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HIGHLY STEREO AND REGIOCONTROLLED SYNTHESIS OF BOTH RACEMIC AND OPTICALLY ACTIVE (-)-BLASTMYCINONE

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Summary.- Two highly stereo and regioselective synthetic pathways are reported to prepare both racemic and unnatural (-)-Blastmycinone, starting from readily available β-angelica lactone derivatives.

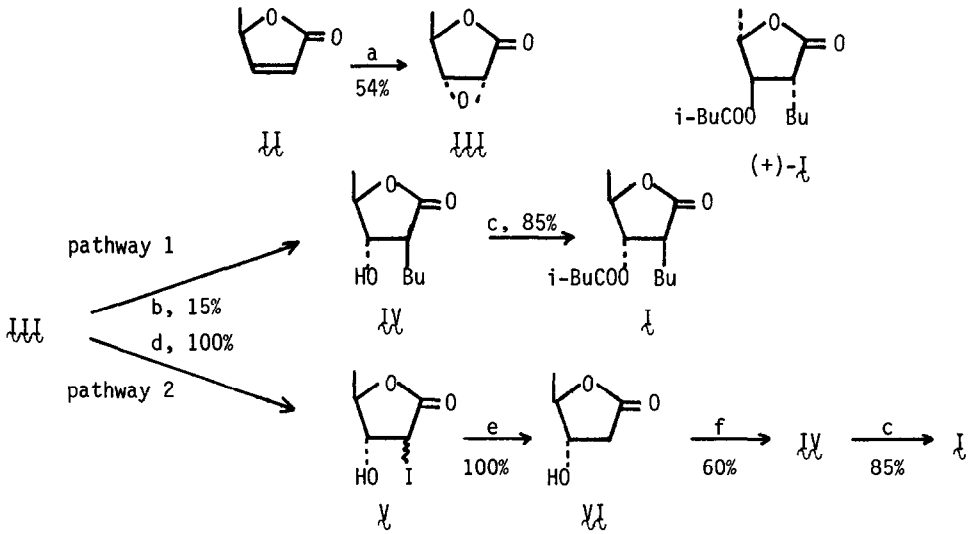
Antimycin A_3 (Blastmycin)[1] is one of the major components of the antibiotic Antimycin A complex, effective against fungi and yeasts. Mild saponification of Antimycin A_3 yields (+)-Blastmycinone, (+)-I, which has been synthesized by several authors[2].

We present in this paper a highly stereocontrolled synthesis of both racemic and unnatural (-)-Blastmycinone, I, starting from (±)- and (-)(S)-β-angelica lactone, II, respectively. The lactone (±)-II is a compound readily available in large scale from commercial levulinic acid[3]. For this reason, we took the cheapest racemic model to begin our studies. Epoxidation of the conjugate double bond in II with NaOCl in pyridine gave selectively the trans-epoxylactone III in 54 % yield. This new product[4] seems to be a useful synthon in the preparation of natural products with β-hydroxy-γ-methylbutyrolactone-type constitution and from it we have envisaged two ways to introduce the butyl group of Blastmycinone.

The first pathway is extremely simple and consists in the regioselective nucleophilic oxirane ring-opening[5] with lithium dibutylcuprate, to give stereoselectively (±)-Blastmycinolactol, IV. Esterification of (±)-IV afforded (±)-Blastmycinone, I, in 13 % yield from the epoxide III. An attempt to improve this yield lead us to explore a second route, that passes through the hydroxylactone VI, as a key intermediate. Thus, since the epoxide III showed a surprising lack of reactivity in front of several common reducing agents[6], VI was obtained in two steps by transforming III in the diastereoisomeric mixture of iodides V[7], followed by quantitative hydrogenolysis. The lithium enolate of VI was stereoselectively alkylated to give (±)-Blastmycinolactol, IV, that gave (±)-Blastmycinone in 50 % overall yield from the epoxyderivative III.

Since we have developed a method to prepare optically active (-)(S)-β-angelica lactone from D-ribonolactone[8], the epoxide (+)-III, $\{\alpha\}_D^{20}$=+42.1° (c=3.28, CH_2Cl_2), was transformed in the hydroxylactone (+)-VI, $\{\alpha\}_D^{22}$=+10.2 (c=2.60, $CHCl_3$), that afforded (+)-Blastmycinolactol, (+)-IV, $\{\alpha\}_D^{22}$=+19.5 (c=1.95, $CHCl_3$), and (-)-Blastmycinone, (-)-I, $\{\alpha\}_D^{22}$=-9.4 (c=1.70, $CHCl_3$).

This synthetic scheme is much shorter and efficient than other synthesis of Blastmycinone reported recently. Studies on the preparation of natural (+)-I from the appropriate chiral precursor are carried out in our laboratory.



a: NaOCl, pyr. rt; b: Bu_2CuLi, ether, -20°; c: i-BuCOCl, pyr, rt; d: NaI, NaOAc, AcOH, acetone; e: H_2, Pd/C, EtOAc; f: i) LDA, THF, -78°, ii) BuI, HMPA, -40°; yield based on transformed starting material.

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Notes and references

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4. All new products gave satisfactory spectroscopical data (IR, ^1H and ^{13}C NMR, MS) and elemental analyses.
5. The reactivity of α-carbonyl oxiranes is manifold. We have rationalized it both on experimental grounds and theoretical calculations. J. Cardellach, J. Font, C. Jaime and R. M. Ortuño, submitted to J. Chem. Soc. Perkin II.
6. Epoxy compound III was inert under several catalytic hydrogenation conditions. Reaction with sodium borohydride gave prior reduction of the carbonyl group[5].
7. This 50:50 mixture of diastereoisomers is the result of an equilibration process. Each single stereoisomer in the presence of catalytic NaI lead to this same mixture.
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