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Microbial Transformations 16. One-step synthesis of a pivotal prostaglandin chiral synthon via a highly enantioselective microbiological Baeyer-Villiger type reaction

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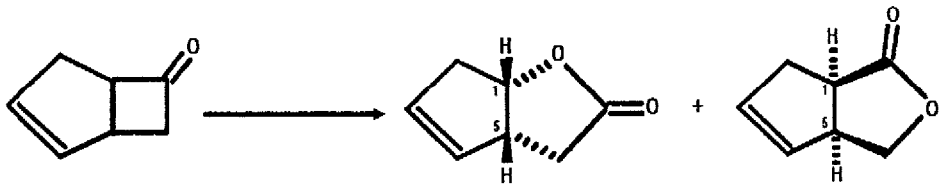
Summary : The bioconversion of bicyclo[3.2.0]hept-2-en-6-one is described. Each one of its enantiomers affords a different lactone via a highly regio and enantiospecific Baeyer-Villiger type process.

The utility of the bioconversion approach to asymmetric synthesis is by now beyond question. The majority of the known examples involve either hydrolysis or oxydoreduction reactions which have been successfully applied to a wide variety of substrates (1). Another very promising reaction type which is presently emerging is asymmetric Baeyer-Villiger oxidation (2). Whereas this type of reaction is involved as a common feature in numerous oxidative degradation pathways (3) only very few examples have been described for chiral organic synthesis (4). In the course of our work related to microbiological oxygenation reactions (5) we studied the biooxydation of ketone 1 which, upon asymmetric Baeyer-Villiger reaction, would lead to chiral lactone 2. This is of particular interest since this lactone happens to be one of the first-row pivotal synthons for prostaglandins synthesis (6). We here describe the one-step preparation of this chiral lactone.

When added to a culture of *Acinetobacter* TD 63 grown on cyclohexanediol (7), ketone 1 (1 g/L) was metabolized in about 5 hours, leading to products 2 and 3 (isolated yields 40 and 37 % respectively). Their structures have been determined using classical ^{1}H and ^{13}C NMR spectroscopy.



(±)-1 (-)-(1S,5R)-2 (-)-(1R,5S)-3

Interestingly, both of these products appear to be optically active. Their ee's have been determined by ^{1}H NMR (200 MHz) analysis in the presence of $Eu(Tfc)_3$ (8). They are both higher than 97 %. The absolute configuration of

2 has been assigned on the basis of its optical rotation. [Found : $[\alpha]^{20}_D$ - 102.2° (c 1.04, MeOH) ; lit. (9) : $[\alpha]^{20}_D$ - 104° (c 1.1, MeOH) ; o.p. 98 %]. Lactone 3 has been hydrogenated (H_2, Pd/C, AcOEt) to its saturated derivative. Its optical rotation [Found : $[\alpha]^{20}_D$ 91.5° (c 0.94, $CHCl_3$); lit. (10) : $[\alpha]^{20}_D$ - 96.9° (c 1.0, $CHCl_3$) ; o.p. 94.4 %]. This allows us to assign the 1(S),5(R) absolute configuration to lactone 2 and the 1(R),5(S) configuration to 3. These values also confirm the very high ee's measured for both 2 and 3.

Several interesting conclusions can be drawn from this result. First, it appears that each one of the enantiomers of 1 reacts with a different regioselectivity for the oxygen atom insertion, which leads to the two different lactones. Compound 2 results from the normal Baeyer-Villiger reaction - whereas 3 has been formed via the unusual reverse pathway. Such abnormal oxygen insertion reactions have been described previously, for instance in the case of cyclopentanones (5) or fenchone (11) but they mainly led to side products. Surprizingly, in the case of the reaction described here, the enantioselectivity (versus regioselectivity) of the reaction appears to be quasi-perfect. Second, we would like to emphasize that, in spite of the fact that this reaction is performed using a whole cell culture of the *Acinetobacter* strain, no noticeable loss of substrate or product is observed. This is quite surprizing with regard to the results we have previously obtained on 2-substituted cyclopentanones, where a divergent metabolic pathway and/or possibly a lactone hydrolase had to be postulated in order to account for relatively high product consumption (5,12). Thus, the use of a more sophisticated technique implying purified enzymes and NADPH recycling systems (4a,4c,11) which makes it possible to avoid competitive undesired reactions, is unnecessary in this case. Finally, it is noteworthy that 2 is an extremely important chiron with can be easily transformed into various products like Corey's lactone (13) which are essential to prostaglandins synthesis. Also, optically pure lactone 3 may be quite a valuable synthon for further synthesis of biologically active compounds.

BIBLIOGRAPHY

(1) Yamada, H.; Shimizu, S. Angew. Chem. Int. Ed. Engl., **1988**, 27, 622.
(2) Walsh, C.T.; Chen, Y.C.J. Angew. Chem. Int. Ed. Engl. **1988**, 27, 333.
(3) (a) Britton, N.L.; Markovetz, A.J. J. Biol. Chem. **1977**, 252 8561. (b) Magor, A.M.; Warburton, J.; Tower, M.K.; Griffin, M. Appl. Environ. Microbiol. **1986**, 52, 665.
(4) (a) Schwab, J.M. J. Am. Chem. Soc. **1981**, 103, 1876. (c) Taschner, M.J.; Black, D.J. J. Am. Chem. Soc. **1988**, 110, 6892. (b) Ouazzani-Chahdi, J.; Buisson, D.; Azerad, R. Tetrahedron Lett. **1987**, 10, 1109.
(5) Alphand, V.; Archelas, A.; Furstoss R. J. Org. Chem. (in press).
(6) Newton, R.F.; Roberts, S.M. Tetrahedron, **1980**, 36, 2163.
(7) Davey, J.F.; Trudgill, P.W. Eur. J. Biochem. **1977**, 74, 115.
(8) Jakovac, I.J.; Jones, A.J. J. Org. Chem. **1979**, 44, 2165.
(9) Nara, M.; Terashima, S.; Yamada, S. Tetrahedron, **1980**, 36, 3161.
(10) Jakovac, I.J.; Goodbrand, H.B.; Lok, K.P.; Jones, J.B. J. Am. Chem. Soc. **1982**, 104, 4259.
(11) Abril, O.; Ryerson, C.C.; Walsh, C.; Whitesides, G.M. Biorganic Chem. **1989**, 17, 41.
(12) Alphand, V.; Archelas, A.; Furstoss, R. Biocatalysis (in press).
(13) Tomoskozi, I.; Gruber, L.; Kovacs, G.; Szekely, I.; Simonidesz, V. Tetrahedron Lett. **1976**, 50, 4639.

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