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Asymmetric alkylation of diphenylmethane derivatives using (−)-sparteine

James A. Wilkinson,[a,*] Stephen B. Rossington,[a] John Leonard[b] and Nigel Hussein[c]

[a]*Centre for Drug Design, Biosciences Research Institute, Cockcroft Building, University of Salford, Salford M5 4WT, UK*
[b]*AstraZeneca, Process R+D, Silk Road, Macclesfield, Cheshire SK10 2NG, UK*
[c]*GlaxoSmithKline Chemical Development, Old Powder Mills, Tonbridge, Kent TN11 9AN, UK*

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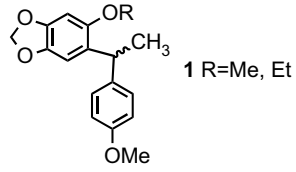
Abstract—Alkylation of 2-oxygenated diphenylmethane derivatives using *sec*-butyllithium and (−)-sparteine gave enantiomeric excesses of up to 60% with allyl bromide but alkylations with methyl electrophiles were poorly selective. When compounds with a free hydroxy in the 2-position were alkylated the selectivity was reversed.

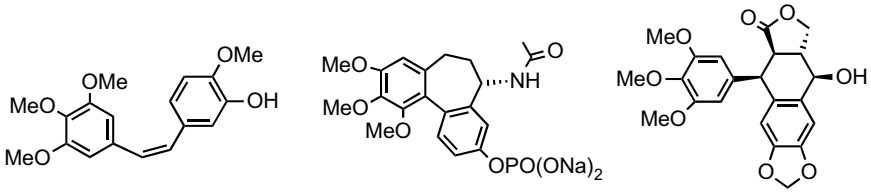
Our group has an interest in agents, which bind to tubulin at the colchicine binding site.[1] Generally these have as common structural features two aromatic rings, often oxygenated, with some linking group. The examples shown are all powerful anticancer agents, which exert their activity as a result of binding to the colchicine site on tubulin (Fig. 1).

Substituted diphenylmethanes structurally related to podophyllotoxin are of considerable interest as tubulin binding ligands. Compounds **1** have been synthesised as racemates and been found to have excellent tubulin binding properties.[2] Single enantiomers have not been made and groups other than methyl at the benzylic position were not investigated. Valuable information about the nature of the colchicine binding site could be gained if enantioenriched compounds could be synthesised and tested and this has led us to investigate new methodologies for the preparation of enantioenriched compounds of this form.



1 R=Me, Et

Existing syntheses of simple substituted diphenylmethanes are generally based on very classical chemistry,[3] but examples exist where lateral lithiation with an alkyllithium has been followed by alkylation.[4] Our



combretastatin A-4 **ZD6126** **podophyllotoxin**

Figure 1. Tubulin binding ligands.

Keywords: Asymmetric; Alkylation; Deprotonation; Diphenylmethane; Sparteine.
* Corresponding author. Tel.: +44-161-295-4046; fax: +44-161-295-5111; e-mail: j.a.wilkinson@salford.ac.uk

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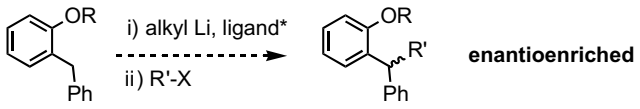
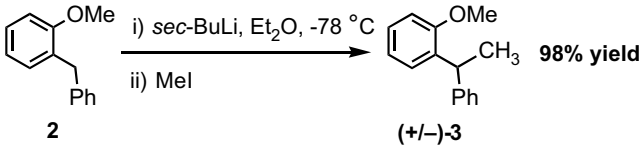
intention was to effect lateral lithiation/alkylation to give an enantioenriched product from a prochiral diphenylmethane derivative (Scheme 1).



Scheme 1.

Excellent results have been obtained in asymmetric alkylation of benzylic CH_2 groups by several researchers using alkyllithiums in conjunction with (−)-sparteine.[5] We report here the initial results of an investigation into lateral lithiation/alkylation of oxygenated diphenylmethanes using sparteine as a chiral control element.



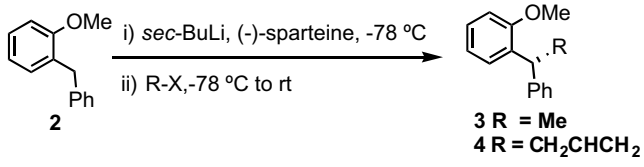
Scheme 2.

The initial starting material investigated was compound **2** (Scheme 2), which is readily available from 2-benzylphenol.[6] The methylated derivative **3** has a known specific rotation, thought to be for enantiomerically pure material, (−49.2) although the absolute stereochemistry of the two enantiomers has not been determined.[7] For this reason, methylation of **2** was chosen as the first testing ground. Attempts to deprotonate **2** with lithium diisopropylamide were unsuccessful (4 equiv LDA in THF at room temperature for 48 h gave ca. 2% incorporation of deuterium). This effectively ruled out any work with chiral lithium amide bases.[8] However, deprotonation with *sec*-butyllithium followed by quenching with excess methyl iodide gave a near quantitative yield of racemic **3**.[9]

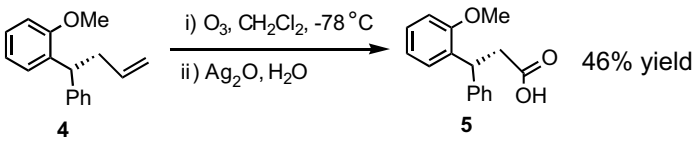
The results of methylations of **2** in the presence of (−)-sparteine are summarised in Table 1 (entries 1–5). Methyl iodide in ether was the only system, which gave an appreciable ee and this was poor. The major enantiomer was tentatively assigned as shown by assuming that the sense of methylation would be identical to that of allylation (vide infra). Other methylating reagents failed to react at all. Attempts to vary the reaction conditions with regard to temperature or the addition sequence failed to give improved enantioselectivity as did the use of a 'warm–cool cycle' according to the method of Beak.[10]

Allylations of **2** were also carried out (Table 1, entries 6–9). The reaction was most successful when the mixture of sparteine/*s*-BuLi and **2** was stirred at −78 °C for 6 h before addition of the electrophile. A warm–cool cycle followed by addition of allyl bromide gave a lower ee (49%) in favour of the *R*-enantiomer. In this case the products were converted to a compound of known optical rotation and absolute stereochemistry **5**,[11] by ozonolysis and oxidation to the carboxylic acid (Scheme 3). As can be seen the results when using allyl bromide in ether were much more encouraging with high yield and an ee of 60% in favour of the *R*-enantiomer.

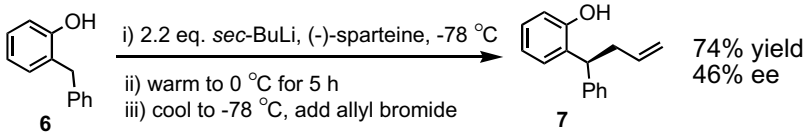
Table 1.



Entry	Product	R–X	Solvent	Yield	Ee	Config.
1	**3**	MeI	Diethyl ether	83	7	(+)
2	**3**	MeI	THF	95	0	
3	**3**	MeI	Toluene	60	0	
4		MeOTs	Diethyl ether	0		
5		MeOTf	Diethyl ether	0		
6	**4**	AllylBr	Diethyl ether	84	60	(*R*)
7	**4**	AllylBr	THF	62	31	(*R*)
8		AllylOTs	Diethyl ether	0		
9		AllylOTf	Diethyl ether	0		



Scheme 3.



Scheme 4.

The hydroxy compound, 2-benzylphenol **6** was also investigated as a substrate for alkylation using *sec*-butyllithium/sparteine (Scheme 4). Two equivalents of base were utilised in order to produce a dianionic species but only 1.1 equiv of sparteine. The reaction with allyl bromide was attempted and proved fairly successful giving the alkylated compound **7** in 74% isolated yield and an ee of 46%. The warm–cool procedure (*sec*-butyllithium was added at −78 °C and the solution warmed to 0 °C and stirred at this temperature for 5 h before cooling to −78 °C and adding the electrophile) was essential to the success of the reaction. The ee was obtained by O-methylation of the product (NaH, THF, MeI) and submitting it to the same procedure as outlined above to give the known **5**. In this case however the opposite *S*-enantiomer had been obtained. Reaction of the dianion derived from **6** with iodomethane gave a 75% yield of racemic product.[12]

This reversal of selectivity opens up the possibility of obtaining either enantiomer of a given derivative, as desired, by using a protected or unprotected starting material. This greatly increases the possibilities for this chemistry since only one enantiomer of sparteine is readily available.[13]

The reasons for our results are not clear. We assume these reactions involve a thermodynamic/kinetic resolution of an equilibrating pair of complexes. The closest literature precedent available is Beak's work on ethylaniline derivatives in which the sparteine/lithiated substrate complexes were configurationally stable at −78 °C but formed in approximately equal amounts (complexes derived from ethyl benzamide were labile at −78 °C, however). The best results were obtained when the mixture was warmed to −25 °C to equilibrate the two complexes.[14] This is not consistent with our results for allylations, which require either a fairly high de in the deprotonation step or a dynamic equilibrium between the two diastereomeric complexes at −78 °C. We suspect that, as in Beak's work, the deprotonation is not especially selective but that, unlike the ethylaniline work, the two complexes equilibrate at −78 °C. The large variation of ee with the electrophile suggests that the two equilibrating complexes react at similar rates with iodomethane but at significantly different rates with allyl bromide. The change in the sense of stereoselection from reactions of **2** to those of **6** is difficult to explain. It could be that a different pathway is followed in reactions of **2** to that followed in **6**. Alternatively, a different level of aggregation or dimerisation may be found in the dilithio species derived from **6**.

Work is currently being carried out to improve these results and probe the origin of the stereoselectivity.

Acknowledgements

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