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DIASTEREOSELECTIVE CYCLISATIONS OF CHIRAL α-ACYLIMINIUM IONS[1]

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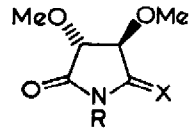
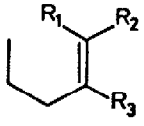
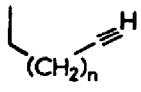
Abstract: (R,R)-tartaric acid has been converted into (R,R)-dimethoxysuccinimide which after coupling with Z-3-hexenol and 5-hexynol followed by $NaBH_4/H^{\oplus}$ reduction can be cyclised to optically pure 2c and 4c.

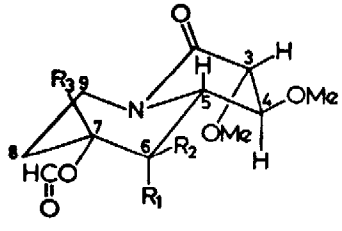
The high stereoselectivity encountered sofar in α-acyliminium olefine cyclisations[2] strongly invited to the use of chiral substrates. In the latter respect the naturally occurring optically active dicarboxylic acids have recently met with considerable interest as a cheap source of starting material[3]. For this work we decided to focus on the largely available (R,R)-tartaric acid dimethyl ether[4] which could easily be converted to the desired optically active (R,R)-2,3-dimethoxy succinimide on a practical scale[5].

In view of the presence of imid OMe substituents primary steric effects are expected both in the $NaBH_4$ reduction of the imid to the α-OH lactam and the HCOOH cyclisation of the latter carbinol. Consequently ring closure may take place most easily from the least hindered side leading to the preferred formation of a single diastereomer. In the light of earlier experiences two types of substrates viz alkene[6] and acetylene[7] derivatives 1a-5a were selected for investigation of the eventual induction of asymmetry at the reacting carbon atoms.

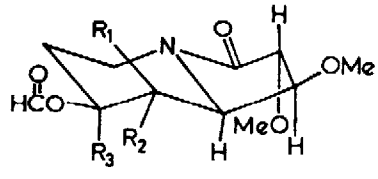
The $NaBH_4/H^{\oplus}$ reduction of the imids 1a-5a proceeds in a highly stereoselective manner affording the C_5-isomers of the chiral ω-OH lactams 1b-5b. The isomer ratios of 1b-5b amounted to approximately 20:1. In view of the fact that the C_5-OH chirality is lost in the cyclisation step - the latter being assumed to take place via the planar α-acyliminium ion - no attempts were carried out



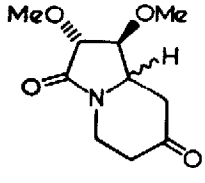
R	n	X=O	X=H,OH	R_1	R_2	R_3
	–	1a	1b	H	H	H
	–	2a	2b	Et	H	H
	–	5a	5b	H	H	Me
	n=1	3a	3b	–	–	–
	n=3	4a	4b	–	–	–



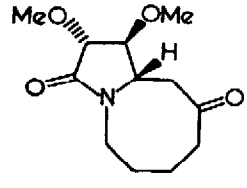
1c,2c,5c



1d,2d,5d



3c,3d



4c

to isolate the pure C_5-epimers.

HCOOH treatment[8] (18 hr/r.t.) of 1b afforded the diastereomeric mixture 1c,d in nearly quantitative yield. According to ^{1}H NMR analysis of the integrated values of the OMe signals the ratio of 1c:1d was estimated as 2:1, indicating a preferred C-C bond formation from the least hindered side opposite of the C_4-OMe substituent, albeit not in a practically useful manner.

On the contrary ring closure of 2b (HCOOH, 18 hr/r.t.) afforded a single isomer 2c as a crystalline material in nearly quantitative yield; m.p. 78.5-80°C; IR($CHCl_3$): 1720 and 1700 (C=O) cm^{-1}; NMR δ($CDCl_3$): 8.02 (s, 1H, CHO), 5.02 (m, H_7ax $W_{½}$ = 21 Hz), 4.11 (m, H_9eq), 3.82 (d, H_3; $J_{3,4}$ = 5.5 Hz), 3.73 (t, H_4, $J_{4,5}$ = 5.5 Hz), 3.68 (s, 3H OMe), 3.46 (s, 3H OMe), 3.38 (t, H_5, $J_{5,6}$ = 3 Hz), 2.73 (m, H_9ax), 2.07 (m, H_6eq). The observed $J_{5,6}$ value again confirms an axial position for the C_5-Et substituent and consequently indicates a synchronous bond formation process. In the latter ring closure three asymmetric centres have been introduced simultaneously with a high degree of stereoselectivity. A rationale for this remarkable effect may be found in a destabilisation of the transition state leading to 2d as a consequence of increased steric interaction of Z-Et and C_4-OMe groups. The degree of stereoselectivity of the olefin cyclisation therefore depends on the relative position of the ring substituents with respect to the incoming nucleophile.

Support for the latter assumption was found in the reaction of the acetylene derivatives 3b and 4b. HCOOH treatment (r.t./118 hr) of the carbinol 3b yielded only a 1:1 mixture of the starting carbinol 3b and its C_5-epimer. However, at 43°C (120 hr, HCOOH) quantitative formation of a 1:1 mixture of 3c and 3d occurred. Presumably the already low reactivity of the acetylene function in this type of cyclisation[9] is even further diminished as a result of added steric factors. The main conclusion of this experiment, however, is the lack of preferential formation of either 3c or 3d. On the contrary, cyclisation of 4b (HCOOH, 30°C, 13 days) exclusively[10] afforded the ketone 4c; m.p. 84-86°C; NMR δ($CDCl_3$): 3.7-4.02 (m, 2H, tert NC<u>H</u> + NC<u>H</u> eq), 3.66 (s, 3H OMe), 3.44 (s, 3H OMe) 2.88 (t, J = 11 Hz, sec NC<u>H</u> ax), 1.3-2.7 (m, 12H). The dramatic change in diastereoselectivity in ring closures of 3b compared with 4b again may be rationalized in terms of a steric repulsion between incoming acetylene moiety and C_4-OMe substituent. In view of the size of the ring to be formed the latter interaction will be more severe in the cyclisation of 4b thus leading solely to the observed product 4c.

Other N-substituents have been examined and were found to exhibit similar behaviour, as for instance in the cyclisation of 5b which gave a 1.5:1 isomer

mixture of the C_4-epimers 5c and 5d. An analogous result has been found earlier in the unsubstituted series[6].

As a final point of interest it is anticipated that enhancing the bulkyness of the C_4-O substituent may further increase the stereoselectivity of the reaction. Studies on this aspect are currently in progress.

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