

AN ALTERNATIVE BIOMIMETIC SYNTHESIS OF ( $\pm$ )-CAMPTOTHECIN

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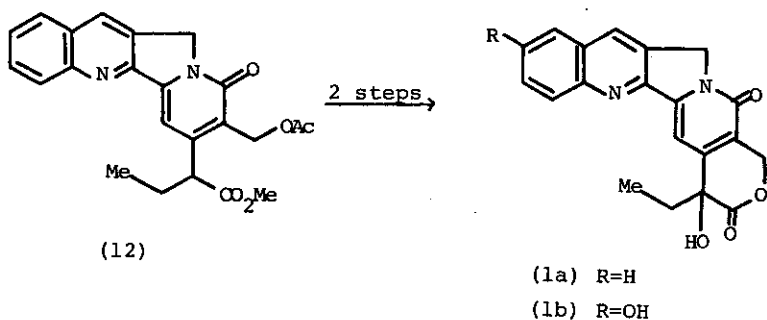
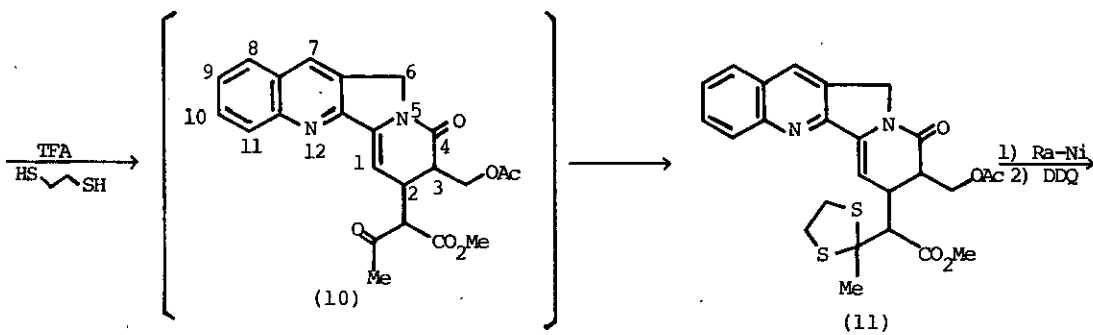
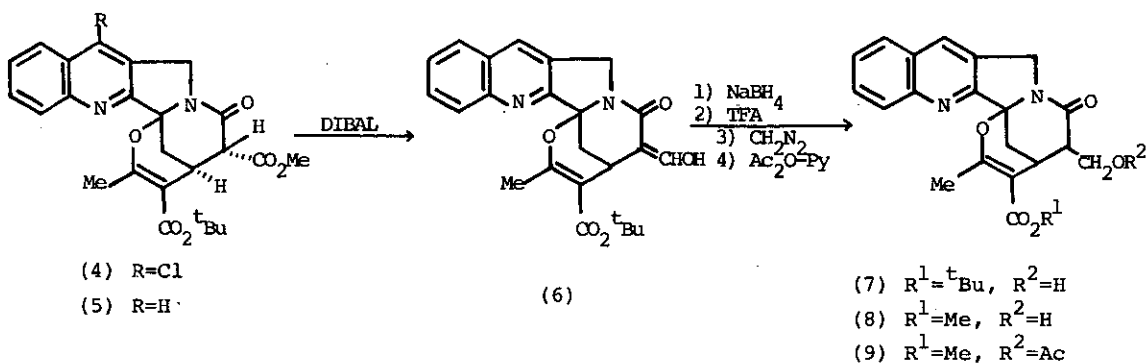
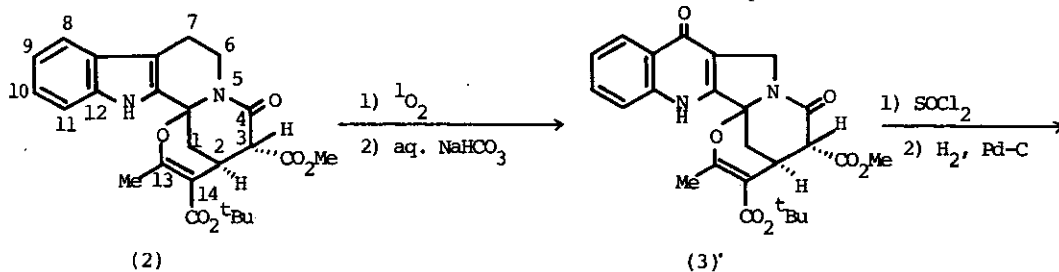
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**Abstract** — 14-tert.-Butoxycarbonyl-12b,2-epoxyetheno-1,12b,2,3-6,7-hexahydro-3-methoxycarbonyl-13-methylindolo[2,3-a]quinolizidin-4-one (2) synthesized by the enamine-imine double annelation method was converted to the acetate (12) which had been correlated with ( $\pm$ )-camptothecin (1a) in two steps. The epoxyetheno-bridge was cleaved by the reaction with a mixture of ethanedithiol and trifluoroacetic acid.

Recently, we had accomplished a total synthesis of ( $\pm$ )-camptothecin (1a) and ( $\pm$ )-10-hydroxycamptothecin (1b) possessing potent antitumor activity<sup>1</sup>, via indoloquinolizidine derivatives prepared by the enamine annelation developed by us<sup>2</sup>. However ethylation at C<sub>20</sub> position had resulted in a poor yield. Therefore we have designed the introduction of the two carbon units at an early stage. Here we wish to report an alternative synthesis of ( $\pm$ )-camptothecin from the pentacyclic lactam (2), having all carbon units required for the construction of (1a), which was assembled in one step by the enamine-imine double annelation from the pyran-2-one, reported in the precedent paper<sup>3</sup>. Since camptothecin is biosynthesized from strictosamide<sup>4</sup>, this synthesis is regarded as a biomimetic one.

Transformation of (2) to ( $\pm$ )-camptothecin was carried out by the modification of the previous syntheses<sup>2,5</sup> and the epoxyetheno-bridge was split under the thioketalization condition as follows.

Photosensitized oxygenation of (2) was conducted at 20 ~ 25°C for 15 hr by irradiation



tion with halogen lamp under oxygen bubbling in the presence of Rose Bengal in methanol-methylene chloride. The resulting mixture was further treated for 2 days with aqueous sodium bicarbonate solution at the ambient temperature to give the pyridone (3),  $m/e$  466 ( $M^+$ ), UV  $\lambda_{max}$  (MeOH) 243, 320 and 333 nm, IR  $\nu_{max}$  ( $CHCl_3$ ) 1740 and 1640  $cm^{-1}$ , in 60.2 % yield from (2). Treatment of (3) with thionyl chloride in dimethylformamide at 0°C gave, in 91 % yield, the chloride (4), which was dechlorinated using palladium charcoal under hydrogen atmosphere to afford, in 80.6 % yield, the quinoline (5),  $m/e$  450 ( $M^+$ ), UV  $\lambda_{max}$  (MeOH) 237, 307 and 322 nm, IR  $\nu_{max}$  ( $CHCl_3$ ) 1735, 1700, 1660 and 1620  $cm^{-1}$ .

The methyl ester of (5) was selectively reduced at  $-65 \sim -60^\circ C$  with di-isobutyl-aluminium hydride<sup>6</sup> in dimethoxyethane, in 83.1 % yield, to the hydroxymethylene (6), mp 202°C (decomp.), which was further reduced with sodium borohydride. Two stereoisomeric alcohols (7),  $m/e$  422 ( $M^+$ ) and the corresponding exomethylene compound were isolated in 47.3 %, 26.9 % and 16.8 % yield, respectively, after silica gel column chromatography. Opening the epoxyetheno-bridge required the more severe conditions than that of the indole derivative<sup>3</sup>. Thus *tert.*-butyl ester was converted in 98 % yield to the methyl ester (8) by the sequential treatments; reaction of the above major alcohol (7) with trifluoroacetic acid at room temperature for 15 min and the O-methylation of the resulting acid with diazomethane. After acetylation with acetic anhydride and pyridine, the acetate (9),  $m/e$  422 ( $M^+$ ), obtained in 94 % yield was subjected to the ring opening reaction.

On refluxing (9) with trifluoroacetic acid, the formation of the  $\beta$ -ketoester (10) was observed on the NMR spectroscopy, which showed the hydrogen at  $C_1$  position at 6.30 ppm as singlet. However retro-Michael reaction considerably occurred. Therefore a mixture of (9) and ethanedithiol in trifluoroacetic acid was heated for 2 hr under refluxing to produce the thioketal (11), IR  $\nu_{max}$  ( $CHCl_3$ ) 1725 and 1650  $cm^{-1}$ ; NMR  $\delta$  ( $CDCl_3$ ) 6.27 ppm (1H, s, 1-H), in 57.7 % yield.

The above thioketal ester (11) was treated with Raney nickel in ethanol for 2 hr and the desulfurized compound, obtained in 57.4 % yield, was then dehydrogenated by refluxing with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone in benzene for 10 min affording the acetate (12) in 54.1 % yield, mp 176  $\sim$  179.5°C (lit.,<sup>7</sup> mp 171  $\sim$  178°C), whose UV (MeOH) and NMR ( $CDCl_3$ ) spectra were consistent with the reported ones<sup>7</sup>. Since (12) had been converted to ( $\pm$ )-camptothecin (1a) in two steps by Rapoport<sup>7</sup>, this work has accomplished a formal total synthesis of (1a).

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