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A ROUTE TO CONFORMATIONALLY RESTRICTED ANTIOESTROGENS BY COUPLING OF A VINYL TRIFLATE WITH AN ARYL ZINC CHLORIDE[1]

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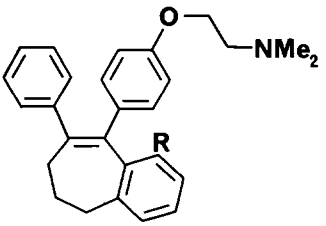
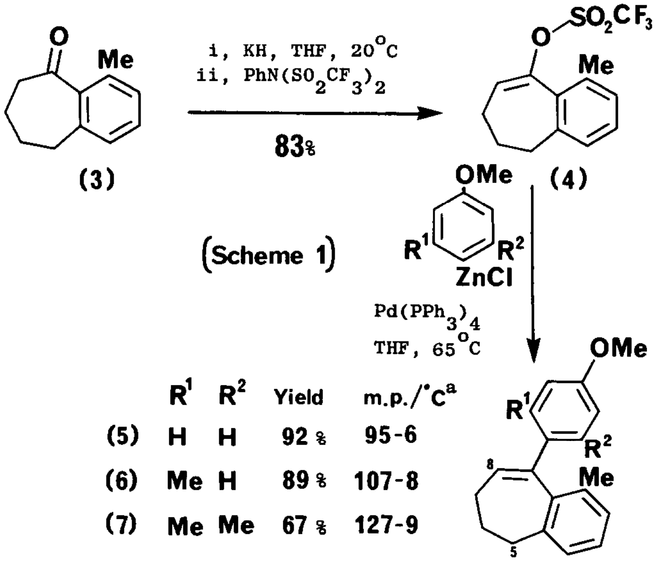
Summary: Palladium complex catalysed coupling of a benzocycloheptenyl triflate with aryl zinc chlorides gives an efficient approach to the synthesis of conformationally restricted antioestrogens.

Triarylethylene antioestrogens having sufficient rigidity to allow their separation into the constituent enantiomeric atropisomers should be useful for a detailed study of the topology of the oestrogen receptor binding surface through structure-activity studies. For this purpose the methyl substituted diarylbenzocycloheptene (**1**) is sought.

Following synthetic strategy used for the simpler analogue (**2**)[2] the methylbenzosuberone (**3**)[3] was treated with 4-methoxyphenylmagnesium bromide but no addition to the ketone function occurred owing to a severe peri-interaction with the methyl group in (**3**). Instead, the enolate of (**3**) was formed.[4] The required olefin (**5**)[5] was however successfully prepared by conversion of the ketone (**3**) into its enol triflate (**4**) and then coupling with 4-methoxyphenyl zinc chloride (prepared in situ from 4-bromoanisole) under palladium catalysis. This method was still successful when the aryl-zinc bond was flanked by one or two methyl groups and hence the encumbered olefins (**6**) and (**7**) could be prepared similarly (Scheme 1).



(1) R=Me
(2) R=H



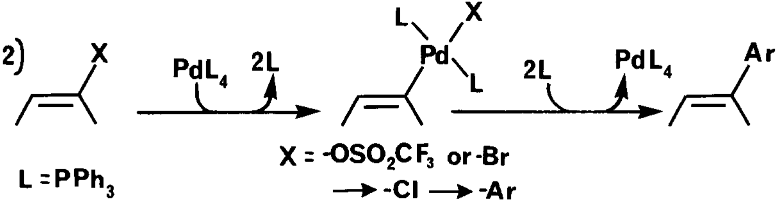
(Scheme 1)

	R^1	R^2	Yield	m.p./°C^a
(5)	H	H	92%	95-6
(6)	Me	H	89%	107-8
(7)	Me	Me	67%	127-9

^{a}Compounds (5)-(7) gave satisfactory analytical data

These results are in contrast to reported observations[6] that vinyl triflates give poor yields of coupled product when treated with phenyltrimethyltin under palladium catalysis even when zinc chloride is added. On the other hand vinyl bromides give high yields of coupled products with aryl zinc chlorides,[2,7] a reaction that can proceed via a catalytically active chloropalladium intermediate, as can the reaction reported here, and as in the coupling of vinyl triflates and vinylstannanes in the presence of a chloride source[6] (Scheme 2).

(Scheme 2)



The vinyl triflate-aryl zinc chloride coupling was superior to the known uncatalysed coupling of vinyl triflates with organocuprates[8] since treatment of the triflate (**4**) with lithium di(4-methoxyphenyl) cuprate in ether gave only a moderate yield (42%) of (**5**) owing to competing cleavage at sulphur reforming the ketone (**3**) (55%).

Procedure for coupling reactions: A stirred solution of the aryl bromide (1.5 mmol, 2.5 eq) in dry THF (5 ml) under N_2 at ca. -75°C was treated with t-BuLi (3 mmol, 5 eq) then with a solution of $ZnCl_2$ (1.5 mmol, 2.5 eq) in THF (1 ml). The mixture was allowed to warm to room temperature, then the triflate (**4**) (0.6 mmol, 1 eq) and $Pd(PPh_3)_4$ (0.02 mmol) were added and the mixture heated under reflux for 2 h. The product was isolated by aqueous work-up and column chromatography on silica gel.

Appendix

Elemental Analysis Data for Arylbenzocycloheptenes (5)-(7)

Compound	Formula	Required	Found
(5)	$C_{19}H_{20}O$	C, 86.32	86.30
		H, 7.63	7.66
(6)	$C_{20}H_{22}O$	C, 86.29	86.23
		H, 7.97	8.04
(7)	$C_{21}H_{24}O$	C, 86.26	86.04
		H, 8.27	8.33

References and Notes

1. This investigation was supported by grants from the Cancer Research Campaign and Medical Research Council.
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3. P. Caubere, G. Guillaumet, and M. S. Mourad, Bull. Soc. Chim. Fr., 1973, 3493.
4. When ketone (**3**) was treated with 4-methoxyphenyllithium then methyl iodide, α-methylated benzosuberones (98%) were obtained.
5. Phenyl group incorporation into the 8-position of (**5**) by the reported method (ref. 2) gave a product in which the benzylic 5-methylene protons gave distinct fully resolved multiplets in the n.m.r. spectrum (at δ2.64 and 2.90) indicating the presence of distinct atropisomers at room temperature. The corresponding protons in (2) gave coalesced signals above -75°C.
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