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PREPARATION OF OPTICALLY ACTIVE 4-ALLYLAZETIDIN-2-ONES. AN ACCESS TO CARBACEPHAMS

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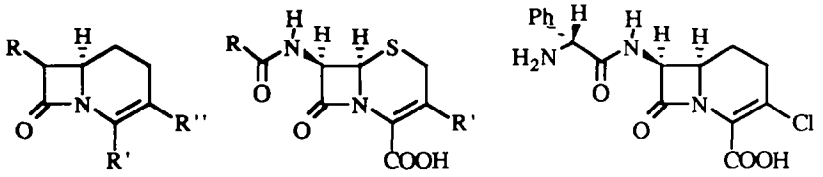
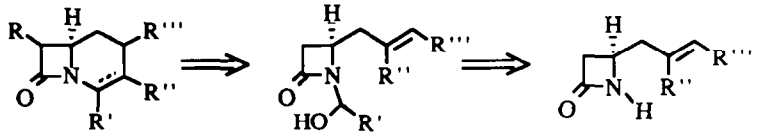
Abstract: Transesterification of 4-allyl-1-hydroxymethylazetidin-2-ones using vinyl acetate in the presence of the lipase from *Pseudomonas cepacia* led to the corresponding (*R*)-acetates and the remaining (*S*)-alcohols in high yields and excellent ee's (E : 32-71). Subsequent reaction with BF_3-Et_2O can lead to the carbacepham framework.

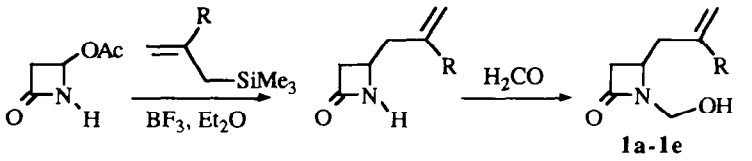
A major problem, which has appeared in the last years, is the bacterial resistance to antibiotics.[1] One way to overcome this difficulty is the design of new products which cannot be obtained by fermentation. Promising results have been recently obtained with carbacephems,[2] which show a microbiological activity comparable to the cephalosporin equivalents, associated with an enhanced physiological half-life.[3] Numerous carbacephem synthetic approaches have been explored,[4] but only a few led to optically active compounds.[5] Lorabid® is the first antibiotic of this new family under clinical development.[6]



We recently reported the enzymatic resolution of γ-butyrolactams by a non-destructive method using a labile N-hydroxymethyl group.[7] We decided to test this method [8] for the preparation of optically active 4-allyl-β-lactams, which could be used as [9] carbacephem precursors.

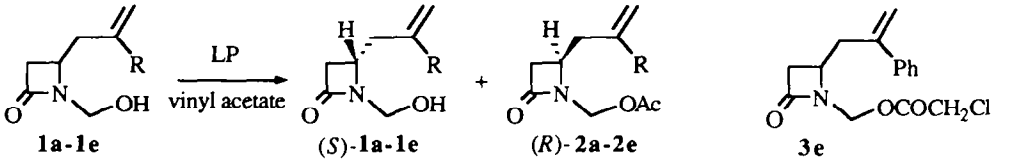


The 4-allyl-1-hydroxymethylazetidin-2-ones **1a-1e** used in this study have been prepared in two steps from 4-acetoxyazetidin-2-one by reaction first with the corresponding allylsilanes, [10] then formaldehyde [7] (50-80% overall yields). The products were fully characterised by ^1H, and ^{13}C NMR, and IR spectroscopies.



The enzymatic resolutions of these alcohols were conducted in *t*-butyl methyl ether in presence of vinyl acetate using the lipase from *Pseudomonas cepacia* supported on Hyflo Super Cel® [7]. Results of the transesterifications are reported in Table 1.

Table 1 : Transesterification of alcohols **1a-1e**, and chloroacetate **3e**



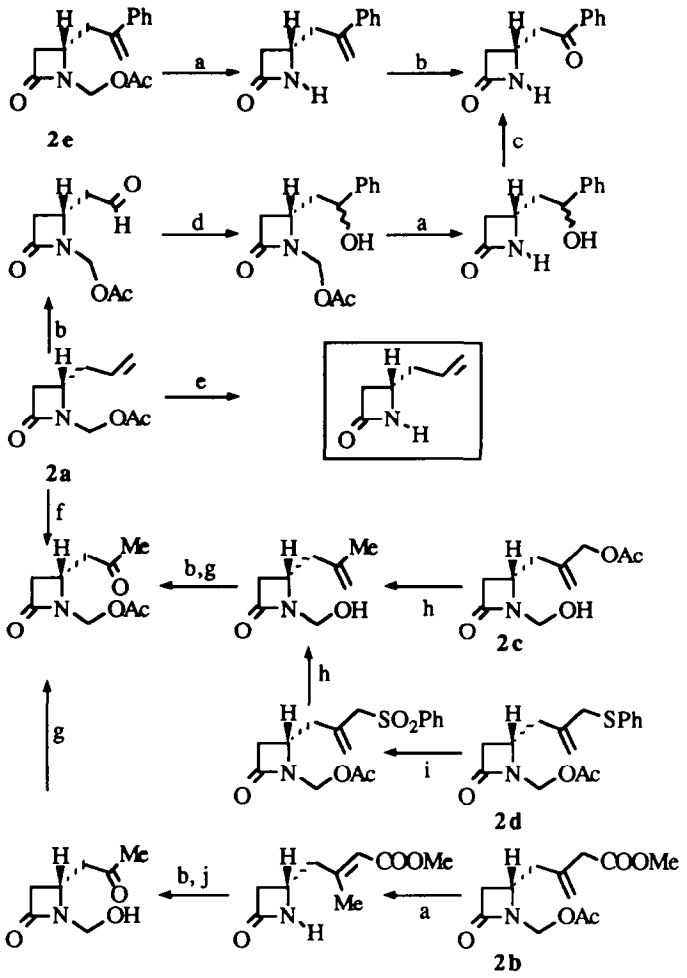
substrate			conversion rate [a]	alcohol **1**			acetate **2**			E [a]
R	n°	reaction time (h)		ee (%)	$[\alpha]_D$ [b]	Conf.	ee (%)	$[\alpha]_D$ [b]	Conf.	
H	**1a**	0.83	0.45	73	-72.5	S	88	-1.6	R	36
CH_2COOMe	**1b**	1.33	0.37	56	-1.3	S	>95	+8.4	R	71
CH_2OAc	**1c**	1.50	0.29	38	-28.5	S	>95	-2.8	R	49
CH_2SPh	**1d**	1.66	0.42	65	-32.4	S	90	+10.3	R	37
Ph	**1e**	6	0.64	90	-60.0	S	50	-5.4	R	9
Ph	**3e**	7	0.25	92	+47.0 [c]	R	31	+5.0 [c]	S	32

a) Calculated as reported in reference 11. b) Measured in CH_2Cl_2 (c = 0.5). c) In THF (c = 1).

The overall yields of the transesterification were ≥ 95%. Except for alcohol **1e**, excellent results were obtained for these transesterifications (E ≥ 36). In the case of the phenyl substituent the result has been improved using the chloroacetate **3e**, prepared by reaction of alcohol **1e** with chloroacetic anhydride (CH_2Cl_2, 1 eq. DMAP, r.t., 85% yield). In *t*-butyl methyl ether in the presence of the lipase from *Pseudomonas cepacia* and n-propanol the transesterification led to alcohol **1e** and the enriched starting chloroacetate (E = 32).

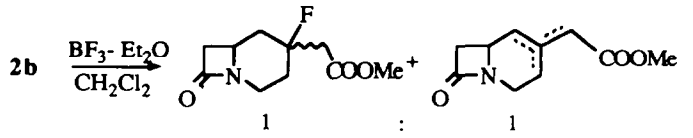
The enantiomeric excesses of the products were measured on the corresponding acetates by ^1H NMR spectroscopy in the presence of $Eu(hfc)_3$. The absolute configurations of these optically active compounds were determined by chemical correlation with (*S*)-4-allylazetidin-2-one [12] as reported in Scheme 1. We deduced from these results that in all cases examined the enzyme substrate were the (*R*)-alcohols. With the chloroacetate **3e** the (*R*)-enantiomer was also the enzyme substrate and gave obviously the (*R*)-alcohol **1e**.

Scheme 1: Determination of the Absolute Configuration of β-Lactams **2a - 2e**

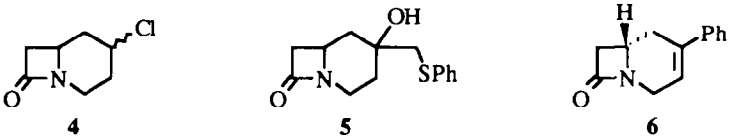


[a] NH_4OH, MeOH (50-60%). [b] O_3, CH_2Cl_2, -78° C then PPh_3 (65-70%). [c] $(COCl)_2$, DMSO, NEt_3 (50%). [d] PhLi, CH_2Cl_2 (12%). [e] LiOH, H_2O_2, H_2O, THF (50%). [f] tBuOOH, $Pd(CF_3COO)_2$ (20%) [g] Ac_2O, NEt_3, DMAP, CH_2Cl_2 (70 %). [h] $Pd(DBA)_2$, PPh_3, $NaBH_3CN$ (55-65%). [i] *m*CPBA, CH_2Cl_2, -30° C (80%). j $(CH_2O)_n$, K_2CO_3 (70%).

Different Lewis acids such as $TiCl_4$, $SnCl_4$, $AlCl_3$ were then tested in the subsequent cyclization reactions to give the carbacepham ring system. The allyl derivative **1a** led to the desirated bicyclic compound **4** when treated with $SnCl_4$ (83% yield). With the substrates **1b-1e** and **2b-2e** better results were obtained with boron trifluoride etherate. The acetate **2b** led to a mixture of products (70% yield), which could not be separated by liquid chromatography.



A much more selective cyclization was observed with the sulfur lactam **2d**. In ether in the presence of $BF_3.Et_2O$ a single compound **5** of unknown stereochemistry was obtained (75% yield). In the same way cyclization of the chloroacetate (*S*)-**3e** gave only **6** (77% yield; $[\alpha]_D$ + 14.2 c=0.6 (THF); ee 33%). All these compounds were easily characterised by spectroscopic methods.



4 **5** **6**

In summary, we have developed a new approach to the carbacepham framework. Extension of this method to the preparation of optically active 1-dethiacephalosporins is under investigation.

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