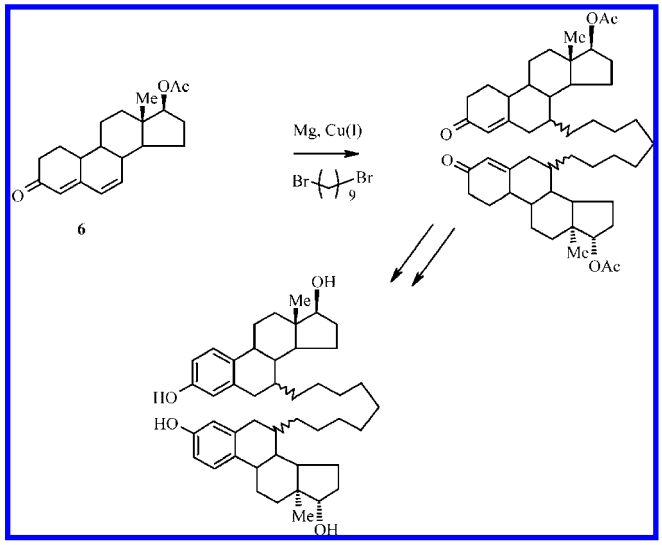


Figure 1. **Sterol dimer.**

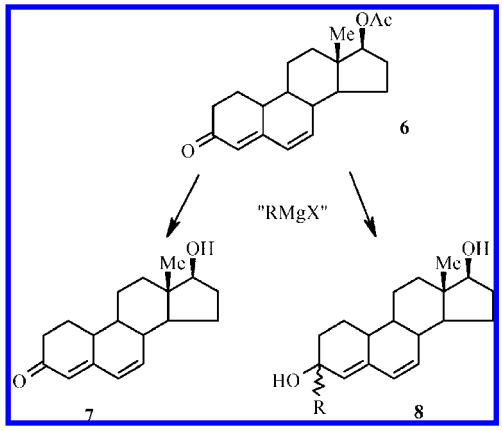
Scheme 2. **Alkylation of 6-oxoestradiol derivatives 3, 4, and 5**



Scheme 3. **Copper-catalysed Grignard addition to dienone substrate 6**



Scheme 4. **Loss of 17-acetate and formation of unwanted 1,2-addition product**



This product was subsequently converted into the desired sterol dimer **2** by aromatisation of the A-ring to compound **10** and hydrolysis of the acetyl groups (Scheme 5).

The successful preparation of the alkylated bis-enone product via the organocuprate process, by analogy with that in Scheme 1, step (a) of the fulvestrant synthesis, may be explained in terms of competing Grignard and organocuprate pathways, Scheme 6,[13,14] eqs 1−4, in which for simplicity the 1,9-di(bromomagnesio)nonane may be represented as "RMgBr", the corresponding intermediate as "CuR", and active cuprate reagent as "R_2CuMgX".

The catalytic dicuprate cycle (eqs 2−4) involves rapid, reversible addition of R_2CuMgX to the dienone to form an adduct which then rearranges slowly to give the product and regenerate CuR.[13] The outcome of the competing pathways depends upon a balance between the rate of addition of the dienone, the level of Cu(I), and the rate of regeneration of the active cuprate species, R_2CuMgX, eqs 3−4. In the original

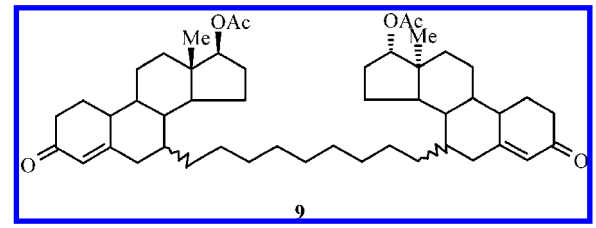


Figure 2. **Alkylated bis-enone.**

dienone addition process, if the catalytic cycle cannot keep up with the rate of addition of dienone, excess dienone will react with Grignard reagent to give unwanted 1,2-adduct formation and acetate loss (compounds **8** and **7**). During the dicuprate pathway, however, provided that the Grignard addition is sufficiently slow to allow regeneration of 'CuR' via the catalytic reaction, eq 4, the Grignard reagent will rapidly form the active cuprate species, eq 3, which in turn will undergo 1,6-addition to the dienone, leading to high yields of the desired product.

In summary, our findings have re-enforced previous studies relating to the benefits of dialkysulfides in the solvation, stabilization, and subsequent reaction of dialkyl cuprates with Michael acceptors such as our dienone substrate. We have also obtained significant yield benefits by a controlled addition of the preformed Grignard reagent to the enone in the presence of catalytic quantities of copper(I) salts at −30 °C in THF and dimethylsulfide.

Experimental Section

General. All glassware was dried at 120 °C prior to assembly and use. All operations prior to and including the reaction quench were performed under a nitrogen atmosphere. Anhydrous THF was used without further purification. Reactions were monitored by thin-layer chromatography using glass backed Merck silica gel $60F_{254}$ plates developing with a vanillin spray and HPLC (see below). NMR spectra were recorded on a Jeol instrument at 270 MHz (^1H) and 67.5 MHz (^{13}C) with tetramethylsilane as internal reference.

HPLC Method. Reaction progress and final products were analysed on a Hewlett-Packard HP1100 HPLC system fitted with a Spherisorb ODS 5 μm (250 mm × 4.4 mm) column and a UV detector set at 220 nm. The mobile phase used was 98% acetonitrile, 2% water set with a flow rate of 2 mL/min. Sample concentrations of 0.1−0.5 mg/mL were used injecting through a 10 μL loop.

Preparation of Alkylated Bis-enone 9 (Figure 2, (13*S*, 13′*S*,17*S*,17′*S*)-7,7′-(Nonane-1,9-diyl)bis(13-methyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[α]phenanthrene-17,7-diyl) diacetate)). 1,9-Di(bromomagnesio)nonane was formed via the portionwise addition of 1,9-dibromononane (4.5 g, 0.5 mol equiv) to magnesium (0.92 g, 1.2 mol equiv) and catalytic quantities of iodine in dry, inhibitor-free THF at 45 °C. The resulting di-Grignard was then added over 2 h (by syringe pump) to a yellow slurry of dienone (10.0 g, 1.0 mol equiv), dimethylsulfide (3.96 g, 2.0 mol equiv), and cuprous chloride (0.39 g, 0.12 mol equiv) in THF held at −30 °C. Transient colour changes from yellow to red (and back to yellow) were observed at the point of contact of the di-Grignard reagent with the slurry. After complete addition, the reaction mixture was stirred at −30 °C for a further 30 min

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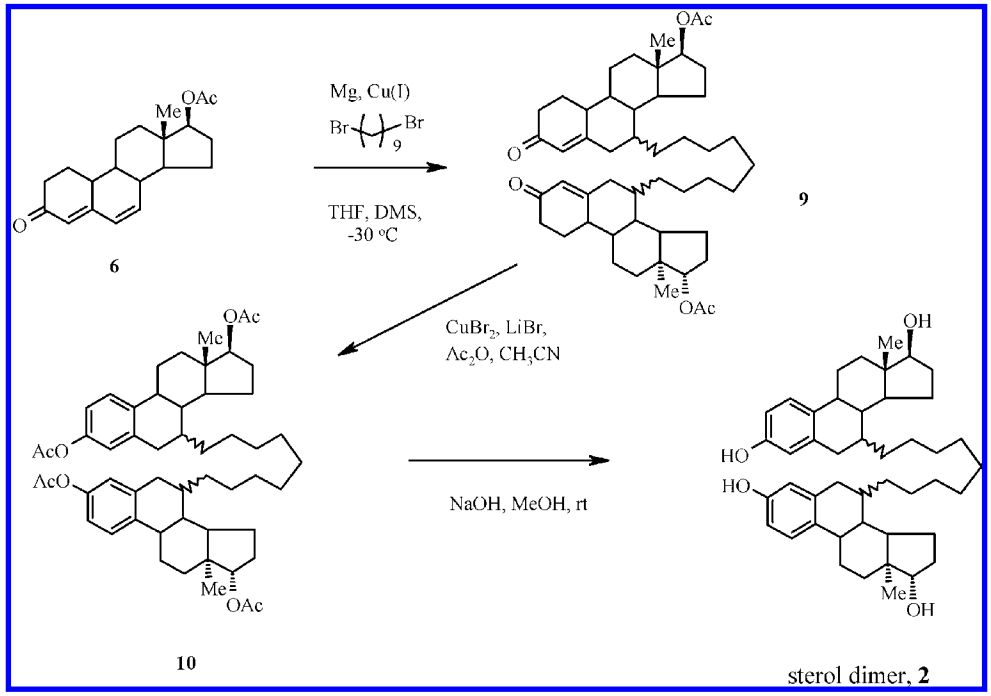
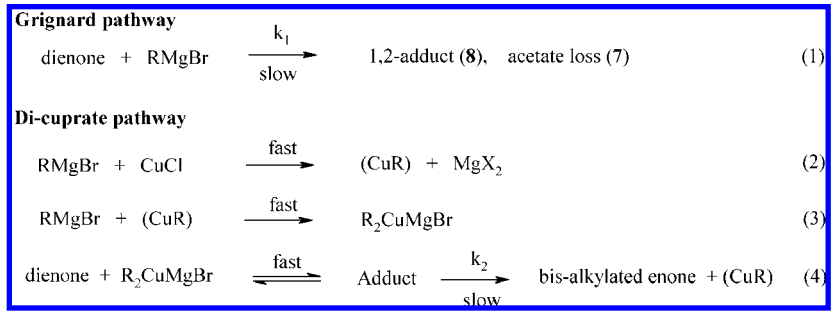
Scheme 5. **Sterol dimer overall synthesis**



Scheme 6. **Competing Grignard/cuprate reaction pathways**



and quenched with glacial acetic acid (4.0 mol equiv). The resulting solution was allowed to warm to room temperature and concentrated by evaporation on the rotary evaporator. Methylene chloride (50 mL) was then added followed by a solution of potassium chloride (~12 g) in water (50 mL). The lower organic layer was separated and washed twice with saturated sodium bicarbonate solution (2 × 50 mL) and finally water (50 mL). The resulting methylene chloride solution was dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford a brown oil. The oil was purified via flash chromatography using Merck 9385 silica gel and ethyl acetate in hexane to give 9.0 g of **9** (Figure 2) as a gummy mixture of diastereomers (at 7,7′αα,$\beta\beta$ and 7,7′αβ,βα) in 75% isolated yield.

Spectral Information for the Alkylated Bis-enone 9. HPLC purity, 95% as mix of diastereomers; ^{1}H NMR ($CDCl_3$): δ 5.82 (s, 1H, O═C−C**H**═C), 5.80 (s, 1H, O═C−C**H**═C), 4.40−4.60 (m, 2H, **H**C−OAc), 2.05 (s, 6H, O−C(O)**CH_3**), 0.80 (s, 6H, 2x −**CH_3**), 1.0−2.70 (complex m, rings and C9 chain, 56H). ^{13}C NMR ($CDCl_3$): δ 199.8, 199.7, 171.2, 167.5, 165.0, 126.7, 126.6, 123.8, 123.7, 82.5, 82.2, 12.2. 11.7. Only significant, readily assigned peaks from the ^{13}C NMR are reported, due to the highly complex nature of the spectrum within the region δ 52 to δ 21. HPLC retention times of the diastereomeric compounds were coincidental with the impurities observed at this stage of the Faslodex synthesis, i.e. 12.47 min (7,7′αα isomer), 13.41 min (7,7′$\beta\beta$ isomer), and 15.75 min (7,7′αβ,βα isomers).

Acknowledgment

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