AN ALTERNATIVE BIOMIMETIC SYNTHESIS OF (±)-CAMPTOTHECIN

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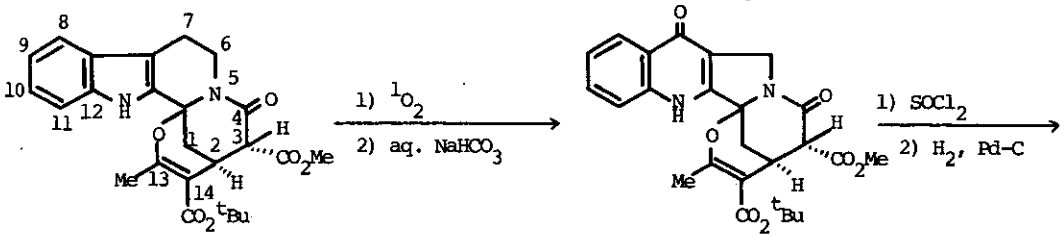
Abstract —— 14-tert.-Butoxycarbonyl-12b,2-epoxyetheno-1,12b,2,3-6,7-hexahydro-3-methoxycarbonyl-13-methylindolo[2,3-a]quinolizin-4-one (2) synthesized by the enamine-imine double annelation method was converted to the acetate (12) which had been correlated with (±)-camptothecin (1a) in two steps. The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

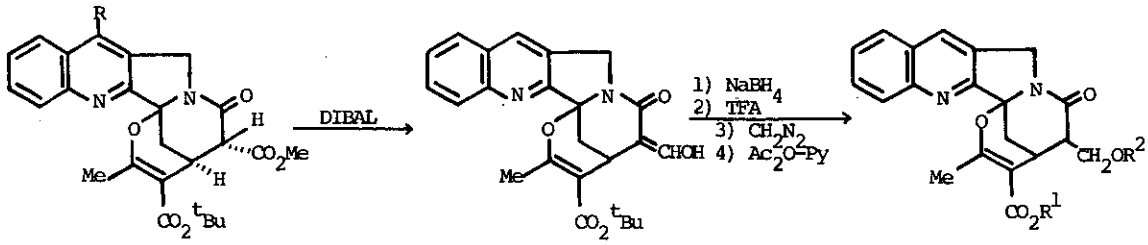
Recently, we had accomplished a total synthesis of (±)-camptothecin (1a) and (±)-10-hydroxycamptothecin (1b) possessing potent antitumor activity[1], via indoloquinolizidine derivatives prepared by the enamine annelation developed by us[2]. However ethylation at C_{20} position had resulted in a poor 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 (±)-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[3]. Since camptothecin is biosynthesized from strictosamide[4], this synthesis is regarded as a biomimetic one.

Transformation of (2) to (±)-camptothecin was carried out by the modification of the previous syntheses[2,5] 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 irradia-



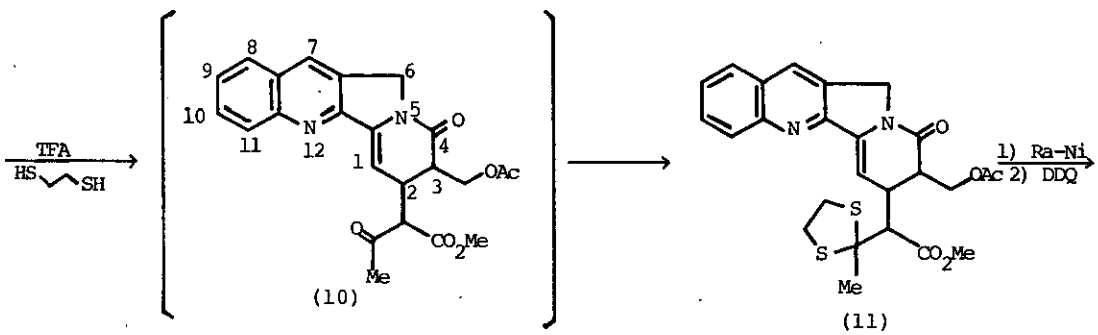
(2) (3)



(4) R=Cl
(5) R=H

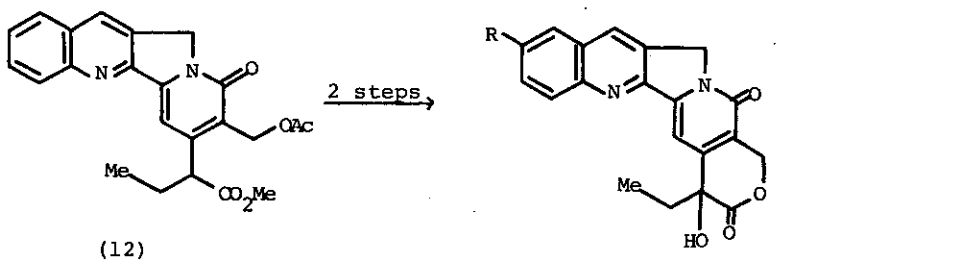
(6)

(7) $R^1={}^tBu$, R^2=H
(8) R^1=Me, R^2=H
(9) R^1=Me, R^2=Ac



(10)

(11)



(12)

(1a) R=H
(1b) R=OH

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 λ_{max} (MeOH) 243, 320 and 333 nm, IR ν_{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 λ_{max} (MeOH) 237, 307 and 322 nm, IR ν_{max} ($CHCl_3$) 1735, 1700, 1660 and 1620 cm^{-1}.

The methyl ester of (5) was selectively reduced at -65 ∿ -60°C with di-isobutylaluminium hydride[6] 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[3]. 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 β-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. Therefor a mixture of (9) and ethanedithiol in trifluoroacetic acid was heated for 2 hr under refluxing to produce the thioketal (11), IR ν_{max} ($CHCl_3$) 1725 and 1650 cm^{-1}; NMR δ ($CDCl_3$) 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 ∿ 179.5°C (lit.,[7] mp 171 ∿ 178°C), whose UV (MeOH) and NMR ($CDCl_3$) spectra were consistent with the reported ones[7]. Since (12) had been converted to (±)-camptothecin (1a) in two steps by Rapoport[7], this work has accomplished a formal total synthesis of (1a).

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