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α-ALKYLATION OF A CYSTEINE DERIVATIVE WITHOUT RACEMIZATION AND WITHOUT THE USE OF A CHIRAL AUXILIARY

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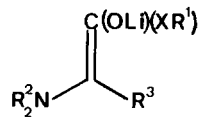
Abstract: The (R,R)-2-t-butyl-1-aza-3-oxa-7-thia-bicyclo[3.3.0]octan-4-one (4a), obtained in two steps from cysteine, is added to aromatic aldehydes to give the diastereomerically and enantiomerically pure 5-(arylhydroxymethyl)-derivatives 6.

Enolates 1 derived from aminoacids are achiral if the substituents R^1, R^2, R^3 do not contain elements of chirality. We have recently shown[2a-c)] that amino-, hydroxy-, and mercaptoacids can be α-alkylated with self-reproduction of chirality through enolates 2 of acetal-type derivatives from pivalaldehyde. Application of this principle to β-heterosubsti-



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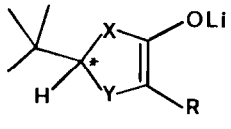

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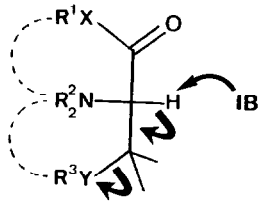

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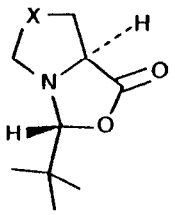
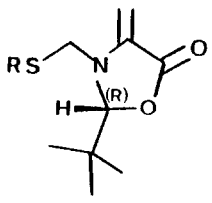
tuted aminoacids, such as serine and cysteine, without an additional asymmetric carbon atom[2d)], was so far not possible because the β-elimination depicted in 3 took place. With cysteine, this was true even if the sulfur atom was tied into the five-membered ring of the bicyclic system[2b)] 4a, in which an elimination is unfavorable[3)]: even after reaction times with lithium diisopropylamide (LDA) as short as 30 minutes at -78°C and quenching with "fast" electrophiles such as benzaldehyde or allyl and benzyl bromide, only monocyclic products of type 5 or their decomposition products could be isolated[2b)].



4a : X = S

4b : X = CH_2



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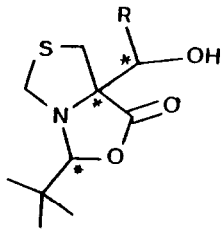

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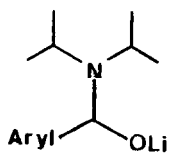
We have now made an - at first sight - peculiar observation which enables us to prepare adducts 6 from the cystein derivative 4a and non-enolizable aldehydes: After addition at -100°C of LDA to a solution of an equimolar mixture of 4a and benzaldehyde in tetrahydrofuran (THF), the temperature can be raised up to *ca.* -60°C without formation of either the product 5 of elimination or an adduct 6! Likewise, no elimination occurs when an LDA solution is first combined at -75°C with the aldehyde, and then the bicyclic compound 4a is added! Upon warming these solutions above -60°C up to room temperature, increasing amounts of the adduct 6 are isolated after aqueous workup.

Of the four possible diastereomers of the adducts 6 to aldehydes, one is usually formed with high diastereoselectivity. For examples, yields[4], selectivities and some characteristic physical data see the accompanying table.

From the fact that no product 5 of elimination is formed under the conditions which lead



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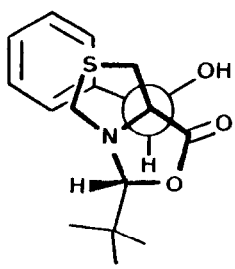
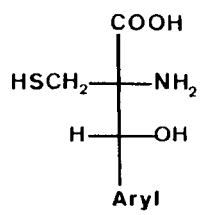


8 (R,R,R)



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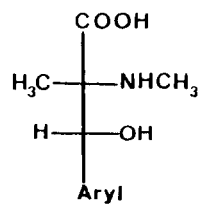

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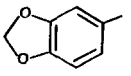
to the formation of adducts 6, we conclude that no free LDA is present. We speculate that the product 7 of addition[5] of LDA to the aldehydes is responsible, both as a base and as a source of the aldehyde for achieving the observed reaction. We also speculate that the confi-

Table. - *Products* 6 *of addition of the bicyclic derivative* 4a *to aryl, heteroaryl, and cinnamic aldehydes.* - The yields are those of chromatographed major isomers. The specific rotations were measured with (c ~ 0.5, $CHCl_3$). The diastereoselectivities (% ds) were determined by glass capillary gas chromatography (SE-54), and confirmed by ^{1}H-NMR spectroscopy. Correct (± 0.3 %) elemental analyses were obtained from all compounds 6.

Aldehyde used	Products 6				
	R	yield %	% ds	$[\alpha]_D^{RT}$ / m.p. of major diastereomer	
cinnamaldehyde	$C_6H_5CH=CH$	48	89	+49.8°	
benzaldehyde	C_6H_5	64	92	+16.3°	/ 144-145°C
p-bromo-benzaldehyde	p-Br-C_6H_4	65	82	+26.6°	/ 125-127°C
anisaldehyde	p-CH_3O-C_6H_4	68	96	+28.5°	/ 138-139°C
piperonal		48	96	+30.0°	/ 98-101°C
furfural		45	88	+51.6°	
thenaldehyde		44	94	+29.9°	/ 107-109°C

guration of the products 6 is as shown in *formula* 8 for the benzaldehyde adduct[6] - the configuration of the corresponding (S)-proline-derived (see 4b) compound has been established by x-ray crystal structure analysis[2b]. Thus, hydrolysis of 6 should lead to the aminoacids 9, *Raney* nickel desulfurization followed by hydrolysis to aminoacids of type 10. The results of investigation of these and other transformations, as well as the application of the technique disclosed here to other substrates will be published elsewhere.

REFERENCES AND FOOTNOTES

1) Part of the projected Ph.D. thesis of T.W., ETH Zürich.

2) a) D. Seebach and R. Naef, *Helv. Chim. Acta* 64, 2704 (1981). - b) D. Seebach, M. Boes, R. Naef, and W.B. Schweizer, *J. Am. Chem. Soc.* 1983, in print. - c) D. Seebach, R. Naef, and G. Calderari, *Tetrahedron* and *Helv. Chim. Acta*, in preparation. - d) In the accompanying paper (D. Seebach and J.D. Aebi, *Tetrahedron Lett.* 1983) a method of alkylating threonine is described.

3) In the *Baldwin* terminology (*J. Chem. Soc., Chem. Commun.*, 1976, 734), this elimination is the reversal of a "5-endo trigonal cyclisation".

4) Besides unreacted aldehydes and compound 4a, varying amounts of reduction products, i.e. the benzylic alcohols (aryl-CH_2OH) are present. It is known from the pioneering work of Wittig [G. Wittig, *Topics in Current Chemistry* 67, 1 (1976) and ref. cited therein], that lithium dialkylamides can act as hydride donors.

5) Cf. the ortho-metallation of adducts of other lithiumamides to aromatic aldehydes: a) D.L. Comins and J.D. Brown, *Tetrahedron Lett.* 4213 (1981). - b) D.L. Comins, J.D. Brown, and N.B. Mantlo, *Tetrahedron Lett.* 3979 (1982).

6) This means that the relative topicity with which these adducts form would have to be specified[3] (*lk, ul*-1.3), see D. Seebach and V. Prelog, *Angew. Chem.* 94, 696 (1982); *Ibid. Int. Ed. Engl.* 21, 584 (1982).

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