New and efficient routes to $CpRe(CO)_3$ substituted steroids

Franck Le Bideau,[a] El Bachir Kaloum,[a] Pierre Haquette,[a] Ulrich Kernbach,[a] Jérôme Marrot,[b] Elie Stephan,[a] Siden Top,[a] Anne Vessières[a] and Gérard Jaouen*[a]

[a] *Ecole Nationale Supérieure de Chimie de Paris, 11 rue Pierre et Marie Curie, 75231 Paris Cedex 05, France. E-mail: jaouen@ext.jussieu.fr*

[b] *Université de Versailles Saint-Quentin-en-Yvelines, IREM, bâtiment Lavoisier, 45 av des Etats-Unis, 78035 Versailles Cedex, France*

Received (in Basel, Switzerland) 21st October 1999, Accepted 2nd January 2000

Two new methods for the formation of $CpRe(CO)_3$ substituted steroids are presented; both imply a one-pot procedure involving a transmetallation process.

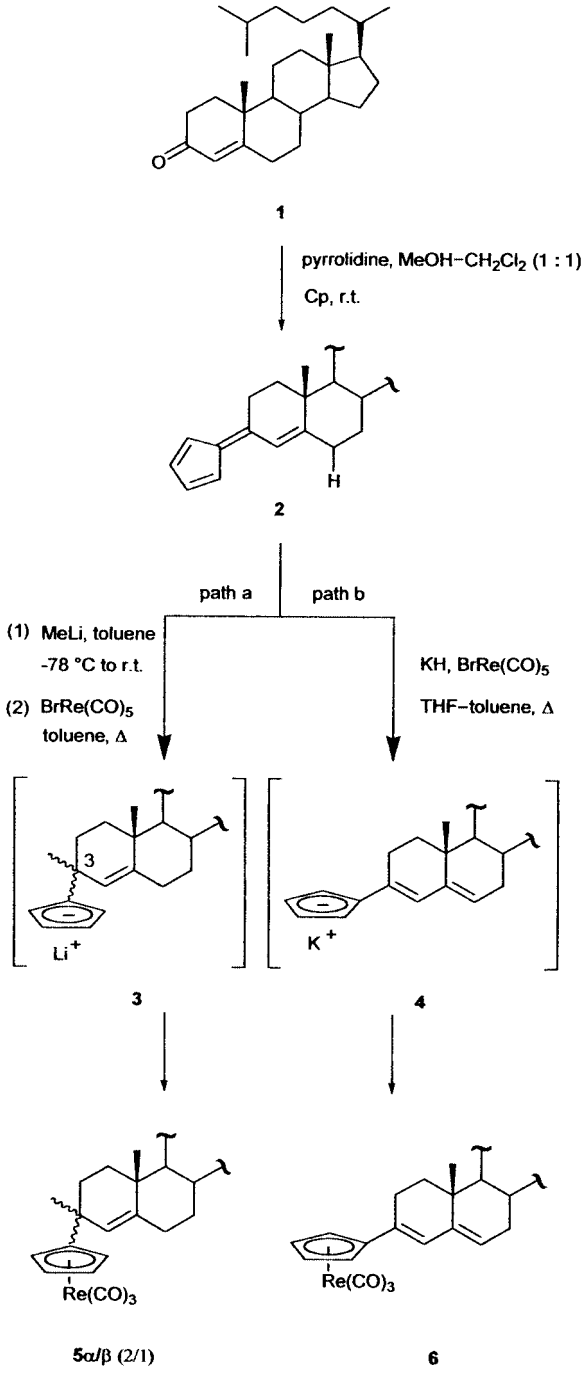
The emergence of bioorganometallic chemistry[1] has benefited from the enormous amount of synthetic work that has been done to prepare all kinds of organometallic compounds over the last half-century. However, access to compounds for use in bioorganometallic chemistry is not always achieved merely by adopting synthetic methods used in classical organometallic chemistry. This is particulary true in the challenging area of low valent organometallic radiopharmaceuticals of ^{186}Re, ^{188}Re and ^{99m}Tc[2] which requires the devising of new reactions in order to introduce the radioactive element onto the bioligand in the last step of the process. The fixation of a small, compact, robust and non polar substituted cyclopentadienyltricarbonylrhenium unit [$CpRe(CO)_3$] appears to be a strategic objective with this respect. In this field, we previously reported the synthesis of a large number of substituted steroids. Among them, a non-radioactive $CpRe(CO)_3$ oestradiol derivative has been shown to have an excellent binding affinity for the oestrogen receptor (ER) when fixed at the 17α position.[3] We present here another route to attach this organometallic unit based on the introduction of fulvenes in other selected positions of steroids, which allows the introduction of the $CpRe(CO)_3$ fragment in the last step of the synthesis.

Fulvenes are easier to characterize and synthesize than the corresponding cyclopentadienes, which are often not stable and exist as mixtures of isomers.[4] As a source of rhenium we chose bromorhenium pentacarbonyl [$BrRe(CO)_5$] which can be used in a transmetallation process leading to substituted $CpRe(CO)_3$. Furthermore, we recently reported[5] a mild one pot access to this reagent starting from ammonium perrhenate, a Re^{VII} precursor which is easily accessible in radioactive forms.[6,7]

In a preliminary study, we began with cholest-4-en-3-one **1**. This compound was first submitted to the conditions reported by Little and Stone[8] for other substrates, to afford the corresponding fulvene **2** in less than 30% yield (Scheme 1). These results were attributed to the poor solubility of starting materials in MeOH. A thorough screening of solvents showed that the use of CH_2Cl_2 as cosolvent (MeOH–CH_2Cl_2 = 1:1) greatly enhanced yield (up to 70%) for the formation of **2**.

According to path (*a*) fulvene **2** was treated with MeLi in toluene at −78 °C and warmed to room temperature for 3 h. The resulting intermediate **3** was then submitted to transmetallation conditions[9]—$BrRe(CO)_5$ was added and the reaction mixture was heated to reflux for 15 h. Under these conditions, two diastereomers **5α/β** were produced in a 2:1 ratio in 39% yield which are distinguished by their relative configuration at the newly formed stereogenic center (steroid carbon center C-3). The major product was crystallized from CH_2Cl_2–hexane. An X-ray structural analysis shows that the newly introduced methyl substituent is attached to the α face of the steroid framework (Fig. 1).†

According to path (b), the fulvene **2**, KH and $BrRe(CO)_5$ were heated (110 °C) in a mixture of THF and toluene for only 1.6 h to give, after flash chromatography, the substituted $CpRe(CO)_3$ **6** in 67% yield.‡ No products resulting from the



Scheme 1

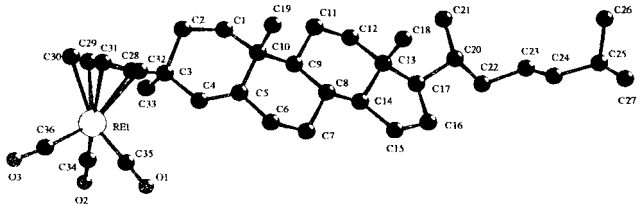
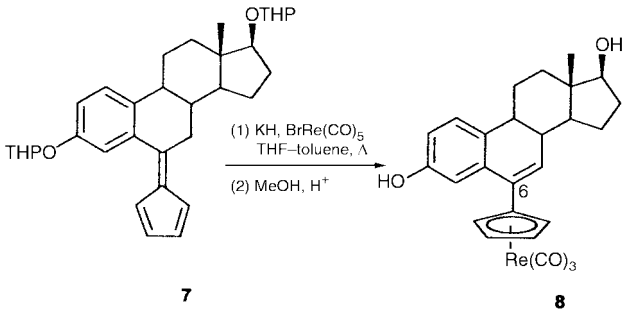


Fig. 1 X-Ray structure of **5α**.



7 **8**

Scheme 2

deprotonation of the C-2 position were isolated using these conditions. In both cases, longer reaction times did not improve the yield, probably because of the degradation of the starting materials.

This second strategy was applied to the synthesis of an oestradiol derivative (Scheme 2). Thus, the fulvene **7**, obtained from the corresponding 6-oxoestradiol,[10] was submitted to the conditions of path (b). An acidic work up (MeOH, cat. TsOH) gives access to **8,** the first oestradiol derivative bearing an organometallic unit at the C-6 position. The relative binding affinity (RBA) of this complex for the ER was measured on lamb uterine cytosol according to a previously reported procedure.[11] Compound **8** is still recognized by the ER even if the RBA value is low (0.5%). This result confirms that a bulky substitution at C-6 induces a dramatic decrease in the affinity of the modified hormone for the ER.[12–14]

In conclusion, the results presented illustrate a new route to $CpRe(CO)_3$ substituted steroids. They show that (i) the introduction of the metal carbonyl unit on a steroid in the last step of the synthesis is possible [for this purpose, fulvenes are more interesting than the corresponding cyclopentadienes because of the great number of products accessible according to the conditions (basic versus nucleophilic) used] and (ii) $BrRe(CO)_5$ is a suitable precursor for the elaboration of $CpRe(CO)_3$ units in organic solvents.[15] We thus hope that this new strategy will greatly enhance progress in the area of organometallic radiopharmaceuticals.

F. L. B. thanks the Société de Secours des Amis des Sciences' for his fellowship

Notes and references

† *Crystal data* for **5α**: $C_{36}H_{51}O_3Re$, M = 717.97, monoclinic, a = 14.992, b = 7.18410(10), c = 15.4819(2) Å, U = 1665.98(3) Å^3, T = 296 K, space group $P2_1$, Z = 2, μ = 3.679 mm^{-1}, 11750 reflections measured, 8046 unique (R_{int} = 0.0457) which were used in all calculations. The final $wR(F^2)$ was 0.003 (all data). The molecular structure shows clearly that the organorhenium moiety is on the β face of the hormone. CCDC 182/1516. See http://www.rsc.org/suppdata/cc/a9/a908481i/ for crystallographic data in .cif format.

‡ *Procedure for the preparation* of **6**: The reaction was carried out in a flame-dried flask, under argon. Fulvene **2** (0.108 g, 0.25 mmol), KH (0.012 g, 0.3 mmol) washed twice with pentane and $BrRe(CO)_5$ (0.122 g, 0.3 mmol) in THF–toluene (2 ml/2 ml) were heated at reflux for 1.6 h. The reaction mixture was cooled to room temperature and diluted in CH_2Cl_2 (20 ml). The organic layer was washed with brine (2 × 20 ml), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (CH_2Cl_2–pentane = 95:5) afforded **6** (0.118 g, 67%) as a white solid. *Selected data* for **6**: δ_H (200 MHz, $CDCl_3$) 6.26 (1H, sl), 5.6–5.5 (3H, m), 5.2–5.3 (2H, m), 2.4–0.9 (29H, m), 0.95 (3H, s), 0.91 (3H, s), 0.87 (3H, s), 0.73 (3H, s); δ_C (50 MHz, $CDCl_3$) 194.4, 141.1, 126.7, 126.6, 124.8, 110.7, 84.4, 83.2, 79.8, 79.4, 56.8, 56.1, 48.1, 42.4, 39.7, 39.5, 36.2, 35.8, 34.9, 33.4, 32.0, 31.7, 28.2, 28.0, 24.6, 24.1, 23.8, 22.8, 22.5, 21.0, 19.0, 18.7, 12.0; ν_{max}(KBr)/cm^{-1} 2950–2850, 2020, 1900, 1466, 822; *m*/*z* 702, 614, 441 (Calc. for $C_{35}H_{47}O_3Re$: C, 59.89; H, 6.75. Found: C, 59.76; H, 6.89%).

1 G. Jaouen, A. Vessières and I. S. Butler, *Acc. Chem. Res.*, 1993, **26**, 361.
2 J. R. Dilworth and S. J. Parrott, *Chem. Soc. Rev.*, 1998, **27**, 43.
3 S. Top, H. El Hafa, A. Vessières, J. Quivy, J. Vaissermann, D. W. Hughes, M. J. McGlinchey, J.-P. Mornon, E. Thoreau and G. Jaouen, *J. Am. Chem. Soc.*, 1995, **117**, 8372. Katzenellenbogen *et al*. recently shifted from their N and S coordinated oxorhenium chelate complexes (R. K. Hom and J. A. Katzenellenbogen, *Nucl. Med. Biol.*, 1997, **24**, 485) to $CpRe(CO)_3$ substituted steroids (F. Minutolo and J. A. Katzenellenbogen, *J. Am. Chem. Soc.*, 1998, **120**, 13 264).
4 N. Neuenschwander, in *The Chemistry of Doubled-Bonded Functional Groups*, ed. S. Patai, Wiley, 1989, p. 1131.
5 S. Top, P. Morel, M. Pankowski and G. Jaouen, *J. Chem. Soc., Dalton Trans.*, 1996, 3611.
6 F. F. Knapp, A. L. Beets, S. Guhlke, P. O. Zamora, H. Bender, H. Palmedo and H.-J. Biersack, *Anticancer Res.*, 1997, **17**, 1783
7 P. P. Venkatesan, S. Shortkroff, M. R. Zalutsky and C. B. Sledge, *Nucl. Med. Biol.*, 1990, **17**, 357.
8 K. J. Stone and R. D. Little, *J. Org. Chem.*, 1984, **49**, 1849.
9 P. A. Deck, W. F. Jackson and F. R. Fronczek, *Organometallics*, 1996, **15**, 5287.
10 R. Tedesco, R. Fiaschi and E. Napolitano, *Synthesis*, 1995, 1493.
11 A. Vessières, S. Top, A. A. Ismail, I. S. Butler, M. Louer and G. Jaouen, *Biochemistry*, 1988, **27**, 6659.
12 E. R. Clark, A. M. E. Omar and G. Prestwich, *J. Med. Chem.*, 1977, **20**, 1096.
13 S. Top, A. Vessières, J.-P. Abjean and G. Jaouen, *J. Chem. Soc., Chem. Commun.*, 1984, 428.
14 G. Eisenbrand, J. Fischer, K. Mühlbauer, G. Schied, J. Schreiber, W. Tang and O. Zelezny, *Arch. Pharm.*, 1989, **322**, 863.
15 Alberto *et al*. recently reported the synthesis of a promising organometallic aqua ion $[^{99}Tc(OH_2)_3(CO)_3]^+$ and its ^{188}Re homologue. These species are very good precursors for potential radiopharmaceuticals in water as exemplified by the formation of $[Tc(PADA)(CO)_3]$; R. Alberto, R. Schibli, A. Egli and A. P. Schubiger, *J. Am. Chem. Soc.*, 1998, **120** , 7987.

Communication a908481i