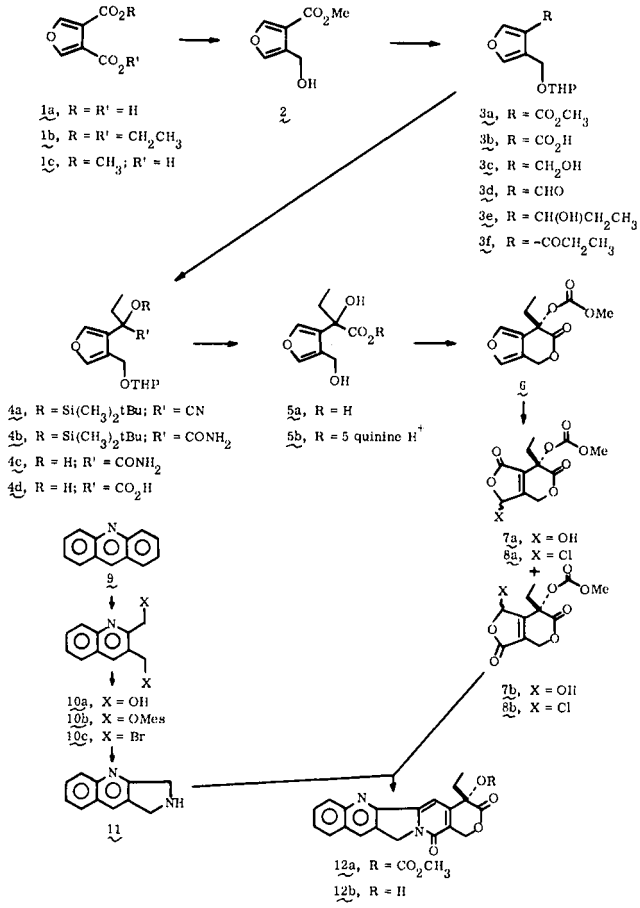
A Total Synthesis of Natural 20(*S*)-Camptothecin

Summary: A total synthesis of natural 20(*S*)-camptothecin (**12b**) is described by a sequence involving intermediates **1–11**; the furancarboxylic acid derivative **5a** was resolved using quinine and was converted to the lactone **6**; photooxidation and chlorination afforded **8b** which upon treatment with the tricyclic amine **11** led to the desired pentacyclic structure (**12**).

Sir: The alkaloid camptothecin (**12b**),[1,2] formerly considered of possible use as an antitumor agent, has attracted the attention of many synthetic groups with the result that several different pathways for synthesis of the racemic form have been demonstrated.[3] We describe herein another approach which actually represents the first successful synthesis of camptothecin in the *naturally occurring* form (*S* configuration at C-20).[2] The synthesis is convergent and involves a convenient resolution at the stage of a relatively early intermediate (**5a**). Since the 20(*S*)-camptothecin now has an important use as a biological reagent which inhibits selectively biosynthesis of ribosomal and messenger RNA's without preventing the biosynthesis of mitochondrial, 4*S* or 5*S* RNA's,[4] this synthesis of natural material may be of some use.

The acid ester **1c** could be prepared either from the diethyl ester **1b** by treatment with sodium methoxide (1 equiv) in 5% aqueous methanol at 25° for 2 hr (78% yield)[5] or from the acid **1a** by reaction with 1.06 equiv of methyl chloroformate and excess triethylamine in tetrahydrofuran (THF) with stirring at 25° for 3 days (75%). Reduction of **1c** with borane (1.2 equiv) in THF for 3 hr at 0° provided the hydroxy ester **2** in 65% yield.[6] The hydroxy ester **2** was protected as the tetrahydropyranyl ether (THP) (benzene–dihydropyran–toluenesulfonic acid) and hydrolyzed (11% potassium hydroxide–methanol) providing the crystalline acid **3b** (mp 64–66°) in an overall yield of 40% based on the acid ester **1c**. Reduction of the acid **3b** was effected quantitatively with 1.05 equiv of borane in THF for 30 hr at 0° to afford the monoprotected diol **3c** which in turn was oxidized to the aldehyde **3d** with manganese dioxide, ethylated to **3e** with ethylmagnesium bromide, and oxidized with Collins' reagent[7] to the keto furan **3f** (69% overall yield from the acid **3b**). The direct conversion of the lithium salt of the acid **3b** to afford **3f** in one step could be accomplished by reaction with 3.5 equiv of ethyllithium in THF at −40° to 0°, but the yield was lower (28%).[8] The ketone **3f** was heated (110°, neat) for 10 days with distilled *tert*-butyldimethylsilyl cyanide[9] (2 equiv), made from *tert*-butyldimethylsilyl chloride and dipotassium mercuric tetracyanide in hexamethylphosphoric triamide (HMPA).[10] Dicyclohexyl-18-crown-6-potassium cyanide was used as a catalyst[11] and was added in portions of 0.1 equiv on days 1, 2, 4, and 6 along with excess *tert*-butyldimethylsilyl cyanide (1 equiv each) added on days 3 and 6. The cyano silyl ether **4a** was isolated by column chromatography (silica gel–methylene chloride) in 85% yield, and the starting ketone **3f** (15%) was recovered for recycling.[12] Hydrolysis of **4a** to a mixture of amides **4b** and **4c** was effected with hydrogen peroxide (30%, 10 equiv) in basic (1.2 equiv of potassium carbonate) methanol at room temperature using 1-heptene (10 equiv) as an oxygen acceptor. Isolation of the acid-sensitive amides **4b** and **4c** required quenching at 0° with aqueous sodium bisulfite and immediate addition of pyrrolidine and potassium carbonate before extractive work-up. The mixture of **4b** and **4c** was heated at reflux in H_2O–KOH–CH_3OH (1.5:14:100) for 4 days to give the hydroxy acid **4d** in 73% overall yield from **3f**. The cleavage of the tetrahydropyranyl ether was then brought about in 30% aqueous acetic acid by heating for 4 hr at 45° to afford pure dihydroxy acid **5a** (65% yield).



The natural base quinine proved to be very satisfactory for the resolution of the acid **5a** via a nicely crystalline solid of composition dihydroxy acid (**5a**)–quinine–water in a ratio of 1:5:2. The use of 5 equiv of quinine trihydrate resulted in a 76% yield of resolved salt **5b** with $[\alpha]^{22}D$ −145° (EtOH) (three recrystallizations from benzene–heptane, 1:1). The chiral lactone **6** was generated by adding triethylamine and methyl chloroformate (34 equiv each) to a methylene chloride solution of **5b**. After 4 hr at room temperature the quinine salt was removed by quaternization with methyl iodide in nitromethane for 18 hr at room temperature. Column chromatography (neutral alumina–methylene chloride) gave a quantitative yield of the resolved lactone **6**,[13] $[\alpha]^{22}D$ +1.10° (MeOH).[14] Photooxidation of **6** was accomplished using 30% 2,6-lutidine in *tert*-butyl alcohol at 25° by irradiation in the presence of oxygen and eosine[16] to afford quantitatively a mixture of pseudo-acids **7a** and **7b** (ratio of 1:2.5)[17] which upon treatment with thionyl chloride and a catalytic amount of Vilsmeier reagent[18] at 50°

for 7 hr led quantitatively to a mixture of the pseudo-acid chlorides **8a** and **8b** (1:2.5, respectively).

The tricyclic diamine **11**[19] was synthesized from acridine by a simple three-step procedure. Oxidation of acridine with ozone (2.2 equiv) in methanol at −40° followed by sodium borohydride (4.4 equiv) reduction of the ozonide resulted in the crystalline diol **10a** (43% yield), mp 115–118°. The diol was converted into the dimesylate **10b** in benzene–triethylamine with methanesulfonyl chloride (3 equiv) at 0° for 1 hr (85% yield). Exposure of **10b** to 15% concentrated ammonium hydroxide in methanol for 2 hr at room temperature gave the tricyclic diamine **11** after work-up (careful exclusion of oxygen) and purification by column chromatography (silica gel–methanol) (48% yield of **11** as tan crystals, mp 92.5–95°).[20]

The mixture of pseudo-acid chlorides **8a** and **8b** (1:2.5) was stirred with the tricyclic diamine **11** (0.85 equiv) in 10% pyridine–acetonitrile for 10 hr at room temperature, and the resulting amide mixture was cyclized using as medium 10% sodium acetate–acetic acid for 20 hr at 25°. After column chromatographic purification (a) on silica gel using 20% CH_3OH in $CHCl_3$ and (b) on silica gel using 3% CH_3OH in CH_2Cl_2, and finally preparative TLC on silica gel plates using 3% CH_3OH in CH_2Cl_2, the pure camptothecin 20-methoxycarbonyl derivative (**12a**) was obtained: uv (20% MeOH in $CHCl_3$) 258 nm (ϵ 20,600), 295 (5000), and 362 (18,100); $[\alpha]^{22}D$ +31.7° ($CHCl_3$).[21] The methoxy carbonyl group of **12a** was removed by reaction with lithium mercaptide in HMPA[22] yielding 90% of 20(*S*)-camptothecin (**12b**) identical in every respect with natural material:[23] found for synthetic **12b**, $[\alpha]^{22}D$ +31.1° (20% MeOH in $CHCl_3$), mp 275–278° dec; found for naturally derived camptothecin, $[\alpha]^{25}D$ +31.3° (20% MeOH in $CHCl_3$),[1] mp 276–278° dec.[24] The NMR, ir, uv, TLC, MS, and mixture melting point all confirmed the identity of synthetic and natural camptothecins.[25]

References and Notes

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(12) The use of the stable *tert*-butyldimethylsilyl derivative was required to avoid desilylation in the next step which would lead to reversal of cyanohydrin formation; the trimethylsilyl cyanide analog of **4a** was not a satisfactory substrate.
(13) This procedure was found to be superior to the isolation of the resolved dihydroxy acid (**5a**) owing to the acid sensitivity and water solubility of **5a**.
(14) Both camptothecin {$[\alpha]^{25}D$ +31.3° (MeOH)} and (+)-atrolactic acid {$[\alpha]^{13.8}D$ +37.7° (EtOH)} have the *S* configuration[3,15] and a positive rotation; it was therefore anticipated that the (+)-lactone **6** should also be of the *S* configuration.
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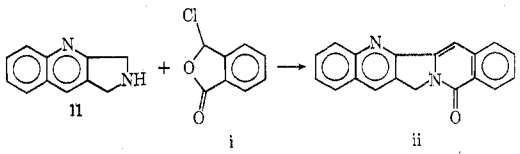
(21) The yield of **12a** obtained in the coupling–cyclization process as described herein is ~6.5%. However, optimum conditions for this transformation have not been extensively studied owing to limitations of time and material (for example, a study of the variation of X in **7** may well be rewarding). It is noteworthy in this regard that the cyclization of the pseudo-acid chloride i with the tricyclic diamine (**11**) in a similar manner to that described for the production of **12a** yielded camptothecin analog ii in quantitative yield.



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Dry Ozonation. A Method for Stereoselective Hydroxylation of Saturated Compounds on Silica Gel

Summary: A convenient preparative method is described for hydroxylation of tertiary carbon atoms by ozonation of saturated compounds adsorbed on silica gel.

Sir: Ozone reacts slowly with saturated hydrocarbons inserting oxygen atoms into their C–H bonds, resulting in alcohols and ketones.[1] This insertion occurs preferentially at the tertiary carbon atoms, with a retention of configuration.

In spite of its preparative potentialities this reaction has been rarely used until now. One of the factors limiting the use of ozone as reagent for hydroxylation of saturated hydrocarbons is its low solubility in organic solvents. Even at low temperatures at which ozone forms stable solutions in saturated hydrocarbons and no reaction is observed, its solubility is slight (~0.1–0.3% by weight at −78°).[2] At higher temperatures necessary for reaction to proceed at reasonable rate, the solubility of O_3 is even smaller, necessitating prolonged ozonation periods.

Furthermore, the reactivity of ozone toward most of the organic solvents[3] limits its practical use as a hydroxylation reagent only to neat hydrocarbons.

Considering that silica gel adsorbs ozone efficiently at low temperatures[4] (its concentration being ~4.5% by weight at −78°), we have used the silica gel as the reaction matrix, thus overcoming the drawbacks arising from ozonations in solutions.

To perform the reaction we have pre-adsorbed the silica gel with the hydrocarbon[5] either by direct mixing or by im-