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Regioselective Synthesis of Camptothecin

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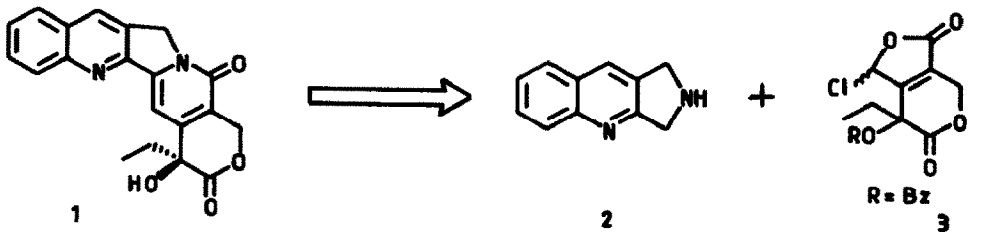
Abstract : A convergent synthesis of (±)camptothecin is described.

Camptothecin (1), isolated by M C Wani and his coworkers[1] from the bark of Camptotheca acuminta, has shown tremendous potential as an antitumor and antileukemic agent.[2] Off late Camptothecin and its anologs have emerged as the most promising compounds for the treatment of solid tumors.[3] Recent findings have shown that camptothecin demonstrated exceptional antiretroviral activity at dose levels well tolerated by cells which prompted its development as an effective drug in the new direction of AIDS chemotherapy.[4] Activity apart, the unusual structural features of the molecule are the α-hydroxy lactone and a pyridone ring fused to a five membered ring, which makes it a challenging synthetic target. Several groups have reported its synthesis[5,6] but many of them either lack in regioselectivity or are linear strategies. Herein, we report an elegant, regioselective and convergent approach to the total synthesis of (±) camptothecin.

The following retrosynthetic analysis (Scheme 1) dictates the convergent approach where the molecule can be disassembled into its retrons 2 and 3.

SCHEME-1



Accordingly, retron 2 was synthesized by a new route starting from commercially available 2-amino benzaldehyde 4 and dimethyl acetylene dicarboxylate 5 as depicted in scheme 2.

Refluxing equimolar quantities of 4 and 5 in anhydrous methanol gave an N-alkylated intermediate which on subsequent refluxing in methanol-chloroform mixture under acidic conditions[7] led to the diester 6 in 95% yield. Diester was reduced to its corresponding diol 7 and converted to its dimesylate 8 in overall 80% yield. Treatment of 8 with methanolic ammonia furnished the desired retron 3 in 82% yield.

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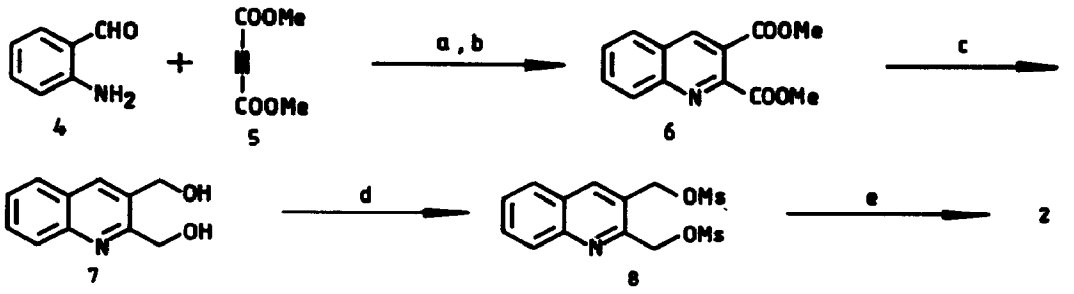
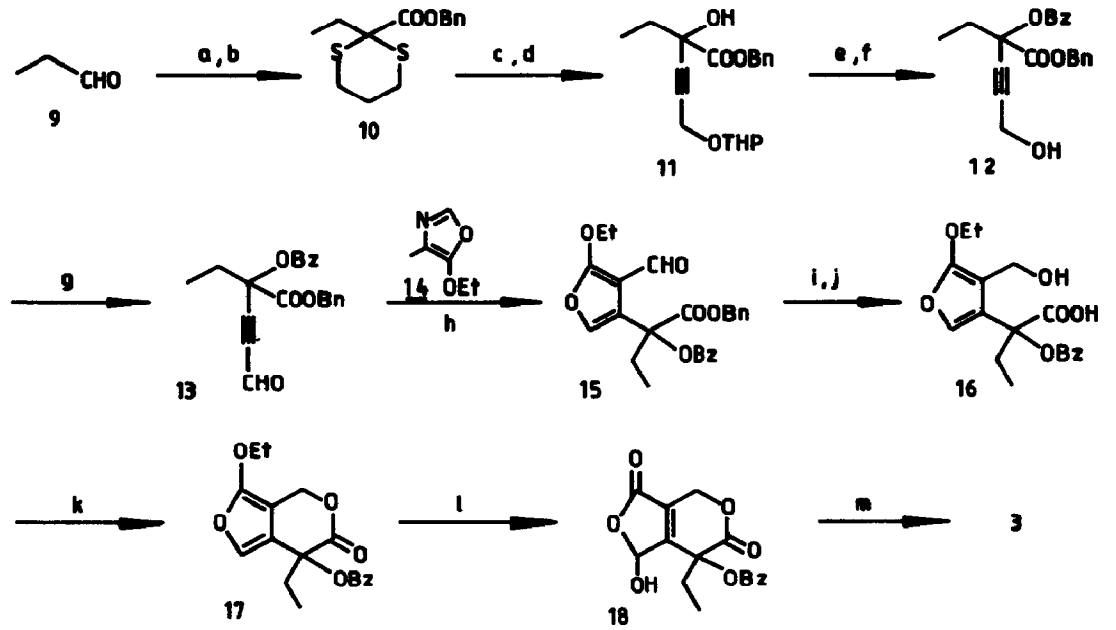
SCHEME-2



a) MeOH, reflux; b) MeOH-$CHCl_3$ (1:1), H_2SO_4, reflux; c) $LiAlH_4$, THF, rt; d) MsCl, TEA, DCM; e) Methanolic ammonia.

Making a convenient application of our methodology,[8] the retron 3 was synthesised in a regioselective fashion starting from propionaldehyde 9 as depicted in scheme 3.

SCHEME-3



a) Propane dithiol, $BF_3(OEt)_2$, DCM, 0°C; b) n-BuLi, -25°C, ClCOOBn, -78°C, THF; c) $AgNO_3$, NBS, CH_3CN:H_2O (4:1), r.t.; d) Li ≡ $-CH_2-OTHP$, THF, -78°C; e) BzCl, TEA, DMAP, DCM, 0°C; f) PTSA, MeOH; g) PCC, DCM: h) Toluene, 110°C; i) $NaBH_4$, MeOH, 0°C; j) H_2/Pd-C, MeOH; k) ClCOOEt, TEA (10 eq, 10 eq), DCM, rt; l) MnO_2-HCl (4:10), -15°C; m) $SOCl_2$, DMF (cat), $CHCl_3$, r.t.

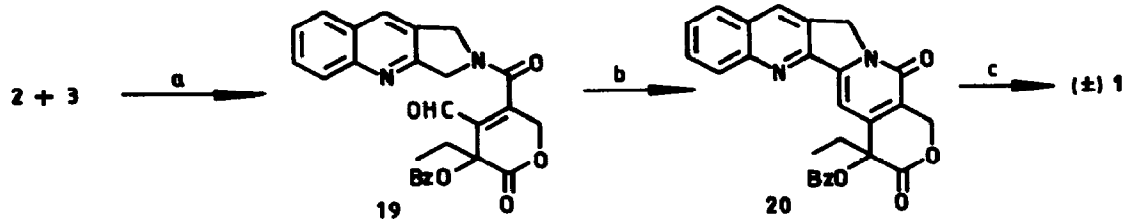
Thus, propionaldehyde 9 was converted to its dithiane derivative[9] which on deprotanation with n-BuLi followed by the treatment with benzyl chloroformate afforded 10. Removal of

dithiane[10] with NBS and $AgNO_3$ and subsequent addition to the lithiated THP protected propargyl alcohol led to synthon **11** in overall 85% yield. Benzoylation of the tertiary alcohol and THP deprotection gave the primary alcohol **12** which on PCC oxidation resulted in crucial dienophile **13** in overall 70% yield. Tandem Diels-Alder and retro Diels-Alder cycloaddition[11] of **13** with 4-methyl-5-ethoxy oxazole **14** delivered the compound **15** in 90% yield. Sodium borohydride reduction of the aldehyde and debenzylation provided the hydroxy acid **16**.

Lactonization of **16** was best performed by using TEA-ethyl chloroformate conditions leading to **17**. The pivotal regioselective MnO_2-HCl oxidation[8] of ethoxy furan moiety in compound **17** led uneventually to **18** in 75% yield. The hydroxy group of **18** was converted to its chloride to get the retron **3**.

Coupling of retrons **2** and **3** and final conversion to the target molecule is illustrated in scheme 4.

SCHEME-4



a) CH_3CN-Pyridine (9:1) 18h, r.t.; b) CH_3COOH, CH_3COONa, r.t.; c) NaOMe (cat), MeOH, 8h, r.t.

The pseudo acid chloride **3** was reacted with tricyclic diamine **2** in acetonitrile - pyridine (9:1) to give aldehyde **19** which was subjected to intramolecular condensation under acetic acid, sodium acetate conditions to realise the pentacyclic system **20** in quantitative yield. Hydrolysis of the benzoate ester was carried out by using catalytic amount of sodium methoxide inmethanol to give rise the target molecule (±) Camptothecin, whose PMR spectrum was superimposable with that of authentic sample. M.P. 272-275°C (reported 275-278°C).[12]

Thus we have demonstrated the convergent approach to Camptothecin, which is flexible and easy to operate. Several analogues can be prepared by incorporating various substituent on aromatic nucleus.

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+ All new compounds are characterized by spectral data and HRMS.

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