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Improved addition of organolithium reagents to hindered and/or enolisable ketones

Vincent Lecomte, Elie Stéphan,* Franck Le Bideau and Gérard Jaouen

Laboratoire de chimie organométallique, Ecole Nationale Supérieure de Chimie et CNRS, 11 rue Pierre et Marie Curie, 75005 Paris, France

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Abstract—A study of the addition of some aryl- and alkyllithium derivatives to some hindered and/or enolisable ketones in different solvents (polar and apolar) and, in some cases, at different temperatures and reaction times, will be presented here. The reversibility of the addition of aryllithium to these specific ketones will be observed and discussed. This approach is then used to prepare new steroids as precursor for potentially interesting substituted testosterones.

Addition of organolithiums to hindered and/or enolisable ketones is often problematic and adduct yields tend to be low. This has led to the development of various methodologies designed to reduce the basicity or increase the nucleophilicity of the organometallic complex. These methods include transmetallation of the organolithiums (or Grignard reagents), using for example titanium[1] or cerium[2] salts, or formation of ate-complexes using $BF_3{\cdot}OEt_2$.[3] Very recently, we showed that the addition of phenyllithium to hindered and/or enolisable ketones occurred in good yields in low-polar media.[4] This economical method permitted in particular the addition of aryllithiums to an 11-oxo-steroid,[5] a reaction that had previously been considered impossible. The present study extends our work on addition reactions of various organolithiums (aryllithiums and alkyllithiums) with a number of hindered and/or enolisable ketones. Whenever the solvent effect did not permit a high alcohol-conversion level, the effects of temperature, reaction time and salts were examined. In particular, this study describes the preparation of new steroids obtained via addition of various organolithiums to protected adrenosterone **7**. The products obtained are precursors of 11-hydroxy-testosterones.

The ketones chosen for this study are listed in Table 1. (1*R*)-(−)-Fenchone **1**, hindered but not enolisable, gives a good indication of the nucleophilicity of organolithiums. The other ketones are variously hindered and are all enolisable. The cyclohexanones **4** and **5**, which possess one or two axial methyl groups, were selected as models of the reactivity of the 11-oxo steroids.

1. Solvent effect

1.1. Addition of aryllithium derivatives to various ketones

The first effect selected for study was that of the reaction solvent. Ketones **1**–**7** were allowed to react with

Table 1. List of hindered and/or enolisable ketones used

Ketone	(1*R*)-(-)-fenchone	(-)-menthone	(1*R*)-(+)-camphor				protected adrenosterone
Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**

Keywords: addition reaction; lithium and compounds; steroid; ketones.

* Corresponding author. Tel.: +33-1-44-27-66-98; fax: +33-1-43-26-00-61; e-mail: stephan@ext.jussieu.fr

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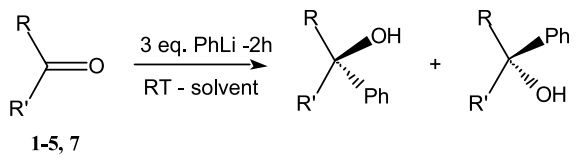


1-5, 7

Scheme 1.

phenyllithium, representative of the aryllithiums, under an inert atmosphere in various solvents. All reactions were carried out in an excess of lithium derivative (3 equiv.) at room temperature for 2 h (Scheme 1). Additionally, the method used appears to play a role. It was normally preferred to add the lithium derivatives to the ketone dissolved in the selected solvent, except, for the sake of convenience, in the case of anisyl- and *para*-*N*,*N*-dimethylaminophenyllithium (see Section 6).

The solvents used were non-polar (toluene), polar (THF or diethyl ether depending on the solubility of the product), or of intermediate polarity (toluene/diethyl ether mixtures). Each result was measured by ^{1}H NMR, comparing the characteristic signals of the starting ketone and the addition product obtained (Table 2—each addition product is numbered following the order of presentation except for the steroid **7**, where a general number, **8**, followed by a letter **a** to **g** according to the nucleophile used was chosen). The addition products using ketones **5**–**7**, which have not been previously reported in the literature, were also characterized completely (see Section 6).

It should be noted at the outset that, irrespective of the solvent, under the specified conditions the addition reaction of phenyllithium to the ketones used is 100% stereoselective, and the stereochemistry observed conforms to the criteria developed by Ashby.[6] This interesting result is different from that obtained, for example, for the addition of phenyllithium to fenchone **1** with activation by $CeCl_3$ in THF, which gives quantitatively a mixture of the alcohols with an *endo*/*exo* ratio of 17/83.[7] In addition, this reaction is complete in **1**, **2** and **6** (Table 2, entries 1, 2, 6). This result is surprising when compared to those previously reported. In fact many authors have chosen to use reaction times of 1 h to one day, under ether or THF reflux, to produce fairly low yields (from 35 to 64% for **1**,[8] 31% for **2**,[8a] 58% for **3**[9]).

Also, a non-polar or low-polar medium is shown to give a higher level of addition (Table 2, entry 4) or equivalent (Table 2, entry 5) to cyclohexanones **4** and **5**. Levels of addition to camphor **3** are all low to moderate (Table 2, entry 3), and the solvent effect is particularly pronounced for the addition to the 11-oxo steroid **7** (Table 2, entry 7).

These low-polar media were used to extend the reaction to other aryllithiums (tolyllithium, anisyllithium and *p*-(*N*,*N*)-dimethylaminophenyllithium—see Scheme 2) and thus to prepare novel and potentially interesting steroids (Table 3).

The organolithiums used were prepared via the action of lithium metal on the corresponding brominated derivative (Table 3, entries 2, 4) or via halogen–metal exchange between the brominated derivative and *n*-butyllithium (Table 3, entry 3). It was not possible to isolate the addition product **8d** by column chromatography. The method used was to precipitate **8d** in its deprotected chlorohydrate form (see Section 6). The results obtained differ from those obtained by other methods reported in the literature; Fonken[10] was unsuccessful in his attempted addition of anisyllithium and phenyllithium to a 11-oxo steroid (pregnan-11-one).

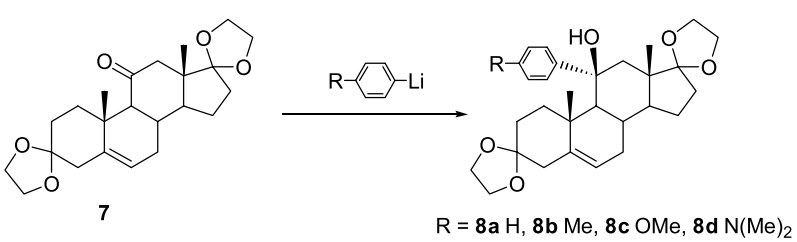
1.2. Addition of alkyllithium derivatives

Buhler[11] chose *n*-butyllithium and *tert*-butyllithium as his

Table 2. Addition of phenyllithium to ketones **1** to **7** in different solvents

Entry	Ketone	Alcohol obtained	Conversion (%)[a]		
			Toluene	Toluene/diethyl ether 6/4	Polar solvent[b]
1	**1**	OH-*endo* **10**	100	100	100
2	**2**	OH-*ax* **11**	98	98	98
3	**3**	OH-*exo* **12**	23	38	42
4	**4**	OH-*ax* **13**	79	73	69
5	**5**	OH-*ax* **14**	78	83	78
6	**6**	**15**	100	100	93
7	**7**	OH-β **8a**	50	–	0[c]

[a] Determined by ^{1}H NMR.
[b] Diethyl ether unless otherwise specified.
[c] THF.



7

R = **8a** H, **8b** Me, **8c** OMe, **8d** $N(Me)_2$

Scheme 2.

Table 3. Preparation of new 11α-hydroxy-11β-aryl-steroids

Entry	Steroid	Conversion[a] (%)	Yield[b] (%)
1	**8a**	55	50
2[c]	**8b**	50	40
3[c]	**8c**	30	20
4[d]	**8d**[e]	50	25

[a] Determined by ^{1}H NMR.
[b] As an isolated product.
[c] Toluene/diethyl ether 6/4.
[d] Toluene/diethyl ether 7/3.
[e] Isolated as the deprotected chlorohydrate.

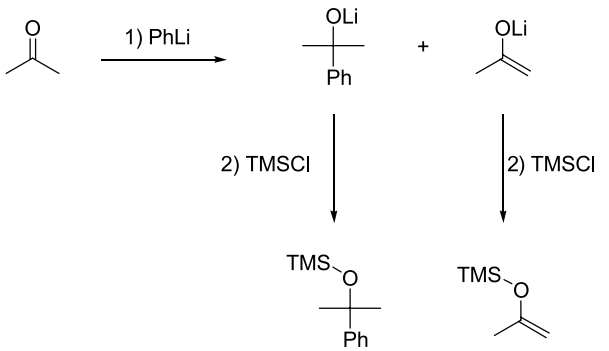
model alkyllithiums for a study of the addition of these organometallic compounds to aldehydes and ketones. He recommends addition of the carbonyl compound in solution in ether or hexane to the alkyllithium at −78°C, followed by stirring of the medium as it warms to room temperature. This method gave very good addition rates for *n*-butyllithium to ketones, but the enolisation reaction competed strongly with the addition reaction of *tert*-butyllithium (44% enolisation for cyclohexanone, for example).

We therefore performed the addition of these two organolithiums to ketones **1**, **2**, **4** and **7** in solution in either toluene or an ethereal solvent (Et_2O or THF). Table 4 summarises the progress made, as well as results from the literature where available.

Each ketone was dissolved in the selected solvent (diethyl ether, THF or toluene), 3 equiv. of organolithium were then added at room temperature and the mixture stirred for 30 min, still at room temperature, before being hydrolysed. The addition products were those obtained after attack on the less-hindered face. The products obtained were either compared to data available in the literature or characterised completely (see Section 6).

The results presented in Table 4 show that toluene is an excellent medium for the addition of the two alkyllithiums to all the ketones studied (conversion to alcohol between 92 and 100%, Table 4).

The conditions used for addition of the organolithiums to the ketones **1**, **2** and **4** also permit an addition with quantitative formation of alcohol in diethyl ether (98–100%). The low yields reported in the literature for the addition of BuLi to the fenchone **1** and to trimethylcyclohexanone **4** obviously were obtained under different experimental conditions (reflux in ether for 1–3 h).



Scheme 3.

The results are less good when THF is used as the reaction medium: the level of addition of *tert*-BuLi to the fenchone **1** (Table 4, entry 2) is lower, probably due to a reaction of the organolithium with the solvent, and this is true also for the addition of both organolithiums to the menthone **2** (Table 4, entries 3 and 4). In the latter case, enolisation is another possible competitive reaction.

Surprisingly, an almost quantitative addition of the two organolithiums to the 11-oxo steroid **7** in THF is obtained at room temperature (Table 4, entries 7 and 8). In this case the addition reaction is faster than the competing reactions.

2. Influence of the reaction time and temperature

The results above show that the lowest levels of conversion to alcohol are those for the addition of phenyllithium to the camphor **3** and the 11-oxo steroid **7** (see Table 2). The influence of reaction time and temperature was therefore studied for these two examples. In each case the progress of the reaction was followed by ^{1}H NMR sampling. There is competition between the addition reaction and the enolisation reaction. Compounds **3** and **7** are in principle susceptible to these reactions. A test with a solution of chlorotrimethylsilane[14] confirms the enolisation of the ketone in this case (see Scheme 3).

Table 4. Addition of *n*-BuLi and *tert*-BuLi to fenchone **1**, menthone **2**, trimethylcyclohexanone **4** and 11-oxo steroid **7**

Entry[a]	Ketone	Organo-lithium	Adduct	Experimental results, conversion (%)			Literature results, conversion (yield) (%)		Ref.
				Et_2O	THF	Toluene	Et_2O	THF	
1	**1**	*n*-BuLi	**16**	100	–	100	– (30)	–	8a
2	**1**	*tert*-BuLi	**17**	100	70	100	–	–	–
3	**2**	*n*-BuLi	**18**	100	–	100	–	50 (30)[b]	12
4	**2**	*tert*-BuLi	**19**	100	–	100	–	56 (47)[b]	12
5	**4**	*n*-BuLi	**20**	100	–	100	– (<10)	–	13
6	**4**	*tert*-BuLi	**21**	98	–	98	–	–	–
7	**7**	*n*-BuLi	**8e**	–	95	92	–	–	–
8	**7**	*tert*-BuLi	**8f**	–	99	98	–	–	–

[a] Conditions: commercial organolithium, 0.5 h, room temperature, conversion determined by means of ^{1}H NMR.
[b] Solvent: THF with pentane as a co-solvent.

Table 5. Conversion of the addition of PhLi to **3** at different times and temperatures in toluene/diethylether 6/4

Entry	T (°C)	t (h)	Conversion (%)[a] alcohol OH-*exo* **12**
1[b]	Room temperature	0	32
2	Room temperature	1/2	52
3[c]	Room temperature	1	40
4	Room temperature	2	38
5	−20	1/2	46
6	−20	1	30
7	−20	2	32

[a] Determined by means of ^{1}H NMR.
[b] Determination done just after the addition of PhLi.
[c] Addition, after 1 h of reaction, of a chlorotrimethylsilane solution.

Table 5 shows the progress of the addition reaction of phenyllithium to **3** over time at two different temperatures.

The addition reaction proves to be quite rapid at room temperature, since a measurement taken just after the addition of organolithium shows that the addition is already at 32% (Table 5, entry 1). The enolisation reaction is in competition and limits the addition, as evidenced by the test with TMSCl which shows that in the reaction medium after 1 h of reaction, there is only the addition product (observed in the form of the silylated ether) and enol (in the form of silylated enol ether) (Table 5, entry 3).

The diminution of the addition level after 0.5 h at room temperature and at −20°C suggests that the addition reaction of phenyllithium to camphor is reversible (Table 5, entries 2 and 3, 5 and 6).

It should be noted that in the case of **7** there may be formation of two different enolates which after hydrolysis give either the carbonylated starting compound **7**, or an epimer of 9β configuration shown as **9** (Scheme 4). The presence of this epimer is indirect proof that enolisation did occur.

Table 6 relates to the addition of phenyllithium to **7** under different time and temperature conditions.

The test with TMSCl (Table 6, entry 1) allows us to conclude that enolisation does not occur until after 2 h of reaction in toluene. At high temperature, or after a long reaction time, the enolisation reaction becomes significant (Table 6, entries 3, 4). These results (Tables 5 and 6 and other unpublished data) clearly show that the addition of aryllithiums to certain hindered ketones may be reversible.

This behaviour had already been noted by some authors, but only in the case of allyl organometallic derivatives. In fact, reversible additions of allyl, crotyl[15] or prenyl[16] organolithiums, organomagnesiums and even organozinc reagents to hindered ketones (di-*tert*-butylketone, di-isopropylketone) have been reported in various solvents (THF or glymes). The role played by steric hindrance was clearly in evidence.

Table 6. Conversion of the addition of phenyllithium to **7** in toluene at different times and temperatures

Entry	T (°C)	t (h)	Conversion (%)[a]	
			8a	**9**
1[b]	Room temperature	2	50	0
2	Room temperature	4	41	0
3	Room temperature	17	44	27
4	60	17	30	38

[a] Determined by means of ^{1}H NMR.
[b] Addition, at the end of the reaction, of a chlorotrimethylsilane solution.

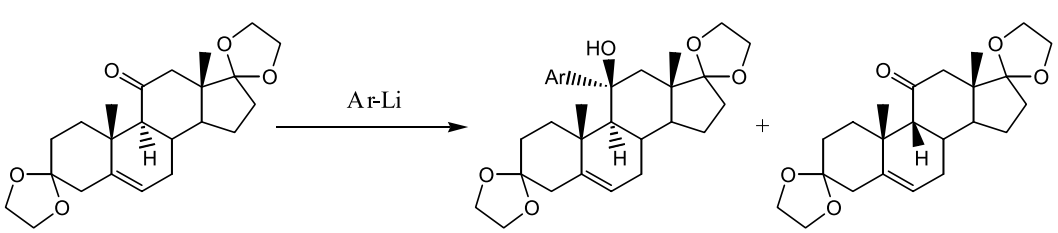
3. Salt effect

The presence of lithium salt in the medium has been described as favouring the addition of organometallics to ketones.[17] Ashby in particular demonstrates the effect of lithium salts on the speed of the addition reaction of various organolithiums to a range of cyclohexanones.[18] Table 7 shows the results obtained from a study of the salt effect in the medium. The salt-free phenyllithium was prepared by halogen–metal exchange with salt-free *n*-butyllithium; to study the effect of 1 equiv. of LiBr, the corresponding quantity of dry LiBr was added to the medium. Commercial phenyllithium in fact contains a small amount of LiBr (around 3%).

For the addition reaction, the salt effect appears to be negligible in the case of an aryllithium (Table 7, entries 1–3) and of an alkyllithium (Table 7, entries 4 and 5). In the case of phenyllithium, however, an increase in enolisation is observed proportionate to the amount of salt in the medium.

4. Discussion

The results previously described show that a good choice of medium, reaction time and temperature generally leads to good rates of addition for organolithiums to hindered and/or enolisable ketones. The order of addition of the



7 **8a-8d** **9**

Scheme 4.

Table 7. Addition of PhLi and MeLi to **7** with or without LiBr

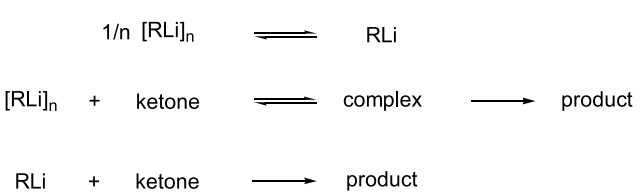
Entry[a]	Aryllithium	LiBr (equiv.)	Conversion (%)[b] addition product	**9**
1[c]	PhLi	0	43 (**8a**)	10
2[c]	PhLi	~0.01	42 (**8a**)	24
3[c]	PhLi	1	45 (**8a**)	32
4[d]	MeLi	0	97(**8g**)	0
5[d]	MeLi	1	95 (**8g**)	0

[a] Conditions: 3 equiv. of RLi at room temperature for 0.5 h.
[b] Determined by means of ^{1}H NMR.
[c] Toluene/ether 55/45.
[d] THF.

organolithium and the ketone also appears to be of some significance.

The lowest rates of addition are those involving the addition of phenyllithium to camphor and to an 11-oxo steroid and of alkyllithiums to menthone and fenchone in THF. A low-polar medium gives satisfactory results in these cases. The medium has an effect both on the state of aggregation of the organolithiums and on the reaction mechanism. The structures of phenyllithium, *tert*-butyllithium, *n*-butyllithium and methyllithium have been elucidated and reported in the literature: in hydrocarbon solvents (cyclohexane, toluene) or in hydrocarbon–ether mixtures,[19] phenyllithium and *tert*-butyllithium are tetramers, while in ether-based solvents (THF or diethyl ether) they adopt a less aggregated form (monomer, dimer or an equilibrium between the two). In the case of *n*-butyllithium, a hexamer is formed in hydrocarbon solvents, and a tetramer/dimer equilibrium occurs in THF.[20] Finally, methyllithium adopts a tetrameric form in THF or diethyl ether.[21] The mechanism of addition of an organolithium to a ketone also depends on the medium. It has in fact been shown[22] that for alkyllithiums in an ether medium, the monomer (formed for example from the dissociation of the dimer) adds directly to the ketone, while in a hydrocarbon solvent there is initial formation of a $[RLi]_n$–ketone complex which rearranges to give the addition product. These different mechanisms are summarized in Scheme 5.

The addition of phenyllithium monomers (in THF) to a ketone appears to be disfavoured by the hindered nature of the ketone, whereas formation of the hindered phenyllithium–ketone complex, and thence formation of the addition product, is possible. The lower reactivity of aryllithium monomers with hindered ketones is attested by the fact that, in the presence of a chelating agent favouring the dissociation of the aggregates, no addition to **7** is observed.[5] Addition of hindered or non-hindered alkyllithiums can in principle be performed via either of the two addition routes described above, i.e. by addition of a monomer or by complexation of an aggregate.



Scheme 5.

The presence of a lithium salt in the medium increases the degree of association of the organolithiums.[23] Thus with a low-polar solvent, the presence or absence of lithium salt has no influence on the addition reaction, since the phenyllithium and methyllithium are already at a high level of aggregation.

Certain results show that the addition reaction of phenyllithium (and of aryllithiums in general) to hindered ketones may be reversible. This result should be compared to the reversibility of the addition reaction of allylorganometallics to this type of ketones. It has clearly been shown[15a] that the increase in steric hindrance of the alcoholate resulting from the addition of the organometallic complex (in order of reactivity organozinc>organolithium>organomagnesium) to the ketone increased the speed of the reversal. Thus we can postulate that, in a similar fashion, the presence of an aryl group in hindered systems such as **3** or **7** sufficiently destabilises the adduct to provoke reversal of the addition. The return to the starting ketone in a basic medium may then, in certain cases, favour enolisation. On the other hand, an alkyl group does not cause sufficient destabilisation and the addition products are stable until hydrolysis. The reactivity of certain ketones should thus be seen as a relative property, dependent on the level of hindrance of the ketone and on the reaction environment.

5. Conclusion

This study examined the addition reaction of various aryl- and alkyllithiums to specific hindered and/or enolisable ketones in a number of solvents. This allowed us to show that a low-polar medium (toluene or toluene/diethyl ether) could give better addition rates than those reported previously, under mild (room temperature) conditions. In the most difficult cases, a brief examination of the influence of reaction time and temperature showed the reversibility of the addition of aryllithiums to hindered ketones, as exemplified by the addition reaction of allylorganometallics.

These results provide an easy access route to new steroidal adducts, and lay the groundwork for a novel preparation method for 11-substituted steroids of potential biological interest.

6. Experimental

^{1}H and ^{13}C NMR spectra were recorded on a 200 MHz Bruker AC 200 spectrometer. Chemical shifts are reported in ppm and referenced to the residual proton resonances of the solvent used. Infrared (IR) spectra were recorded by using a BOMEN MB spectrometer. Mass spectra were obtained on NERMAG R1010C apparatus. Melting points were measured on a Büchi B-510 apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F 254. Silica gel Merck Gerudan SI (40–63 μm) was used for column chromatography using the Still method.[24] Elemental analyses were measured at the microanalysis laboratory of the Pierre et Marie Curie University (Paris, France). All solvents and

reagents were purified when necessary using standard procedures. The ketones **1**–**3**, **5**, **6**, phenyllithium, *n*-butyllithium, *tert*-butyllithium, methyllithium (Aldrich) and **4** (Fluka) were used as received. Compound **7** was prepared, as previously described,[25] from the adrenosterone (Aldrich).

6.1. General procedure for the addition of phenyllithium to ketones 1 to 7

The ketone (3 mmol) and the dry solvent (25 ml) were introduced into a three-necked flask under argon. Phenyllithium (9 mmol) was added slowly by syringe. The mixture was stirred at room temperature for 2 h then hydrolysed. After the usual work-up the conversion level of the addition reaction was determined from ^{1}H NMR spectra of the crude product. After purification on a silica gel chromatographic column (petroleum ether/dichloromethane 1/1) the product obtained was compared with literature data (the results may differ from those presented in the article owing to other procedures required for preparation and isolation of the adducts): (1*R*,2*R*)-2-*endo*-hydroxy-2-*exo*-phenyl-1,3,3-trimethylbicyclo[2.2.1]heptane **10**,[26] (1*S*,2*S*,5*R*)-1-phenyl-2-isopropyl-5-methyl-cyclohexan-1-ol **11**,[12] (1*R*,2*R*)-2-*exo*-hydroxy-2-*endo*-phenyl-1,7,7-trimethylbicyclo[2.2.1]heptane **12**,[27] (1*S*,5*R*)- and (1*R*,5*S*)-1-phenyl-3,3,5-trimethylcyclohexan-1-ol **13**[28] or fully characterized. The configurations were attributed on the basis of ^{13}C NMR considerations.

6.1.1. 1-*eq*-Phenyl-3,3,5,5-tetramethylcyclohexa-1-*ax*-ol 14. Viscous oil, 63% yield (80% conversion). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.99 (s, 6H, $CH_3$3ax and $CH_3$5ax), 1.25 (d, J=13.8 Hz, 2H, H-2), 1.37 (s, 6H, $CH_3$3eq and $CH_3$5eq), 1.53 (d, J=13.8 Hz, 2H, H-2), 1.67 (s, 2H, H-4), 7.23–7.42 (m, 3H H_p+H_m), 7.51–7.57 (m, 2H, H_o) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.7 (CH_3ax), 31.7 (C3), 36.5 (CH_3eq), 50.2 (C2), 51.6 (C4), 76.2 (C1), 124.6 (C_o), 126.5 (C_p), 128.4 (C_m), 150.9 (C_i) ppm; IR (NaCl, neat) 3560, 1366, 1223, 1053, 749, 639 cm^{-1}; MS (EI 70 eV) *m*/*z* 232 ($M^{+\cdot}$), 217 (M^+-H_2O), 199, 161, 105, 77, 55, 41. Anal. calcd for $C_{16}H_{24}O$: C 82.70, H 10.41. Found: C 82.60, H 10.56.

6.1.2. 2,4-Dimethyl-3-phenylpentan-3-ol 15. Viscous oil, 90% yield (97% conversion). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.78 (d, J=6.9 Hz, 6H, CH_3), 0.87 (d, J=6.6 Hz, 6H, CH_3), 2.33 (heptuplet, J=6.8 Hz, 2H, H-2 and H-4), 7.24–7.45 (m, 5H, H arom) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.5–17.4 (C1, C6, C7, C5), 33.7 (C2, C4), 80.9 (C3), 126.1, 126.6, 127.2 (C_p,C_m,C_o), 142.8 (C_i) ppm; IR (NaCl, neat): 3601, 3505, 980, 759, 705 cm^{-1}.

6.1.3. 11β-Hydroxy-11α-phenyl-3,3,17,17-(ethylenedioxy)-androst-5-ene 8a. White powder: mp 182°C, 50% yield (55% conversion); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.19 (s, 3H, CH_3-18), 1.34 (s, 3H, CH_3-19), 3.67–3.92 (m, 8H, CH_2-ketal), 5.35 (s, 1H, H6), 7.15 (d, $H_{mm'}$), 7.30 (t, H_p), 7.40 (m, $H_{oo'}$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.0, 21.8, 23.3, 30.8, 31.1, 32.5, 34.2, 37.6, 40.3, 41.4, 44.9, 51.2, 52.5, 56.7, 63.9–64.9 (C-ketal), 79.4 (C11), 108.6 and 119.5 (C17 and C3), 121.0 (C6), 125.7, 127.7, 141.4 (C5), 152.5 ppm; MS (EI 70 eV) *m*/*z* 466 ($M^{+\cdot}$), 448 ([M−H_2O]$^{+\cdot}$), 346, 105, 99, 83, 55, 43; IR (NaCl, $CHCl_3$) 668, 757, 1109, 1212, 2888, 2973, 3018, 3493 cm^{-1}. Anal. calcd for $C_{29}H_{38}O_5$: C 74.65, H 8.21. Found C 74.51, H 8.21.

6.1.4. 11β-Hydroxy-11α-tolyl-3,3,17,17-(ethylenedioxy)-androst-5-ene 8b. Lithium (450 mg, 65.2 mmol) was washed with petroleum ether, cut into small pieces and introduced into a three-necked flask under argon. Diethyl ether (40 ml) and *para*-bromotoluene (5.1 g; 30 mmol) in 5 ml diethyl ether were then added. The mixture was stirred for 22 h at room temperature, after which bisethylene ketal of adrenosterone **7** (1.8 g, 4.6 mmol) in 30 ml toluene was added. The mixture was stirred at room temperature for 4.5 h and then hydrolysed. The organic layer was separated and the aqueous layer extracted with dichloromethane. The organic layers were combined, dried on magnesium sulfate, and evaporated. The crude product was purified on a silica gel chromatographic column (petroleum ether/ethylacetate 6/4) to give 0.5 g (40% yield—50% conversion) of a white powder: mp 171°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.19 (s, 3H, CH_3-18), 1.34 (s, 3H, CH_3-19), 3.54–3.72 (m, 8H, CH_2-ketal), 5.33 (s, 1H, H6), 7.11 (d, $H_{mm'}$), 7.29 (m, $H_{oo'}$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.9, 20.8, 21.8, 23.3, 30.8, 31.1, 32.5, 34.2, 40.3, 41.3, 44.9, 51.2, 52.6, 56.6, 63.9–64.8 (C-ketal), 79.3 (C11), 108.7 and 119.5 (C17 and C3), 121.0 (C6), 128.4, 135.0, 141.5 (C5), 149.6 ppm; MS (EI 70 eV) *m*/*z* 480 ($M^{+\cdot}$), 462 ([M−H_2O]$^{+\cdot}$), 361, 346, 233, 206, 185, 140, 119, 99, 83, 69, 55, 43; IR (NaCl, $CHCl_3$) 668, 759, 1104, 1212, 2889, 2974, 3019, 3493 cm^{-1}. Anal. calcd for $C_{30}H_{40}O_5$: C 74.97, H 8.39. Found C 74.86, H 8.57.

6.1.5. 11β-Hydroxy-11α-anisyl-3,3,17,17-(ethylenedioxy)-androst-5-ene 8c. *para*-Iodoanisole (3 mmol; 702 mg) was introduced into a three-necked flask under argon. Diethyl ether (3 ml) was then added followed by *n*-BuLi 2.5 M (1.53 ml; 3 mmol). The mixture was stirred for 0.5 h at room temperature. This anisyllithum solution was immediately added to a solution of 388 mg of **7** (1 mmol) in 11 ml of toluene. The mixture was stirred at room temperature for 3.5 h and then hydrolysed. The organic layer was separated and the aqueous layer extracted with dichloromethane. The organic layers were combined, dried on magnesium sulfate, and evaporated. The crude product was purified on silica gel chromatographic column (petroleum ether/ethylacetate 7/3) to give 0.1 g (20% yield—30% conversion) of a white powder: mp 153°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.18 (s, 3H, CH_3-18), 1.33 (s, 3H, CH_3-19), 3.69–3.85 (m, 8H, CH_2-ketal), 3.79 (s, CH_3-anisyl), 5.29 (s, 1H, H6), 6.81 (d, $H_{mm'}$), 7.33 (m, $H_{oo'}$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.0, 21.8, 23.3, 30.9, 31.1, 32.5, 34.2, 37.6, 40.3, 41.4, 45.0, 51.2, 52.6, 55.1, 56.8, 63.9–64.9 (C-ketal), 79.1 (C11), 108.7 and 113.7 (C17/3), 119.5, 121.1 (C6), 126.5, 141.5 (C5), 144.8, 157.5 ppm; MS (EI 70 eV) *m*/*z* 496 ($M^{+\cdot}$), 346, 227, 167, 152, 137, 121, 109, 99, 94, 84, 77, 71, 65, 55, 49, 42; IR (KBr) 1247, 1509, 2832, 2878, 2944, 3491 cm^{-1}. Anal. calcd for $C_{30}H_{40}O_6$+1H_2O: C 70.01, H 8.23. Found C 70.33, H 7.95.

6.1.6. 11β-Hydroxy-11α-(*p*-*N*,*N*-dimethylaminophenyl)-androst-4-ene-3,17-dione hydrochlorid 8d. Lithium (83 mg, 12 mmol) was washed with diethyl ether, cut into

small pieces and introduced into a three-necked flask under argon. Diethyl ether (1 ml) was then added and, slowly, *p*-bromo-*N*,*N*-dimethylaniline (1.2 g; 6 mmol) diluted in 2 ml of diethyl ether. The mixture was stirred for 2 h at the reflux temperature. Compound **7** (777 mg; 2 mmol) in 12 ml toluene were added to the lithium derivative solution. The mixture was stirred at room temperature for 4.5 h and then hydrolysed. The organic layer was separated and the aqueous layer extracted with dichloromethane. The organic layers were combined, dried on magnesium sulfate, and evaporated. The crude product was crystallized in cyclohexane and filtered. The solid was introduced into a solution of THF (10 ml) and HCl 0.2 M (10 ml), and the mixture was stirred for 15 min. The solvent was evaporated, then toluene was added. The resulting chlorohydrate precipitate was filtered and washed with toluene to give 250 mg (25% yield—30% conversion) of a blue powder. ^{1}H NMR (200 MHz, CD_3OD) δ 1.16 (s, 3H, CH_3-18), 1.45 (s, 3H, CH_3-19), 3.59 (s, 6H, CH_3-N^+), 5.58 (s, 1H, H6), 7.60 −7.89 (m, H_{arom}) ppm; ^{13}C NMR (50 MHz, CD_3OD) δ 15.2, 23.1, 23.8, 33.0, 34.5, 36.3, 37.3, 43.5, 47.4, 52.0, 52.2, 59.6, 64.2, 80.6, 121.2, 122.8, 127.9, 129.9, 142.1, 156.4, 176.2, 202.4 ppm; IR (NaCl, CH_2Cl_2) 1633, 1720, 2315, 2858, 2914, 2941, 3415, 3468 cm^{-1}. Anal. calcd for $C_{27}H_{36}NO_3Cl$: C 70.01, H 8.23. Found C 70.33, H 7.95.

6.2. General procedure for the addition of *n*-buLi and *tert*-buLi to ketones 1, 2, 4 and 7

The ketone (0.5 mmol) and the dry solvent (3 ml) were introduced into a three-necked flask under argon. *n*-BuLi resp. *tert*-BuLi (1.5 mmol) was added slowly by syringe. The mixture was stirred at room temperature for 30 min, after which water was added. After usual work-up the crude product obtained was compared with literature data: (1*S*,2*S*,5*R*)-1-butyl-2-isopropyl-5-methyl-cyclohexan-1-ol **18**,[12] (1*S*,2*S*,5*R*)-1-*tert*-butyl-2-isopropyl-5-methyl-cyclohexan-1-ol **19**,[12] (1*S*,5*R*)- and (1*R*,5*S*)-1-*tert*-butyl-3,3,5-trimethylcyclohexan-1-ol **21**[13] or fully characterized.

6.2.1. (1*R*,2*S*)-2-*endo*-Hydroxy-2-*exo*-butyl-1,3,3-trimethylbicyclo[2.2.1]heptane 16. Viscous oil, 76% yield (100% conversion). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.86–0.94 (m), 0.96 (s, 3H), 0.99 (s, 3H), 1.05 (s, 3H), 1.08 (bd, 1H), 1.23–1.75 (m), 1.98 (m, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.0, 18.0, 22.5, 23.7, 24.8, 27.1, 27.5, 30.6, 35.4, 40.9, 44.2, 50.1, 52.5 (C1), 80.9 (C2) ppm; MS (EI 70 eV) *m*/*z* 210 ($M^{+\cdot}$), 192 ([$M^{+\cdot}-H_2O$]), 181, 167, 153, 135, 128, 109, 81, 69, 57, 43, 41; IR (NaCl, neat) 995, 1105, 1375, 1458, 2871, 2963, 3509, 3630 cm^{-1}. Anal. calcd for $C_{14}H_{26}O$: C 79.94, H 12.46. Found C 79.74, H 12.64.

6.2.2. (1*R*,2*S*)-2-*endo*-Hydroxy-2-*exo*-*tert*-butyl-1,3,3-trimethylbicyclo[2.2.1]heptane 17. White powder: mp 110°C, 58% yield (70% conversion). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85–1.01 (m, 2H), 1.03 (s, 3H), 1.06 (d, *J*=1.7 Hz, 1H), 1.11 (s, 6H), 1.28 (s, 3H), 1.29 (s, 3H), 1.32 (s, 3H), 1.35–2.11 (m, 5H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.4, 23.3, 23.5, 26.3, 29.5, 30.0, 30.3, 35.7, 41.5, 43.6, 49.6, 51.1, 54.3, 84.8 ppm; MS (EI 70 eV) *m*/*z* 210 ($M^{+\cdot}$), 193 ([$M-H_2O+H]^+$); IR (NaCl, neat) 984, 1050, 1476, 2938, 3627 cm^{-1}. Anal. calcd for $C_{14}H_{26}O$: C 79.94, H 12.46. Found C 79.27, H 12.65.

6.2.3. (1*S*,5*R*)- and (1*R*,5*S*)-1-Butyl-3,3,5-trimethylcyclohexan-1-ol 20. Viscous oil, 74% yield (100% conversion). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.66–0.82 (m, 3H), 0.86 (d, *J*=6.6 Hz, 3H, CH_3-5), 0.86 (s, 3H, CH_3-3), 1.08 (s, 3H, CH_3-3), 1.23–1.43 (m, 7H), 1.59 (bd, 1H), 1.92 (17 lines, 1H, H-5) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.0, 22.4, 23.2, 24.0, 25.1, 27.3, 31.1, 34.4, 45.4, 45.9, 48.5, 48.6, 73.1 (C-1) ppm; MS (ICP/NH_3 70 eV) *m*/*z* 216 ([$M+NH_4]^+$), 198 ([$M^{\cdot}-H_2O+NH_4]^+$), 181([$M^{\cdot}-H_2O+H]^+$); IR (NaCl, neat) 759, 1216, 1457, 2930, 2953, 3464 cm^{-1}. Anal. calcd for $C_{13}H_{26}O$: C 78.72, H 13.21. Found C 78.53, H 13.33.

6.2.4. 11β-Hydroxy-11α-*n*-butyl-3,3,17,17-(ethylenedioxy)-androst-5-ene 8e. White powder: mp 130°C, 88% yield (100% conversion); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, *J*=6.6 Hz, 2H), 1.05 (s, 3H, CH_3-18), 0.25–1.38 (m, 5H), 1.38 (s, 3H, CH_3-19), 1.50–2.25 (m, 10H), 2.60 (dd, *J*=2.5 Hz, 14.5 Hz, 1H), 3.85–3.95 (m, 8H, CH_2-ketal), 5.31 (m, 1H, H-6) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.0, 15.2, 21.3, 23.2, 23.5, 27.1, 30.9, 32.6, 33.1, 33.9, 37.3, 41.1, 41.6, 44.4, 46.3, 47.6, 49.6, 53.7, 64.1–64.9 (C-ketal), 77.4 (C11), 108.8–118.9 (C3-C7), 121.6 (C6), 142.2 (C5) ppm; MS (ICP/NH_3 70 eV) *m*/*z* 446 ($M^{+\cdot}$), 428 ([$M-H_2O]^{+\cdot}$), 389, 346, 327, 284, 257, 232, 129, 99, 85, 57; IR (KBr) 2872, 2952, 3503 cm^{-1}. Anal. calcd for $C_{27}H_{42}O_5$: C 72.61, H 9.48. Found C 72.63, H 9.44.

6.2.5. 11β-Hydroxy-11α-*tert*-butyl-3,3,17,17-(ethylenedioxy)-androst-5-ene 8f. White powder, 85% yield (98% conversion). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.97 (s, 9H, CH_3–*tert*-butyl), 1.04 (s, 3H, CH_3-18), 1.46 (s, 3H, CH_3-19), 3.90–4.12 (m, 8H, CH_2-ketal), 5.39 (s, 1H, H6) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.2, 19.7, 23.3, 26.9, 31.3, 33.3, 33.8, 36.1, 38.1, 42.3, 43.0, 44.4, 44.9, 45.4, 51.4, 64.3, 65.2, 80.6, 109.2, 119.9, 122.9, 144.8 ppm; MS (EI 70 eV) *m*/*z* 446 ($M^{+\cdot}$), 428 ([$M-H_2O]^{+\cdot}$), 389, 346, 327, 284, 199, 121, 99, 84, 75, 57, 49, 43; IR (KBr) 1370, 1468, 2876, 2957, 3535 cm^{-1}. Anal. calcd for ($C_{27}H_{42}O_5$+1/3AcOEt) C 71.49, H 9.46. Found C 71.46, H 9.64.

6.2.6. 11β-Hydroxy-11α-methyl-3,3,17,17-(ethylenedioxy)-androst-5-ene 8g. Compound **7** (140 mg; 0.33 mmol) and dry THF (10 ml) were introduced into a three-necked flask under argon. 'Salt-free' methyllithium (1 mmol; 1.6 M) was added slowly and the yellow mixture was then stirred at room temperature for 0.5 h. After hydrolysis, the organic phase was washed, dried and the solvent was evaporated. The product was purified on a silica gel chromatographic column (petroleum ether/ethyl acetate 6/4) to give 122 mg (84%) of a white powder (mp 176°C) in agreement with Ref. 29 and ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.03 (s, 3H, CH_3), 1.34 (s, 3H), 1.43 (s, 3H), 1.60–2.26 (m, 15H), 2.58 (bd, *J*=14.3 Hz, 1H), 3.92 (m, 8H, ketal), 5.27 (bs, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.2, 21.0, 23.4, 31.0, 32.7, 33.9, 37.2, 38.1, 40.5, 41.5, 44.8, 50.0, 50.4, 56.7, 64.0–65.0, 75.3, 108.7, 119.5, 121.4, 141.7 ppm; MS (EI 70 eV) *m*/*z* 404 ($M^{+\cdot}$), 386 ([$M-H_2O]^{+\cdot}$), 346, 284, 99, 86; IR (KBr) 1118, 2879, 2945, 2965, 3507 cm^{-1}.

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