A FACILE SYNTHESIS OF (±)-CAMPTOTHECIN BY ENAMINE ANNELATION

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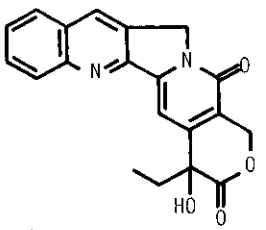
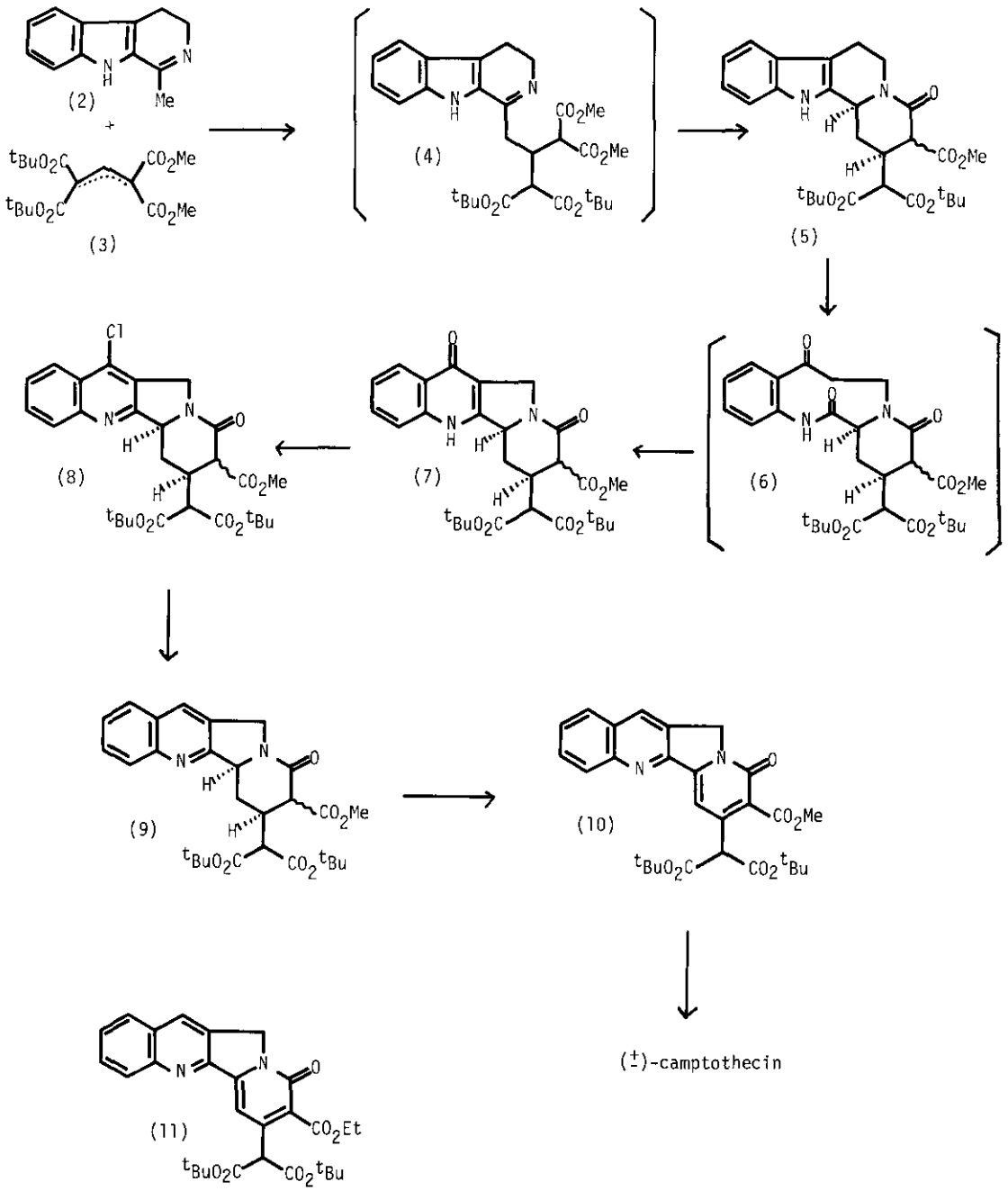
Abstract —— A formal total synthesis of (±)-camptothecin (1) was achieved via the key steps of enamine annelation and subsequent dye-sensitized photooxygenation.

Using the reaction between a 3,4-dihydro-1-methylisoquinoline and α,β-unsaturated esters, we developed a one step synthesis of benzo[a]quinolizines[1] and later applied this enamine annelation for a total synthesis of emetine[2]. Further work along this line led to an efficient synthesis of the indolo[a]quinolizine skeleton from a substituted 3,4-dihydro-1-methyl-β-carboline[3]. We now wish to report here a facile formal total synthesis of (±)-camptothecin (1)[4] using this enamine annelation approach.



(±)-camptothecin

Condensation of 3,4-dihydro-1-methyl-β-carboline (2) with a mixture of the tetra ester (3) (prepared from methoxymethylene dimethylmalonate and di-tert-butyl malonate in benzene in the presence of sodium hydride) in tetrahydrofuran at room temperature for 2 days afforded the Michael adduct (4). This intermediate (4), without purification, was reduced with sodium borohydride in methanol at room temprature to give, with concurrent cyclisation, the indolo[a]quinolizin-4-ones (5) (m/e 512) in 80.1 % overall yield. Although cyclisation took place selectively on the methyl ester, the product was an epimeric mixture at the C_3-position. Transformation of the indolo[a]quinolizinone ring to an indolizino[1,2-b]quinolone ring


(2)
Me
(3)
(4)
(5)
(6)
(7)
(8)
(9)
(10)
(11)
(±)-camptothecin

was achieved by a modification of Winterfeldt's method[5]. Photooxygenation of 5 in the presence of Rose Bengal as sensitizer in methanol using a 500 W halogen lamp at 20 ∿ 25°C for 2 h yielded the keto amide (6), which was subsequently subjected to a recyclization reaction. Namely, stirring the keto amide (6) in methanol-water with saturated sodium hydrogen carbonate solution[6] gave the indolizino[1,2-b]-quinolone (7) in 56.9 % overall yield from 5. Although this product was shown to be homogeneous by thin layer chromatographic analysis, its stereochemistry remains undefined. Treatment of 7 with thionyl chloride in dimethylformamide at 0°C[5] afforded the chloride (8) which was dehalogenated, by hydrogenolysis over palladium on barium sulfate in methanol[5], to give the quinoline (9) in fair overall yield. Dehydrogenation of 9 with 2,3-dichloro-5,6-dicyano-p-benzoquinone in refluxing dioxane[7] produced, in moderate yield, the pyridone (10), the spectral data of which were consistent with those of the ethyl ester (11)[5] provided by Professor E. Winterfeldt.

Since this pyridone (10) has already been converted to 1[5b], the present work constitutes a formal total synthesis of (±)-camptothecin.

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