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Microbiological Transformations. 24. Synthesis of Chiral Building Blocks via Stereoselective Dihydroxylation of Citronellol Enantiomers

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Abstract : The stereoselective oxidation of citronellol N-phenylcarbamate is described using the fungus Aspergillus niger. This allows the unequivocal straightforward synthesis of all four stereoisomers of the corresponding 6,7-diols, one of them being a possible key-building block of the California Red Scale pheromone.

We have recently described the formal dihydroxylation of geraniol N-phenylcarbamate **1** and of 7-geranyloxycoumarin **2** *via* a microbiologically mediated transformation performed by the fungus *Aspergillus niger*[1,2,3]. In the course of those studies, we have highlighted the unique possibility of controlling the stereochemical outcome of these bioconversions, simply by changing the pH of the medium Indeed, the mechanism of this bioconversion implies, as a first step, a stereoselective formation of the (6S)-epoxide. The second step involves hydrolysis of this key intermediate via a spontaneous acid-catalyzed hydrolysis at pH 2, giving the (6S)-diol, or an enzymatic hydrolysis at pH 6-7 leading to the (6R)-diol. This reaction, which implies in both cases the stereoselective oxidation of the *si* enantiotopic face of a prochiral substrate, allows to prepare either enantiomer of the corresponding diol with enantiomeric purities as high as 95%. Interestingly, these bioconversions offer a very efficient short-cut to rather lengthy multistep conventionnal synthetic procedures.[4] Indeed, the one-step, stereoselective oxidation, of compounds such as **1** and **2** has not been described up to now using more classical chemistry.

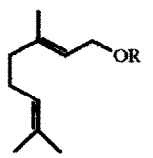
Because of the high potential of these biooxidations for the preparation of valuable chiral synthons, we decided to study further these biotransformations. Several questions were raised by our preceeding results : - is this reaction substrate specific for geraniol derivatives or would it be possible to oxidize other similar compounds ? - would it be possible to start with a substrate already bearing a stereogenic center ? - what would be the influence of such a preexisting chirality on the stereochemical outcome of the bioconversion and, in particular, would a possible match / mismatch process modify the obtained ees ?[5] In order to answer these questions, we investigated the bioconversion of citronellol N-phenylcarbamate **3**, a substrate quite similar to the

previously used geraniol derivatives, but which bears a prebuilt stereogenic center at carbon C3. This article describes the results of these experiments.

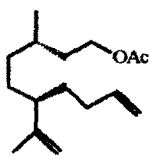
RESULTS AND DISCUSSION

Starting from both commercially available citronellol enantiomers we have prepared the corresponding N-phenylcarbamates **3** by condensation with phenylisocyanate. These two substrates were not optically pure since (3S)-(-)-citronellol was contaminated with 5% of the (3R)-enantiomer (ee 90%) and the (3R)-(+)-citronellol contained 2% of the (3S) enantiomer (ee 96%). The two N-phenylcarbamates **3** were then submitted as previously described[3] to resting cells of the fungus *A. niger* suspended in a solution buffered either at pH2 or at pH6. The results obtained are summarized on Scheme 1 and on Table I.

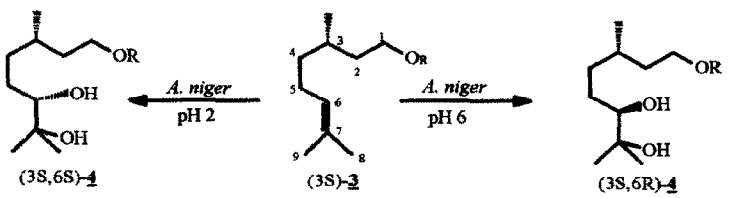
Scheme 1

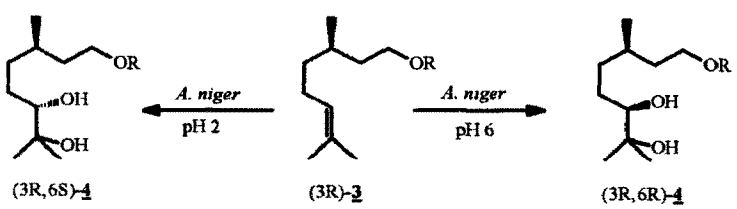


1 R = $CONHC_6H_5$
2 R = Coumarine



5





R = $CONHC_6H_5$

As can be seen, the corresponding diols **4** are formed in all cases as expected. The yields are of about 60% and the observed diastereomeric proportions of the expected diols are in the region of 80-95%. Recrystallization from benzene of these diastereomeric mixtures allowed the four diols **4** to be obtained easily

in a high state of diastereomeric purity. The absolute configurations of each one of the thus obtained diols have been unambigously established by HPLC comparison with authentic samples prepared from the corresponding 6(S) and 6(R) geranyl N-phenylcarbamate diols[1] and involving hydrogenation of the 2,3-double bond.

Our results show - that this type of bioconversion is not restricted to geraniol derivatives but can also by applied to citronellol - that both enantiomers are processed by the oxidising enzyme, which means the reaction is *not* enantioselective - that, however, this transformation remains highly stereoselective in each case, and, finally - that the preexisting stereogenic center has only little influence on the stereochemical outcome of the reaction. Indeed, the absolute configuration of the preferentially formed diol is always 6(S) at pH2 and 6(R) at pH6, though a better stereoselectivity was obtained from (3R)-**3** than from (3S).

Table I. Diastereomeric compositions of diols **4** obtained by bioconversion with the fungus *A. niger*

		pH	(3S,6S)-4	(3S,6R)-4	(3R,6S)-4	(3R,6R)-4	d.e. (d)
(3S)-3	(a)	2	**88%**	7%	5%	0%	85%
	(b)		**89%**	5%	6%	0%	89%
(3S)-3	(a)	6	13%	**82%**	0%	5%	73%
	(b)		1%	**93%**	0%	6%	98%
(3R)-3	(a)	2	0.5%	0.5%	**94%**	5%	90%
	(c)		0%	0%	**97%**	3%	94%
(3R)-3	(a)	6	0.5%	0.5%	4%	**95%**	92%
	(c)		0%	0%	3%	**97%**	94%

The diastereomeric compositions were determined by HPLC analysis of (-)-camphanyl derivatives using a 5-μm silica gel column (50x0.4cm) using a mixture of hexane/n-propanol (95/5) as eluent.
(a) - After bioconversion
(b) - After bioconversion and two recrystallizations from benzene
(c) - After bioconversion and one recrystallization from benzene
(d) - Corrected diastereomeric excess (calculated on the base of optically pure substrates)

As far as synthesis is concerned, we have shown previously that such diols can be transformed without loss of enantiomeric purity to the corresponding epoxide of opposite absolute configuration.[2] Thus, for instance, diol (3S,6R)-**4** can be cyclised to the corresponding (3S,6S) epoxide. This constitutes a possible key chiral building block for further synthesis of the (3S,6R)-3-methyl 6-isopropenyl-9-decen-1-yl acetate **5**, one of the two constituents of the California red scale (*Aonidiella laurentii*) pheromone, a major pest of citrus over the world.[6] Indeed, the synthesis of this compound has been previously described, in its racemic form, starting from such an epoxide [7] Work is in progress in our laboratory in order to further study the scope and limitations of these bioconversions.

EXPERIMENTAL PART

(S)-(-)-citronellol was purchased from Fluka, its R enantiomer from Sigma. Their ees were determined using HPLC analysis of the carbamate diastereoisomers obtained after chemical epoxidation of the double bond, acid hydrolysis of the oxirane ring then derivatization of the formed diols with (S)-(-)-camphanic acid chloride. The procedure used to carry out the bioconversions has been described in detail previously[3]. The obtained data for the diastereoisomers **4** are as follows.

Citronellol N-phenylcarbamate-6,7-diols 4.

(3S,6S)-4: Yield 60%; mp 97-99°C; $[\alpha]^{22}_D$ -18.8 (c 1.6, MeOH). After two recristallizations from benzene : mp 103-104°C; $[\alpha]^{22}_D$ -22.4 (c 1.36, MeOH). IR ($CHCl_3$, cm^{-1}) : 3450, 1735; ^1H NMR ($CDCl_3$, 200 MHz) : 0.94 (d, 3H, J=6Hz, CH_3), 1.17 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 1.40-1.70 (m, 7H), 2.13 (s, 2H, OH), 3.35 (d, 1H, J=7Hz, C(6)-H), 4.15-4.3 (m, 2H, C(1)-H), 6.80 (1H, s, NH) 7.05, (1H, t, J=7Hz, para aromatic), 7.26-7.40 (4H, aromatic); ^{13}C NMR ($CDCl_3$) : 19.5 (C10)), 23.55 (C8*), 26.59 (C9*), 28.74(C5), 29.86(C3), 33.61 (C4#), 36.09 (C2#), 63.79 (C1); 73.18 (C7), 78.62 (C6), 118.9, 123.47, 129.08, 138.15 (ar.), 153.82 (C=O). Analysis for $C_{17}H_{27}NO_4$: found (calcd) : C, 66.23 (65.99) ; H, 8.81 (8.80) ; N, 4.45 (4.53)

(3S,6R)-4: Yield 60%; mp 93-94°C, $[\alpha]^{22}_D$ +18.2 (c 1.4, MeOH). After two recristallizations from benzene : mp 89-90°C; $[\alpha]^{22}_D$ +16.9 (c 1.46, MeOH). IR ($CHCl_3$, cm^{-1}) : 3450, 1735; ^1H NMR ($CDCl_3$, 200 MHz) : 0.94 (d, 3H, J=6Hz, CH_3), 1.15 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 1.25-1.73 (m, 7H), 2.46 (s, 2H, OH), 3.32 (d, 1H, J=7Hz, C(6)-H), 4.20 (t, 2H, J=6Hz, C(H)-1), 7.04 (m, 2H, NH and para aromatic), 7.25-7.41 (m, 4H, ar.); ^{13}C NMR ($CDCl_3$) 19.83 (C10)), 23.53 (C8*), 26.57 (C9*), 29.2(C5), 30.29(C3), 34.18 (C4#), 35.60 (C2#), 63.67 (C1); 73.24 (C7), 79.18 (C6), 118.89, 123.44, 129.08, 138.18 (ar.), 153.79 (C=O). Analysis for $C_{17}H_{27}NO_4$: found (calcd) C, 66.26 (65.99) ; H, 8.50 (8.80) ; N, 4.54 (4.53).

(3R,6S)-4: Yield 85%; mp 93-96°C; $[\alpha]^{22}_D$ -16.2 (c 1.6, MeOH) After one recristallization from benzene : mp 91-92°C. $[\alpha]^{22}_D$ -16.5 (c 1.35, MeOH) The spectral data are identical to those of its enantiomer (3S,6R)-4. Analysis for $C_{17}H_{27}NO_4$: found (calcd) : C, 65.89 (65.99) ; H, 8.97 (8.80) ; N, 4.35 (4.53).

(3R,6R)-4: Yield 60%; mp 91-93°C, $[\alpha]^{22}_D$ +19.7 (c 1.5, MeOH). After one recristallization from benzene : mp 105°C; $[\alpha]^{22}_D$ +24.6 (c 1.49, MeOH). The spectral data are identical to those of its enantiomer (3S,6S)-4. Analysis for $C_{17}H_{27}NO_4$: found (calcd) : C, 66.23 (65.99) ; H, 8.81 (8.80) ; N, 4.52 (4.53).

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