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A Novel Regiodivergent Resolution Reaction Mediated by a Homochiral Lithium Amide Base

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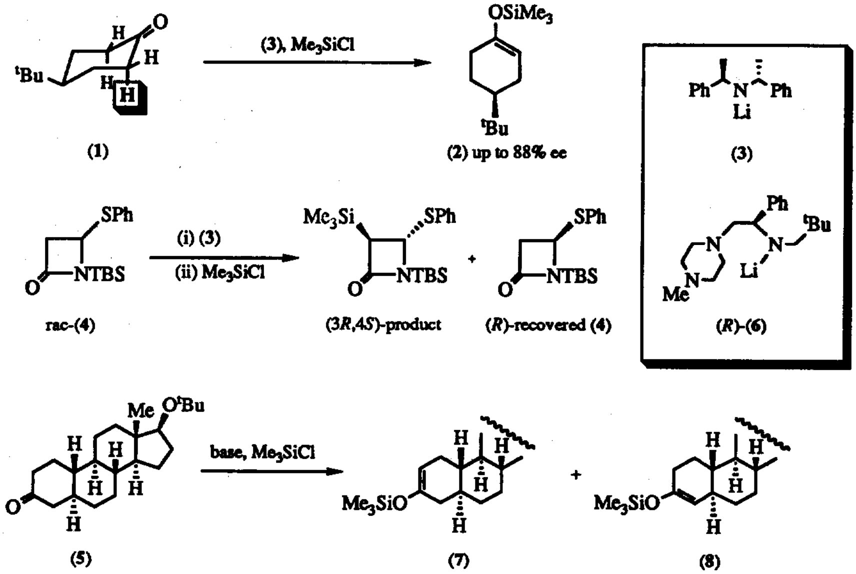
Abstract: The reaction of a racemic perhydroisoquinolone derivative **9** with the homochiral lithium amide base **3** in the presence of Me_3SiCl proceeds in an regiodivergent fashion to give the two non-racemic regioisomeric enol silanes **10** and **11**. Conversion of **10** into enone **15**, an intermediate useful in the synthesis of the alkaloid (+)-yohimbine, was also possible.

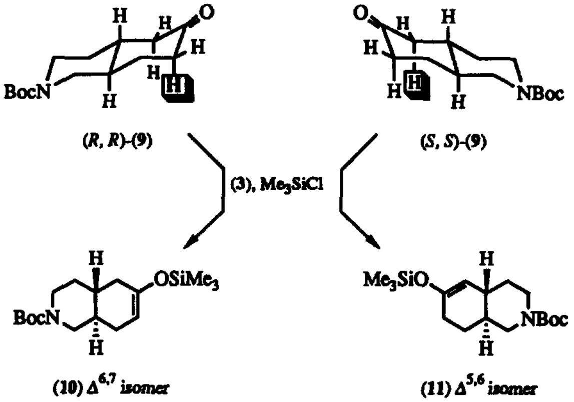
Recent reports from several groups, including our own, have described the use of homochiral lithium amide (HCLA) bases for novel asymmetric transformations, particularly those which involve the breaking of a plane of symmetry in a prochiral cyclic ketone, e.g. 1 → 2 using the base 3.[1] Other types of transformation which have been described include kinetic resolution, e.g. using the β-lactam 4,[2] and highly regiocontrolled enolisation of certain homochiral steroidal ketones such as 5,[3] Scheme 1.



	(7)		(8)
LDA	64	:	36
(*R*)-(6)	95	:	5
(*S*)-(6)	24	:	76

Scheme 1

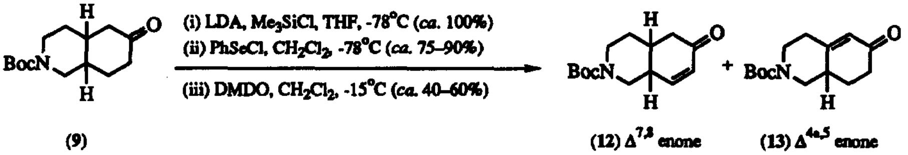
Kinetic resolutions of the type shown necessarily involve only partial conversion of the starting material, since if the reaction is carried to completion a racemic product will result. In the regioselective enolisation of a homochiral ketone, such as **5**, it was shown that the "normal" enolisation preference inherent in the substrate (substrate control) could be enhanced or reversed by the use of a HCLA base (reagent control). The predominant formation of **7** when (*R*)-**6** is used as the base, and **8** when (*S*)-**6** is employed, therefore represent matched and mismatched situations respectively.[4] We were intrigued by the possibility of combining the two ideas of kinetic resolution of a racemic ketone and regiocontrol in unsymmetrically substituted ketones, and here we describe the results of our study of the enolisation of the perhydroisoquinolone derivative **9**, Scheme 2.



Scheme 2

Assuming that, as in the case of 5, reagent control dominates the direction of enolisation, we anticipated that the use of base **3** would result in the removal of the axial hydrogens shown highlighted for each enantiomer of **9**, since this follows the pattern shown for **1**. The predicted selectivity has the remarkable consequence that the two enantiomers of **9** should be transformed into the two different regioisomeric enol silanes **10** and **11** - even if the reaction is carried to complete conversion!

Initial experiments indicated that the two enol silanes **10** and **11** are very difficult to separate, and that the direct measurement of the enantiomeric excess (ee) of the two components was not possible. Estimation of the ee of the two enol silanes therefore required their conversion to some form of derivative which would allow regioisomer separation, and then estimation of the ee of each component. This task proved difficult, especially since many conceivable reactions of the enol silanes would introduce additional asymmetric centres, and therefore complicate matters further. We found that the most satisfactory way to overcome these problems was to treat the mixture of **10** and **11** with PhSeCl in CH_2Cl_2, and then to oxidise the so-formed α-selenyl ketones with dimethyldioxirane (DMDO) in order to effect conversion to the enones **12** and **13**, Scheme 3.



Scheme 3

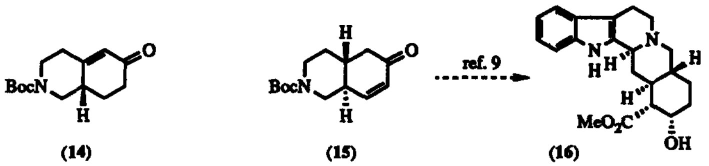
We were delighted to find that the enones **12** and **13** could be separated, and that the ee of each component could be estimated by examination of the ^1H NMR spectrum in the presence of (-)-2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE). As shown, the chemical yields for the first two steps are excellent, whereas the yield for the selenoxide elimination using DMDO is somewhat lower, and is dependent on the initial ratio of the regioisomeric enol silanes.[5] With this analytical procedure in hand, we proceeded to examine the enolisation of **9**, in both racemic and homochiral form, and then carry out the conversion to the two enones shown in Scheme 3. The results of these experiments are summarised in the Table.[6]

Table: Enolisation of ketone **9** with base **3**, followed by conversion to **12** and **13**

	temp (°C)[a]	enol silane[b] $\Delta^{6,7}$: $\Delta^{5,6}$	selenide	$\Delta^{7,8}$ enone	$\Delta^{4a,5}$ enone
(*R*, *R*)-**9**	-92	94 : 6	76%	56% yield optically pure $[\alpha]_D$ -56.2 (c 1.6, $CHCl_3$)	3% yield
(*S*, *S*)-**9**	-92	21 : 79	88%	11% yield	25% yield optically pure $[\alpha]_D$ +68.9 (c 1, $CHCl_3$)
rac-**9**	-70	60 : 40	91%	34% yield 46% ee	16% yield 78% ee
rac-**9**	-96	55 : 45	83%	39% yield 60% ee	20% yield 83% ee

a - Internal temperature
b - Quantitative crude yield (no starting ketone detected by TLC or ^1H NMR)

When each of the pure enantiomers of **9** (of known absolute stereochemistry)[7] were subjected to enol silane formation using **3** under the usual conditions similar results to those found previously for **5** were obtained, the maximum regioselectivity being 94 : 6 in favour of the $\Delta^{6,7}$ enol silane with (*R*, *R*)-**9** (compared to only a *ca.* 2 : 1 ratio with LDA). When racemic **9** was employed in this sequence (deprotonation at -96°C), and the mixture of enol silanes reacted as in Scheme 3, the minor product was the (*S*)-$\Delta^{4a,5}$ enone **14** of 83% ee, and the major product was the (*R*, *R*)-$\Delta^{7,8}$ enone **15** of 60% ee, Scheme 4.



Scheme 4

The ee of these products, determined using the TFAE method, closely matches the expected values calculated using the isomer ratios obtained using the optically pure ketones.[8] The absolute configurations shown also follow from comparison with the enones obtained from the optically pure starting materials, and, as shown in Scheme 4, enone **15** has recently been employed in an asymmetric synthesis of yohimbine, indicating the usefulness of this type of intermediate in synthesis.[9]

The above results demonstrate that synthetically useful non-racemic products can be accessed by a novel HCLA base-mediated regiodivergent resolution of racemic ketones. Further investigations of the HCLA base reactions of **9**, along with those of other systems, are currently underway.

Acknowledgements

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References and Footnotes

1. For a review, see P. J. Cox and N. S. Simpkins, *Tetrahedron:Asymmetry*, **1991**, *2*, 1. See also P. J. Cox and N. S. Simpkins, *Synlett*, **1991**, 321; M. Majewski and G-Z Zheng, *Synlett*, **1991**, 173; H. Wild and L. Born, *Angew. Chem. Int. Ed. Engl.*, **1991**, *30*, 1685; D. Sato, H. Kawasaki, I. Shimada, Y. Arata, K. Okamura, T. Date, and K. Koga, *J. Am. Chem. Soc.*, **1992**, *114*, 761; M. Majewski and D. M. Gleave, *J. Org. Chem.*, **1992**, *57*, 3599.
2. P. Coggins and N. S. Simpkins, *Synlett*, **1992**, *3*, 313. See also P. Coggins and N. S. Simpkins, *Synlett*, **1991**, 515; H. Kim, H. Kawasaki, M. Nakayima, and K. Koga, *Tetrahedron Lett.*, **1989**, *30*, 6537.
3. M. Sobukawa, M. Nakajima, and K. Koga, *Tetrahedron:Asymmetry*, **1990**, *1*, 295.
4. S. Masamune, W. Choy, J. S. Petersen, and L. R. Sita, *Angew. Chem. Int. Ed. Engl.*, **1985**, *24*, 1.
5. The ratio of the $\Delta^{7,8}$ and $\Delta^{4a,5}$ enones does not reflect the initial ratio of the enol silanes due to the difficulty in achieving complete conversion in the selenoxide elimination step (this is due to the *trans*-diaxial nature of the selenoxide group and the ring-junction hydrogen in one diastereomer).
6. In a typical experiment the starting ketone **9** was added to an excess (1.4 eq.) of the lithium amide **3**, according to the procedures described previously, see C. M. Cain, R. P. C. Cousins, G. Coumbarides, and N. S. Simpkins, *Tetrahedron*, **1990**, *46*, 523. The crude mixture of enol silanes was obtained in near quantitative yield, with none of the starting ketone detected (although some traces of the secondary amine corresponding to **3** were sometimes evident). The ratio of the $\Delta^{5,6}$ and $\Delta^{6,7}$ enol silanes was determined from the ^{1}H NMR spectrum by integration of the signals due to the vinylic hydrogens at δ 4.67 (s) and 4.82 (m), respectively.
7. The single enantiomers of **9** were prepared from the corresponding *N*-methyl compounds, which have been prepared previously by resolution and shown to be $\geq 97\%$ ee, see T. M. Hotten, G. H. Timms, and D. E. Tupper, US Patent No. 4963558 (**1990**); R. C. Harden and D. M. Rackham, *J. High Resol. Chromatogr.*, **1992**, *15*, 407.
8. Assuming that each enantiomer in the racemic mixture behaves in a similar way to when it is enolised separately, the ee of each of the enol silanes (and hence the resulting enones) can be calculated from the ratios of enol silanes produced from each single enantiomer of **9**. Thus, the expected ee of the $\Delta^{7,8}$ enone is given by $(94\text{-}21)/(94+21) \times 100 = 63\%$ (compared to 60% ee measured), and that of the $\Delta^{4a,5}$ enone is given by $(79\text{-}6)/(79+6) \times 100 = 86\%$ (compared to 83% ee measured).
9. This paper confirms both our assignment of absolute configuration for the compounds shown, and the rotation data for optically pure **15**, see Y. Hirai, T. Terada, T. Yamazaki, and T. Momose, *J. Chem. Soc., Perkin Trans. 1*, **1992**, 517

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