- H, 7.4), 232 (12), 217 (100), 169 (8.4), 153 (b + Me_3Si - CH_3, 21), 147 (26), 96 (b + H, 5.0), 73 (74).

1-(β-D-**Ribopyranosyl**)**hexahydropyrimidin-2-one** (**7**). The nucleoside **15** (0.118 g, 0.52 mmol) was dissolved in water (12 mL) and hydrogenated at 30 psi in the presence of 50 mg of 5% Rh/Al_2O_3. After 12 h the catalyst was filtered off and the aqueous solution lyophilized to give 0.1 g (83%) of a white solid: mp ~110 °C. Anal. ($C_9H_{16}N_2O_5 \cdot 0.6H_2O$) C, H, N, H_2O.

Acknowledgment. We thank Dr. Karl P. Flora, Pharmaceutical Resources Branch, NCI, and Dr. Evelyn Murrill, Midwest Research Institute, for their assistance in obtaining the ^{13}C NMR data. These spectra were obtained under Contract NO1-CM-87234, which was awarded to Midwest Research Institute. We are also indebted to Kathy Brown for her valuable assistance in typing this manuscript.

Registry No. **2**, 18771-50-1; **3**, 104051-87-8; **4**, 77249-72-0; **5**, 104051-88-9; **6**, 19149-48-5; **7**, 104051-86-7; **8**, 74024-66-1; **9**, 104051-89-0; **10**, 104111-90-2; **11**, 104051-90-3; **13**, 52523-22-5; **14**, 104051-85-6; **15**, 65025-04-9; CDA, 9025-06-3; 1,2-dihydropyrimidin-2-one, 557-01-7; tetra-*O*-acetyl-D-ribopyranose, 4627-30-9.

Plant Antitumor Agents. 23.[1] Synthesis and Antileukemic Activity of Camptothecin Analogues

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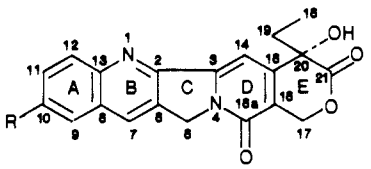
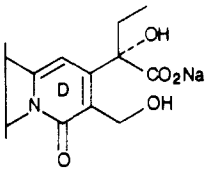
Eight optically active and nine racemic ring A modified analogues of 20(*S*)-camptothecin were prepared and evaluated for antitumor activity in the L-1210 leukemia system. The ring A mono- and disubstituted analogues displayed a wide variance in activity and potency. It was found that monosubstitution by NH_2 or OH at positions 9, 10, or 11 yielded compounds with activity much higher than the parent compound, camptothecin, whereas substitution at position 12 greatly reduced activity. In general, disubstitution in ring A greatly reduced antileukemic activity. Replacement of ring A by heterocyclic rings (thiophene or pyridine) leads to analogues with only moderate activity.

The discoveries of the naturally occurring compound 20(*S*)-camptothecin (**1**) in 1966[2] and the corresponding 10-hydroxy-20(*S*)-camptothecin (**2**) and 10-methoxy-20-(*S*)-camptothecin (**3**) a few years later[3] have led to much interest in this type of pentacyclic system because of the marked activity of **1** and **2** in a number of experimental rodent leukemia and solid tumor systems.[4] The search for analogues of **1**, such as the water-soluble sodium salt **4**, was undertaken with the practical goal of finding a



1. R = H
2. R = OH
3. R = OMe



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clinically useful anticancer drug, and, to this end, our laboratory has directed considerable efforts.

Previously, we have reported the synthesis and biological activity of various camptothecin analogues.[5,6] These analogues were obtained by modifications of the natural alkaloids or by total synthesis.[5,6,7] The former approach yields optically active 20*S* analogues; the latter is more versatile and capable of generating a wider variety of analogues but suffers from yielding only racemic 20*RS* compounds with half the potency of the corresponding 20*S* analogue. More recently we have described the isolation of 11-hydroxy-20(*S*)-camptothecin and the total synthesis and biological activity of the corresponding racemic compound **13**.[1]

We have found that monohydroxylation in ring A at positions 10 or 11 results in analogues with significant increase in the activity against L1210 or P-388 mouse leukemia.[1,5] The rationale behind our current efforts has been to further define the optimal substituent and position in ring A for maximal antitumor activity. In this paper we wish to report the synthesis and mouse antileukemic activity of a new series of totally synthetic and semisynthetic analogues of camptothecin.

Chemistry. The compounds **10–18a** were prepared by total synthesis and were racemic (20*RS*). The formation of the final pentacyclic ring system involved the Friedlander condensation of the amino aldehydes (or protected aldehydes) **5a**,[8] **5b**,[9] **5c**,[10] **5d**,[11] **6**,[12] and **7**[13] with the key racemic oxytricyclic ketone **8**. Details of the preparation

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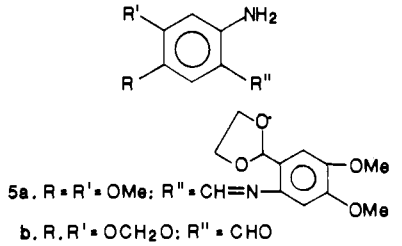
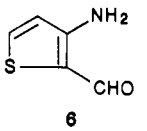


5a. R = R' = OMe; R" = CH=N

b. R, R' = OCH_2O; R" = CHO

c. R = NO_2; R' = H; R" = CHO

d. R = NHAc; R' = H, R" = CHO



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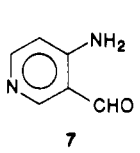

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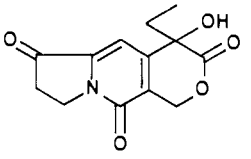

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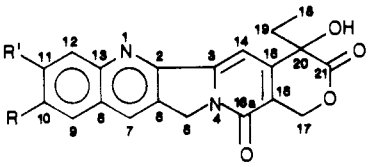
of the key intermediate 8 have been presented earlier.[1,6] In general, we noted that this reaction was retarded by the presence of electron-withdrawing sibstituents in 5. However, this same effect contributed to the stability of the amino aldehydes and minimized the problems of the decomposition and self-condensation associated with such structures. The 10-nitro analogue 14 was further transformed by catalytic hydrogenation into the corresponding amino analogue 15.



9. R = R' = H

10. R = R' = OMe

11. R, R' = OCH_2O

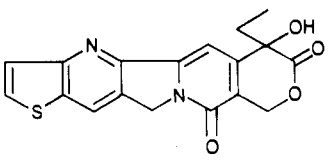
12. R = H; R' = OMe

13. R = H; R' = OH

14. R = NO_2; R' = H

15. R = NH_2; R' = H

16. R = NHAc; R' = H



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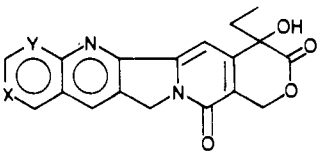
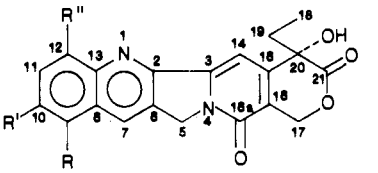


18a. X = N; Y = CH

b. X = CH; Y = N

The semisynthetic analogues 19–26 were derived from the natural substrates 1–3 and have the 20S configuration. Thus, nitration of 20(S)-camptothecin (1) gave a mixture of the 9-nitro and 12-nitro analogues 19 and 20, respectively, whereas nitration of 2 and 3 gave the corresponding 9-nitro derivatives 23 and 25. As might be expected, nitration of ring A in substrates 2 and 3 was much more facile than that in 1. The orientation of nitration was determined by ^1H NMR spectroscopy. In agreement with the assigned structures, the proton at C-7 in the 9-nitro analogue 19 appeared at a lower field than the one in the 12-nitro analogue 20 (δ 10.22 vs. 9.73). The ^1H NMR spectra of the disubstituted derivatives were consistent with the presence of ortho protons at C-11 and C-12. Catalytic hydrogenation of 19 gave the amine 21, and chemical reduction[14] of the nitro compounds 20 and 23 gave the corresponding amines 22 and 24. The amino-



19. R = NO_2; R' = R" = H

20. R = R' = H; R" = NO_2

21. R = NH_2; R' = R" = H

22. R = R' = H; R" = NH_2

23. R = NO_2; R' = OMe; R" = H

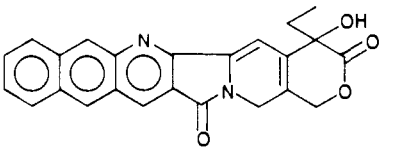
24. R = NH_2; R' = OMe; R" = H

25. R = NO_2; R' = OH; R" = H

26. R = NHAc; R' = OH; R" = H

27. R = R" = H; R' = OCH_2CO_2Na

28. R = R" = H; R = $OCH_2CH_2NEt_2 \cdot HCl$



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phenol resulting from the catalytic hydrogenation of 25 was unstable and was therefore characterized as the acetamido derivative 26.

Structure–Activity Relationships (SARs). Assays in P-388 and L-1210 leukemia were conducted by contractors for the National Cancer Institute by standard procedures.[15] The mouse antileukemic activity of the various ring A oxygenated camptothecin analogues is shown in Table I. The data for similar nitrogen analogues and for ring A modified analogues are shown in Tables II and III, respectively. In most cases camptothecin or an analogue with well-defined activity was also assayed at the same time as a positive control, and the data are shown in table footnotes. In this manner the relative antileukemic activity of the various compounds can be compared.

In a previous study we found that the C-20-hydroxyl and C-21-lactone moieties were essential for in vivo activity[5] and that the 20S configuration of the hydroxyl moiety was the "active" form, since synthetic 20(RS)-camptothecin (9) has only half the potency of the naturally occurring 20S analogue.[6] The presence of the intact lactone ring is also required, since it was found that the sodium salt 4 has only one-tenth the potency of 1 in mouse leukemia assays.[6] Horwitz has found that the conjugated fused ring ABCD is required for in vitro activity,[16] and we have noted that this is also a requirement for in vivo antileukemic activity.[5,7]

It is evident from previous data obtained for 10-hydroxy-20(S)-camptothecin (2) in P-388[5] and in the current study with L-1210 leukemia assay that hydroxylation at C-10 in the 20S series increases the activity and potency of the compound as compared to the parent compound 1 (Table I). Hydroxylation at C-11 (e.g., 13) in the 20RS series was found to lead to an even more active compound with T/C in L-1210 greater than 300 and three out of six cures. Data for 9- and 12-hydroxy analogues are

(14) Catalytic hydrogenation of the 12-nitro compound 20 gave a mixture of compounds probably due to incomplete reduction.

(15) Compounds 10, 17, 18a, 18b, and 27–29 were tested by Arthur D. Little, and compounds 11–16 and 19–26 were evaluated at the Southern Research Institute under contract by the National Cancer Institute according to standard procedure of Geran, R. I.; Greenberg, N. H.; McDonald, M. M.; Schumacher, A. M.; Abbott, B. J. *Cancer Chemother. Rep., Part 3* **1972**, *3*, 1.

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Table I. Comparative Activities and Potencies of Ring A Oxygenated Camptothecin Analogues in Mouse Leukemia Assays[a,b]

compound	max %T/C (dose, mg/kg)	no. cures out of 6	K_E[c] at max %T/C	active dose range, mg/kg	toxic dose, mg/kg
10-OH-20(*S*)-**2**[a,d]	297 (3.1)	0		0.4[e]–3.1	6.25
10-OMe-20(*S*)-**3**[a,d]	167 (1.6)	0		0.4[e]–1.6	3.1
11-OH-20(*RS*)-**13**[b,f]	357 (60.0)	3	≥5.68	7.5[e]–60.0[g]	>60.0
10,11-diOMe-20(*RS*)-**10**[b,h]	inactive				>50.0[g]
10,11-OCH_2O-20(*RS*)-**11**[b,i]	325 (2.0)	2	≥5.97	2.0[e]–4.0	>8.0
10-OCH_2CO_2Na-20(*S*)-**27**[a,d]	inactive				
10-$Et_2N(CH_2)_2O$-20(*S*)-**28**[a,d]	183 (16.0)	0		2.0[e]–32.0[g]	>32.0

[a] Denotes testing in P-388 system; treatment schedule Q04D×03; %T/C = survival time of treated/control animals × 100; IP using Klucel emulsifier. [b] Denotes testing in L-1210 system; treatment schedule Q04D×02; %T/C = survival time of treated/control animals × 100; IP using Klucel emulsifier. [c] Log_{10} of initial tumor cell population minus log_{10} of tumor cell population at end of treatment. [d] 20(*S*)-Camptothecin (1) and 20(*S*)-camptothecin sodium (4) were used as reference standards: for 1, %T/C (4.0 mg/kg) = 197; for 4, %T/C (40.0 mg/kg) = 212. [e] Lowest dose administered. [f] Compounds 1 and 4 were used as reference standards: for 1, %T/C (8.0 mg/kg) = 164; for 4, %T/C (40.0 mg/kg) = 178. [g] Highest dose administered. [h] Compound 4 was used as a reference standard: %T/C (25.0 mg/kg) = 206. [i] Compound 1 was used as a reference standard: %T/C (5 mg/kg) = 166.

Table II. Comparison of Activities and Potencies of Ring A Nitrogen Substituted and Ring A Nitrogen/Oxygen Disubstituted Analogues in L-1210 Mouse Leukemia Assays[a]

compound	max %T/C (dose, mg/kg)	no. cures out of 6	K_E[b] at max %T/C	active dose range, mg/kg	toxic dose, mg/kg
10-NO_2-20(*RS*)-**14**[c]	219 (15.5)	1	≥5.86	7.5[d]–15.5	31.0
10-NH_2-20(*RS*)-**15**[c]	329 (8.0)	3	≥5.86	4.0[d]–16.0	32.0[e]
10-NHAc-20(*RS*)-**16**[c]	318 (40.0)	1	≥5.86	5.0[d]–40.0[e]	>40.0
9-NO_2-20(*S*)-**19**[f]	348 (10.0)	5	≥5.86	2.5[d]–20.0	40.0[e]
12-NO_2-20(*S*)-**20**[f]	151 (40.0)	0	0.34	2.5[d]–40.0[e]	>40.0
9-NH_2-20(*S*)-**21**[f]	348 (2.5)	4	≥5.86	2.5[d]–5.0	10.0
12-NH_2-20(*S*)-**22**[f]	inactive				
9-NO_2-10-OMe-20(*S*)-**23**[f]	160 (40.0)	0	1.03	2.5[d]–40.0[e]	>40.0
9-NH_2-10-OMe-20(*S*)-**24**[f]	186 (40.0)	0	2.92	2.5[d]–40.0[e]	>40.0
9-NO_2-10-OH-20(*S*)-**25**[f]	131 (20.0)	0	−1.12	2.5[d]–40.0[e]	>40.0
9-NHAc-10-OH-20(*S*)-**26**[f]	220 (40.0)	0	5.50	2.5[d]–40.0[e]	>40.0

[a] Treatment schedule Q04D×2; %T/C = survival time of treated/control animals × 100; IP using Klucel emulsifier. [b] Log_{10} of initial tumor cell population minus log_{10} of tumor cell population at end of treatment. [c] 20(*S*)-Camptothecin (1) and 10-hydroxy-20(*S*)-camptothecin (2) were used as reference standards: for 1, %T/C (8.0 mg/kg) = 197; for 2, %T/C (24.0 mg/kg) = 230. [d] Lowest dose administered. [e] Highest dose administered. [f] Compounds 1 and 2 were used as reference standards: for 1, %T/C (10.0 mg/kg) = 267; for 2, %T/C (20.0 mg/kg) = 348.

Table III. Comparative Activities of Ring A Modified and Homologated Camptothecin Analogues in Mouse Leukemia Assays[a,b]

compound	max %T/C (dose, mg/kg)	no. cures out of 6	K_E[c] at max %T/C	active dose range, mg/kg	toxic dose, mg/kg
10-aza-20(*RS*)-**18a**[a,d]	162 (2.5)	0	1.61	1.25[e]–2.5	5.0
12-aza-20(*RS*)-**18b**[b,f]	175 (32.0)	0		8.0–32.0	>32.0
A-nor-9-thia-20(*RS*)-**17**[a,d]	193 (25.0)	0	−0.94	3.12[e]–25.0	50.0[g]
benz[*j*]-20(*RS*)-**29**[b,f]	198 (16.0)	0		1.0[e]–16.0	32.0[g]

[a] Denotes testing in L-1210 system; treatment schedule Q04D×2; %T/C = survival time of treated/control animals × 100; IP using Klucel emulsifier. [b] Denotes testing in P-388 system; treatment schedule Q04D×3; %T/C = survival time of treated/control animals × 100; IP using Klucel emulsifier. [c] Log_{10} of initial tumor cell population minus log_{10} of tumor cell population at end of treatment. [d] 20(*S*)-Camptothecin sodium (4) was used as a reference standard: %T/C (40.0 mg/kg) = 215. [e] Lowest dose administered. [f] 20(*S*)-Camptothecin (1) was used as a reference standard: %T/C (4.0 mg/kg) = 197. [g] Highest dose administered.

not available at this time, but from data in the corresponding amino series (vide infra), it would be expected that the former would be highly active and the latter weaker or inactive.

Steric or electronic factors can play an important role in SAR in the camptothecin series. Thus, while hydroxylation at positions 10 or 11 increases activity, 10-methoxy-20(*S*)-camptothecin (**3**)[3] is somewhat less active than camptothecin (**1**),[6] and we now find that the 10,11-dimethoxy-20(*RS*) derivative **10** is inactive and nontoxic in L-1210 over a wide dosage range. 10,11-Methylenedioxy-20(*RS*) analogue **11** is of much greater activity and potency in the L-1210 assay than the natural 20(*S*)-camptothecin (**1**).

We have also found earlier[6] that the water-soluble carboxylate salt **27** prepared as an ether from **2** was inactive. The corresponding water-soluble amine hydrochloride **28** had the same order of activity in P-388 leukemia as **1**, but was only one-sixth as potent. The in vivo activity of the latter may be due to slow cleavage to the parent compound **2**.[6] Thus it is again evident that steric and/or electronic interactions may play an important role in the reduced activity of these water-soluble ring A salts.

The 12-nitro-20(*S*) analogue **20** was nontoxic and only marginally active, whereas the corresponding 12-amino analogue **22** was completely inactive and showed no toxicity (Table II). In great contrast substitution at C-9 or C-10 particularly with the amino functionality led to the most highly active compounds (e.g., **21** or **15**) in the entire series in the L-1210 assay with T/C greater than 300 and 3–5/6 cures. In the 20*S* series the 9-nitro and the corresponding 9-amino analogues **19** and **21** were considerably more active than **1**. The analogue **21** with T/C 348 at 2.5 mg/kg is the most active analogue obtained to date. The 10-amino-20(*RS*) analogue **15** was also highly active but less potent than **21** probably due to the former being a racemate. It is interesting to note that the 10-acetamido-20(*RS*) analogue **16** was nontoxic at all dose levels up to 40 mg/kg and at this high dose exhibited T/C greater than 300 in L-1210. This compound and the

various nitro compounds may be prodrugs for the corresponding amino compounds because of enzymatic hydrolysis or reduction. This is consistent with the observation that despite drastic electronic differences, both the 9-nitro **19** and the 9-amino **21** analogues are quite active. The modest activity of the 12-nitro **20** and the inactivity of the 12-amino **22** analogues may be due to steric and electronic disturbances at the quinoline nitrogen, which might interfere with interaction with DNA.[6]

As with other ring A ortho disubstituted analogues, compounds with substituents at both positions 9 and 10 (**23–26**) demonstrated a marked drop in activity and/or potency probably due to steric interaction. It is noteworthy that the incorporation of biological activity enhancing features found in **2** and **19** into the structure **25** led to near inactivity even at high doses.

Two aza analogues (**18a** and **18b**) in the 20*RS* series have been prepared. The 12-aza analogue **18b** was found previously to be modestly active in P-388 leukemia, but was less active and much less potent than **1** in this assay (Table III).[6] The 10-aza analogue **18a** prepared in the current study was tested only in L-1210 and was rather toxic at doses of 5–40 mg/kg but had modest activity at lower doses. The previously prepared hexacyclic analogue **29** was of the same order of activity as **1** in the P-388 assay but was less potent. The currently prepared thiophene analogue **17** was as active in L-1210 as 20(*S*)-camptothecin (**1**) but of much lower potency. It is apparent that while most of the major ring modifications (other than substitution) discussed here produced active compounds, none lead to real improvement in activity and potency or reduction in toxicity.

Mode of Action. The mode of action of camptothecin is still not clearly understood. However, at least three important regions in the molecule can be identified. A conjugated planar area defined by rings ABCD is required for in vitro inhibition of RNA and depolymerization of DNA as well as for in vivo activity.[16,17] Although it is tempting to believe this is due to the binding to DNA by intercalation, camptothecin has never been shown to produce this form of binding. A second important area is defined by the 20,21-hydroxylactone moiety. Lown and Chen have shown that an oxygen-dependent single-strand scission of DNA occurs after photoactivation[18] and have evidence that is due to a free-radical mechanism involving the action of singlet oxygen on the 20,21-hydroxylactone moiety. Another explanation may be the high reactivity of the lactone moiety in camptothecin toward nucleophiles such as OH, NH_2, or SH. A third region of importance involves the 9, 10, 11, and 12 positions in ring A. Depending on the type, number, and location of substituents, highly active or inactive analogues can be obtained.[19]

Experimental Section

Melting points were determined with a Kofler hot stage melting point apparatus. Thin-layer chromatography was carried out on precoated 0.25-mm layers of silica gel 60F-254 (Merck). Locations of spots on the chromatograms were determined by one or a combination of the following: short-wave UV, long-wave UV, and/or charring by heating plates sprayed with ceric sulfate and phosphomolybdic acid. ^1H NMR spectra were obtained on a Bruker 250 250-MHz nuclear magnetic resonance spectrometer. Infrared spectra were obtained on a Perkin-Elmer 267 spectrophotometer in the solid phase (KBr) and were consistent with the assigned structures. Exact mass determinations were made on a MS-902 mass spectrometer. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA, and are correct within ±0.4% of theory for variously hydrated species. Attempts to render many camptothecin analogues anhydrous by prolonged heating under high vacuum resulted in decomposition. In the case of compound **25**, a partial $CHCl_3$ solvate was observed. Optical rotations were determined by a Perkin-Elmer 141 polarimeter. HPLC was performed on a Waters system incorporating a Model 6000A pump operating at a flow of either 1.5 or 2.0 mL/min, a Model 450 absorbance detector at 254 nm, a Model U6K injector, and a Whatman Partisil PXS 10/25 PAC column. The PAC column was used in the normal-phase mode, employing mixtures of MeOH and $CHCl_3$.

10,11-Dimethoxy-20(*RS*)-camptothecin (10). A suspension of 4,5-dimethoxy-2-[(2-amino-4,5-dimethoxybenzylidene)-amino]benzaldehyde ethylene acetal (**5a**)[8] (290 mg, 0.75 mmol) and **8**[1,6] (233 mg, 0.89 mmol) in toluene (30 mL) was heated to reflux to effect solution and then cooled, and *p*-toluenesulfonic acid was added. The reaction mixture was refluxed for 1 h using a Dean-Stark trap. The precipitate obtained after cooling the reaction mixture was filtered, and the crude product was purified by elution from silica gel (50 g) using 2% MeOH in $CHCl_3$ followed by crystallization from 13% MeOH–$CHCl_3$ and EtOAc (53 mg, 15%): mp 265–267 °C; IR (KBr) 1740 (lactone), 1660 (pyridone) cm^{-1}; ^1H NMR (TFA-d_1) δ 1.10 (t, 3, J = 7 Hz, H-18), 2.13 (q, 2, J = 7 Hz, H-17), 4.20 (s, 3, OCH_3), 4.23 (s, 3, OCH), 5.67 (s, 2, H-5), 5.66 (ABq, 2, J = 17 Hz, Δγ = 85 Hz, H-17), 7.53 (s, 1, H-9), 7.65 (s, 1, H-12), 8.13 (s, 1, H-14), 9.02 (s, 1, H-7). Anal. ($C_{22}H_{20}N_2O_6 \cdot 0.5H_2O$) C, H, N.

10,11-Methylenedioxy-20(*RS*)-camptothecin (11). The amino aldehyde **5b** was prepared from 2-nitropiperonal by literature procedure.[9] Compound **5b** (60 mg, 0.36 mmol) and the oxytricyclic ketone **8** (53 mg, 0.20 mmol) were refluxed for 8 h in toluene (30 mL) containing *p*-TsOH·H_2O (8 mg). The solvent was removed in vacuo, and the red residue was adsorbed onto Celite (1 g) and chromatographed through silica gel (10 g) using 3% MeOH in $CHCl_3$. Concentration of the appropriate fractions gave analogue **11** (36 mg, 45%) as a pale-tan solid. Crystallization of this material from $CHCl_3$ gave **11** as a cream-colored solid: mp >250 °C dec; IR (KBr) 1750 (lactone), 1655 (pyridone), 1585 (aromatic) cm^{-1}; ^1H NMR (TFA-d_1) δ 1.15 (t, 3, J = 7 Hz, H-18), 2.16 (q, 2, J = 7 Hz, H-19), 5.76 (ABq, 2, J = 17 Hz, Δγ = 85 Hz, H-17), 5.73 (s, 2, H-5), 6.44 (s, 2, OCH_2O), 7.55 (s, 1, H-14), 7.69 (s, 1, H-9), 8.16 (s, 1, H-12), 9.05 (s, 1, H-7). Anal. Calcd for $C_{21}H_{16}N_2O_6$: 392.1008. Found: 392.1009. ($C_{21}H_{16}N_2O_6 \cdot 1.0H_2O$) C, H, N.

10-Nitro-20(*RS*)-camptothecin (14). A mixture of 2-amino-5-nitrobenzaldehyde (**5c**)[10] (95 mg, 0.57 mmol) and the tricyclic ketone **8** (150 mg, 0.57 mmol) was heated at 120 °C for 10 min. The temperature was raised to 160 °C, and the dark molten mass was kept at this temperature for 1.5 h with occasional stirring. Chromatography of the residue through silica gel (20 g) using 0.5% MeOH in $CHCl_3$ afforded compound **14** (108 mg, 48%) as a yellow solid: mp 297–300 °C dec; IR (KBr) 3450 (OH), 1745 (lactone), 1660 (pyridone), 1620 (aromatic) cm^{-1}; ^1H NMR (TFA-d_1) δ 1.14 (t, 3, J = 7 Hz, H-18), 2.15 (m, 2, H-19), 5.88 (s, 2, H-5), 5.68 (ABq, 2, J = 17 Hz, Δγ = 85 Hz, H-17), 8.43 (s, 1, H-14), 8.70 (d, 2, J = 8 Hz, H-12), 9.05 (d, 2, J = 8 Hz, H-11), 9.35 (s, 1, H-9), 9.60 (s, 1, H-7). Anal. Calcd for $C_{20}H_{15}N_3O_6$: 393.0960. Found: 393.0965. ($C_{20}H_{15}N_3O_6 \cdot 0.3H_2O$) C, H, N.

10-Amino-20(*RS*)-camptothecin (15). A suspension of 10-nitro-(20*RS*)-camptothecin (**14**) (100 mg, 0.254 mmol) and 10% Pd/C (40 mg) in absolute EtOH (40 mL) was stirred in an atmosphere of H_2 at room temperature for 30 min. Filtration through Celite and removal of the solvent under reduced pressure gave **15** as a tan-yellow solid (86 mg crude). Recrystallization from 13% MeOH–$CHCl_3$ gave the pure product **15** (30 mg, 32%) as an olive-yellow solid: mp softening at 135 °C, gradual blackening upon further heating: IR (KBr) 3440 (OH, NH_2), 1750 (lactone), 1660 (pyridone) cm^{-1}; ^1H NMR (TFA-d_1) δ 1.06 (t, 3, J = 7 Hz, H-18), 2.08 (q, J = 7 Hz, H-19), 5.89 (s, 2, H-5), 5.70 (ABq, 2, J = 17 Hz, Δγ = 85 Hz, H-17), 8.34 (d, J = 9 Hz, H-12), 8.64 (d,

(17) Wall, M. E.; Wani, M. C. *Nat. Prod. and Drug Develop., Alfred Benzon Symp. 20*; Krogsgaard-Larsen, P., Brogger Christensen, S., Kofod, H., Ed.; Munksgarrd: Copenhagen, 1984; pp 253–266.

(18) Lown, J. W.; Chen, H. H. *Biochem. Pharm.* **1980**, *29*, 905.

(19) A full report on preparation and antitumor activity of a number of one-carbon substituents at C-11 will be presented at a later time.

J = 9 Hz, H-11), 9.26 (s, 1, H-9), 9.43 (s, 1, H-7). Anal. Calcd for $C_{20}H_{17}N_3O_4$: 363.1218. Found: 363.1216. ($C_{20}H_{17}N_3O_4 \cdot 1.4H_2O$) C, H, N.

10-Acetamido-20(*RS*)-camptothecin (16). 5-Acetamido-2-nitrobenzaldehyde was prepared according to literature procedure.[11] The 2-nitro group was reduced using $Na_2S \cdot 9H_2O$ in EtOH and H_2O. The 2-amino compound **5d** from this reduction was used in the next step without complete characterization because of the instability of this intermediate.

A solution of 2-amino-5-acetamidobenzaldehyde (**5d**) (101 mg, 0.421 mmol), the tricyclic ketone **8** (100 mg, 0.380 mmol), and p-TsOH·H_2O (5 mg) in toluene (15 mL) was refluxed for 2 h using a Dean-Stark trap. The solvent was removed under reduced pressure and the residue chromatographed through silica gel (50 g) using 3% MeOH–$CHCl_3$. Evaporation of the appropriate fractions gave compound **16** (43 mg, 27%) as a rusty-yellow solid: mp 335–337 °C dec; IR (KBr) 3440 (OH), 1750 (lactone), 1660 (pyridone), 1590 (aromatic) cm^{-1}; ^1H NMR (TFA-d_1) δ 1.15 (t, 3, J = 7 Hz, H-19), 2.16 (m, 2, H-18), 2.50 (s, 3, $COCH_3$), 5.81 (s, 2, H-5), 5.70 (ABq, 2, J = 17 Hz, $\Delta\gamma$ = 85 Hz, H-17), 8.27 (d, 1, J = 8 Hz, H-12), 8.30 (s, 1, H-9), 8.47 (d, 1, J = 8 Hz, H-11), 9.16 (s, 1, H-14), 9.39 (s, 1, H-7). Anal. Calcd for ($M^+ - CO_2$) $C_{21}H_{19}N_3O_3$: 405.1324. Found: 405.1324. ($C_{22}H_{19}N_3O_5 \cdot 2.2H_2O$) C, H, N.

***A*-Nor-9-thia-20(*RS*)-camptothecin (17).** A solution of 3-amino-2-formylthiophene (**6**)[12] (79 mg, 0.62 mmol) and **8** (96 mg, 0.37 mmol) in toluene (1.5 mL) was brought to reflux and then cooled before adding a crystal of p-toluenesulfonic acid. The mixture was refluxed for 2.5 h under N_2 and cooled and the precipitate filtered. The crude material was chromatographed on silica gel (20 g) by elution with 2% MeOH in $CHCl_3$. Crystallization of the product from 13% MeOH–$CHCl_3$ and EtOAc yielded **17** as a yellow solid (19 mg, 15%): mp 297–298 °C; IR (KBr) 1740 (lactone), 1655 (pyridone) cm^{-1}; ^1H NMR (TFA-d_1) δ 1.05 (t, 3, J = 7 Hz, H-18), 2.07 (q, 2, J = 7 Hz, H-19), 5.60 (ABq, 2, J = 17 Hz, $\Delta\gamma$ = 85 Hz, H-17), 5.65 (s, 2, H-5), 7.89 (d, J = 6 Hz, H-11), 8.05 (s, 1, H-14), 8.57 (d, J = 6 Hz, H-10), 9.23 (s, 1, H-7). Anal. ($C_{18}H_{14}N_2O_4S$) C, H, N.

10-Aza-20(*RS*)-camptothecin (18a). A solution of 4-aminonicotinaldehyde (**7**)[13] (24.2 mg, 0.20 mmol), the tricyclic ketone **8** (53.5 mg, 0.20 mmol), and p-TsOH·H_2O (2 mg) in toluene (25 mL) was refluxed for 4 days using a Dean-Stark trap. The solvent was removed under reduced pressure, and the residue was chromatographed through silica gel (20 g) using $CHCl_3$–acetone–MeOH (5:1:1). The product **18a** (46 mg, 67%) was crystallized from 13% MeOH in $CHCl_3$ and EtOAc: mp 289–292 °C; IR (KBr) 3320 (OH), 1730 (lactone), 1650 (pyridone), 1600 (aromatic) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (t, 3, J = 7.3 Hz, H-18), 1.92 (m, 2, H-19), 5.35 (s, 2, H-5), 5.53 (ABq, 2, J = 18 Hz, $\Delta\gamma$ = 85 Hz, H-17), 7.74 (s, 1, H-14), 8.04 (d, 1, J = 5.5 Hz, H-12), 8.53 (s, 1, H-7), 8.84 (d, J = 5.5 Hz, H-11), 9.4 (s, 1, H-9). Anal. Calcd for $C_{19}H_{15}N_3O_4$: 349.1066. Found: 349.1061. ($C_{19}H_{15}N_3O_4 \cdot 1.0H_2O$) C, H, N.

9-Nitro-20(*S*)-camptothecin (19)[20] and 12-Nitro-20(*S*)-camptothecin (20).[21,22] 20(*S*)-Camptothecin (1) (700 mg, 2.82 mmol) was dissolved/suspended in concentrated H_2SO_4 (40 mL) at −5 °C, and to the stirred suspension was added fuming HNO_3 (0.9 mL) over 20 s. The yellow turbid suspension rapidly turned black initially. The stirred mixture was permitted to warm to room temperature and then left overnight. The clear yellow solution thus obtained was poured over ice (350 g), and the resulting turbid yellow mixture was extracted with CH_2Cl_2 (2 × 150 mL). The extract was backwashed with H_2O (75 mL) and dried (Na_2SO_4) and the solvent removed in vacuo to afford a yellow solid. The crude mixture of **19** and **20** was dissolved in MeOH–$CHCl_3$ and adsorbed onto Celite (4.5 g). The resulting powder was loaded onto a column of silica gel 60 (50 g, Merck), and the column was eluted using a gradient of 1 L each of $CHCl_3$ and MeOH–$CHCl_3$ (3:97). Compound **19** was the first to elute, and evaporation of the appropriate fractions gave 191 mg of **19** (23% of total theory). Compound **20** was similarly isolated from later fractions giving 337 mg (41% of total theory).

9-Nitro-20(*S*)-camptothecin (**19**) was a yellow solid, which gave a yellow amorphous powder from MeOH–$CHCl_3$ (13:87): mp 182–186 °C; [lit.[20] mp 190–192 °C]; IR (KBr) 3430 (OH), 1750 (lactone), 1660 (pyridone), 1590 (aromatic), 1530 (NO_2) cm^{-1}; ^1H NMR (TFA-d_1) δ 1.15 (t, 3, J = 7 Hz, H-18), 2.18 (q, 2, J = 7 Hz, H-19), 5.78 (ABq, 2, J = 18 Hz, $\Delta\gamma$ = 85 Hz, H-17), 5.91 (s, 2, H-5), 8.42 (s, 1, H-14), 8.43 (t, 1, J = 7 Hz, H-11), 8.88 (d, 1, J = 7 Hz, H-10), 8.91 (d, 1, J = 7 Hz, H-12), 10.22 (s, 1, H-7), $[\alpha]^{23}_D$ 27° (c 0.2, MeOH–$CHCl_3$, 1:4); HPLC retention time 2.9 min (1.5 mL/min; $CHCl_3$–MeOH, 985:15). Anal. Calcd for $C_{20}H_{15}N_3O$: 393.0960. Found: 393.0965. ($C_{20}H_{15}N_3O_6 \cdot 0.9H_2O$) C, H, N.

12-Nitro-20(*S*)-camptothecin (**20**) was a yellow solid, which gave a yellow amorphous powder from MeOH–$CHCl_3$ (13:87): mp 276–279 °C dec [lit.[21] mp 268–270 °C]; IR (KBr) 3400 (OH), 1752 (lactone), 1655 (pyridone), 1590 aromatic), 1536 (NO_2) cm^{-1}; ^1H NMR (TFA-d_1) δ 1.17 (t, 3, J = 7 Hz, H-18), 2.19 (q, 2, J = 7 Hz, H-19), 5.81 (ABq, 2, J = 18 Hz, $\Delta\gamma$ = 85 Hz, H-17), 5.94 (s, 2, H-5), 8.35 (t, 1, J = 8 Hz, H-10), 8.65 (s, 1, H-14), 8.89 (d, 1, J = 8 Hz, H-9), 9.37 (d, 1, J = 8 Hz, H-11), 9.73 (s, 1, H-7); $[\alpha]^{23}_D$ 26° (c 0.2, MeOH–$CHCl_3$, 1:4); HPLC retention time 4.3 min (1.5 mL/min; $CHCl_3$–MeOH, 985:15). Anal. Calcd for $C_{20}H_{15}N_3O_6$: 393.0960. Found: 393.0965. ($C_{20}H_{15}N_3O_6$) C, H, N.

9-Amino-20(*S*)-camptothecin (21).[20] A mixture of 9-nitro-20(*S*)-camptothecin (**19**) (167 mg, 0.425 mmol) and PtO_2 (75 mg) in absolute EtOH (75 mL) was subjected to 1 atm of H_2 for 1 h. The catalyst was removed by filtration through Celite. Additional adsorbed product was rinsed through by thorough washing of the filter cake with MeOH–$CHCl_3$. The crude **21** was obtained as 148 mg of orange solid upon removal of the solvent in vacuo. The sample was chromatographed as a dispersion on Celite (0.9 g) through silica gel 60 (30 g, Merck) employing a gradient of 1 L each of $CHCl_3$ and MeOH–$CHCl_3$ (4:96). There resulted 70 mg of **21** as an orange-yellow solid (45%), which was obtained as an orange-yellow amorphous powder from MeOH–$CHCl_3$ (13:87): mp 300 °C gradual dec; IR (KBr) 3430, 3370, 3250 (OH, NH_2), 1740 (lactone), 1650 (pyridone), 1585 (aromatic) cm^{-1}; ^1H NMR (TFA-d_1) δ 1.15 (t, 3, J = 7 Hz, H-18), 2.17 (q, 2, J = 7 Hz, H-19), 5.78 (ABq, 2, J = 18 Hz, $\Delta\gamma$ = 85 Hz, H-17),, 5.86 (s, 2, H-5), 8.35–8.43 (m, 3, H-10, H-11, H-14), 8.65 (d, 1, J = 7 Hz, H-12), 9.78 (s, 1, H-7); $[\alpha]^{23}_D$ 16° (c 0.05, MeOH–$CHCl_3$, 1:4); HPLC retention time 9.7 min (1.5 mL/min; $CHCl_3$–MeOH 985:15). Anal. Calcd for $C_{20}H_{17}N_3O_4$: 363.1219. Found: 363.1216. ($C_{20}H_{17}N_3O_4 \cdot 0.8H_2O$) C, H, N.

12-Amino-20(*S*)-camptothecin (22).[21,22] 12-Nitro-20(*S*)-camptothecin (**20**) (50 mg, 0.127 mmol) was added in portions to a stirred solution/suspension of absolute EtOH (0.5 mL), concentrated HCl (0.6 mL), Sn powder (4 mg), and $SnCl_2 \cdot 2H_2O$ (127 mg) at −7 °C. After 1.5 h, the mixture was neutralized with 1 N NaOH and evaporated to dryness in vacuo. The residue was adsorbed onto Celite by evaporation of a solution of the crude **22** in MeOH–$CHCl_3$. Silica gel chromatography in the usual fashion afforded **22** (38 mg, 82%). Compound **22** was obtained as an orange-yellow amorphous solid from MeOH–$CHCl_3$ (13:87): mp gradual dec above 215 °C; [lit.[21] mp 278 °C]; IR (KBr) 3200–3400 (OH, NH_2), 1738 (lactone), 1652 (pyridone), 1593 (aromatic) cm^{-1}; ^1H NMR (TFA-d_1) δ 1.19 (t, 3, J = 7 Hz, H-18), 2.20 (q, 2, J = 7 Hz, H-19), 5.80 (ABq, 2, J = 18 Hz, $\Delta\gamma$ = 85 Hz, H-17), 5.74 (s, 2, H-5), 7.92 (t, 1, J = 8 Hz, H-10), 8.20 (d, 1, J = 8 Hz, H-9), 8.30 (d, 1, J = 8 Hz, H-11), 8.32 (s, 1, H-14), 8.80 (s, 1, H-7); $[\alpha]^{23}_D$ 18° (c 0.05, MeOH–$CHCl_3$, 1:4); HPLC retention time 3.2 min (1.5 mL/min; $CHCl_3$–MeOH, 985:15). Anal. Calcd for $C_{20}H_{17}N_3O_4$: 363.1219. Found: 363.1216. ($C_{20}H_{17}N_3O_4 \cdot 0.8H_2O$) C, H, N.

9-Nitro-10-methoxy-20(*S*)-camptothecin (23). 10-Methoxy-20(*S*)-camptothecin (**3**) (600 mg, 1.59 mmol) was dis-

(20) After we had completed our studies of compounds **19** and **21**, variations of our synthetic procedures were reported to give **19** and **21**, but without complete characterization: Yakult Honsha Co., Ltd. Japan Patent 59-51288, 1984; Chem. Abstr. 1984, *101*, 91322z.

(21) Although compounds **20** and **22** were reported earlier, experimental details and full characterization were lacking: Pan, P. C.; Pan, S. Y.; Tu, Y. H.; Wang, S. Y.; Owen, T. Y. *Hua Hsueh Hsueh Pao* **1975**, *33*, 71.

(22) We have given a brief account of the synthesis of **20** and **22** as part of another study: Ronman, P. E.; Wani, M. C.; Wall, M. E. *J. Labelled Compd. Radiopharm.* **1981**, *18*, 319. We wish to point out that the designation of **20** and **22** in that reference as racemic should be corrected to read as 20*S* configuration.

solved/suspended in concentrated H_2SO_4 (30 mL) at 0 °C. After 15 min, concentrated HNO_3 (0.75 mL) was added resulting in a gradual color change from yellow to lime over 15 min. After 30 min, the reaction mixture was poured into ice/H_2O (150 mL) and the resulting suspension extracted with portions of $CHCl_3$. The extracts were washed with H_2O, dried (Na_2SO_4), and evaporated to give compound **23** as a yellow solid (509 mg, 76%). Recrystallization of the sample from MeOH–$CHCl_3$ (13:87) gave pure **23** as a yellow microcrystalline solid: mp gradual dec and blackening above 220 °C; IR (KBr) 3440 (OH), 1752 (lactone), 1655 (pyridone), 1590 (aromatic), 1532 (NO_2) cm^{-1}; ^1H NMR (TFA-d_1) δ 1.16 (t, 3, J = 7 Hz, H-18), 2.19 (q, 2, J = 7 Hz, H-19), 4.32 (s, 3, OCH_3), 5.78 (ABq, 2, J = 18 Hz, $\Delta\gamma$ = 85 Hz, H-17), 5.85 (s, 2, H-5), 8.31 (d, 1, J = 9 Hz, H-11), 8.48 (s, 1, H-14), 8.85 (d, 1, J = 9 Hz, H-12), 9.28 (s, 1, H-7); $[\alpha]^{23}_D$ 21° (*c* 0.10, MeOH–$CHCl_3$, 1:4); HPLC retention time 5.1 min (2.0 mL/min; $CHCl_3$–MeOH, 995:5). Anal. Calcd for $C_{21}H_{17}N_3O_7$: 423.1066. Found: 423.1065. ($C_{21}H_{17}N_3O_7$), C, H, N.

9-Amino-10-methoxy-20(*S*)-camptothecin (24). A stirred solution/suspension of $SnCl_2 \cdot 2H_2O$ (600 mg) and Sn powder (25 mg) in a mixture of absolute EtOH and concentrated HCl (3 mL each) was cooled to 0 °C and treated portionwise with solid compound **23**. The turbid mixture was permitted to warm to room temperature during which time there was a color change from lemon to orange. After 4.5 h, the solvents were removed in vacuo. The tan residue was suspended/dissolved in MeOH (50 mL) and the pH adjusted to 6–7 using concentrated NH_4OH. The sample was diluted with $CHCl_3$ and adsorbed onto Celite (3 g). Chromatography through silica gel (20 g; gradient: 500 mL MeOH–$CHCl_3$, 2:98; 500 mL MeOH–$CHCl_3$, 7:93) afforded pure **24** as an orange solid (142 mg, 75%). Compound **24** resulted as an amorphous orange solid by precipitation from MeOH–$CHCl_3$ (13:87): mp 276–280 °C dec; IR (KBr) 3465, 3378 (NH_2), 3150 (OH), 1750 (lactone), 1650 (pyridone), 1585 (aromatic) cm^{-1}; ^1H NMR (TFA-d_1) δ 1.15 (t, 3, J = 7 Hz, H-18), 2.16 (q, 1, J = 7 Hz, H-19), 4.37 (s, 3, OMe), 5.78 (ABq, 2, J = 18 Hz, $\Delta\gamma$ = 85 Hz, H-17), 5.82 (s, 2, H-5), 8.29 (d, 1, J = 9.5 Hz, H-11), 8.35 (s, 1, H-14), 8.76 (d, 1, J = 9.5 Hz, H-12), 9.61 (s, 1, H-7); $[\alpha]^{23}_D$ 27.5° (*c* 0.04, MeOH–$CHCl_3$, 1:4); HPLC retention time 3.3 min (2.0 mL/min; $CHCl_3$–MeOH, 98:2). Anal. Calcd for $C_{21}H_{19}N_3O_5$: 393.1324. Found: 393.1329. ($C_{21}H_{19}N_3O_5 \cdot 0.5H_2O$) C, H, N.

9-Nitro-10-hydroxy-20(*S*)-camptothecin (25). 10-Hydroxy-20(*S*)-camptothecin (**2**) (160 mg, 0.44 mmol) was dissolved/suspended in 30% aqueous HNO_3 (10 mL) at room temperature. After 1 h, concentrated HNO_3 (70%, 1 mL) was added to the stirred, turbid orange mixture, and the reaction was left for 18 h. The clear orange solution was extracted repeatedly with $CHCl_3$, and the resulting yellow solution was washed with H_2O, dried (Na_2SO_4), and evaporated in vacuo to give crude **25** as a yellow solid (193 mg). The usual chromatography of the Celite-adsorbed material on silica gel using MeOH–$CHCl_3$ (1:9) gave pure **25** (85 mg, 47%). Recrystallization (MeOH–$CHCl_3$, 13:87) gave the compound as a microcrystalline solid: mp 206–210 °C; IR (KBr) 3405 (OH), 1741 (lactone), 1657 (pyridone), 1590 (aromatic), 1528 (NO_2) cm^{-1}; ^1H NMR (TFA-d_1) δ 1.15 (t, 3, J = 7 Hz, H-18), 2.17 (q, 2, J = 7 Hz, H-19), 5.79 (ABq, 2, J = 18 Hz, $\Delta\gamma$ = 85 Hz, H-17), 5.88 (s, 2, H-5), 7.26 (s, $CHCl_3$), 8.12 (d, 1, J = 9.5 Hz, H-11), 8.33 (s, 1, H-14), 8.74 (d, 1, J = 9.5 Hz, H-12), 10.36 (s, 1, H-7); $[\alpha]^{23}_D$ 33° (*c* 0.1, MeOH–$CHCl_3$, 1:4); HPLC retention time 4.2 (2.0 mL/min; $CHCl_3$–MeOH, 94:6). Anal. Calcd for $C_{20}H_{15}N_3O_7$: 409.0910. Found: 409.0911. ($C_{20}H_{15}N_3O_7 \cdot 0.25CHCl_3$) C, H, N.

9-Acetamido-10-hydroxy-20(*S*)-camptothecin (26). Compound **25** (150 mg, 0.367 mmol) was combined with PtO_2 (50 mg) in absolute EtOH (50 mL) and subjected to 1 atm of H_2 for 1.5 h. The catalyst was removed by filtration (Celite), and the filter pad was washed free of adsorbed organics using $CHCl_3$–MeOH. Concentration of the gold-colored filtrate (~250 mL) containing the unstable aminophenol intermediate to half its volume gave a turbid tan-yellow solution, was further treated with Ac_2O (1 mL). After 2.5 h, the resulting clear yellow solution was adsorbed onto Celite (0.75 g) and chromatographed by silica gel column (15 g; MeOH–$CHCl_3$, 1:9) to give the pure acetamido analogue **26** as a rusty-yellow solid (69 mg, 45% overall). Precipitation from MeOH–$CHCl_3$ (13:87) afforded **26** as a pale-orange powder: mp 255–258 °C dec; IR (KBr) 3200–3450 (OH, NH), 1740 (lactone), 1655 (pyridone, amide), 1590 (aromatic) cm^{-1}; ^1H NMR (TFA-d_1) δ 1.15 (t, 3, J = 7 Hz, H-18), 2.17 (q, 2, J = 7 Hz, H-19), 2.66 (s, 3, CH_3CO), 5.78 (ABq, 2, J = 18 Hz, $\Delta\gamma$ = 85 Hz, H-17), 5.83 (s, 2, H-5), 8.11 (d, 1, J = 9.5 Hz, H-11), 8.29 (s, 1, H-14), 8.41 (d, 1, J = 9.5 Hz, H-12), 9.34 (s, 1, H-7); $[\alpha]^{23}_D$ 25.4° (*c* 0.067, MeOH–$CHCl_3$, 1:4); HPLC retention time 4.7 min (2.0 mL/min; $CHCl_3$–MeOH, 8:2). Anal. Calcd for $C_{22}H_{19}N_3O_6$: 421.1273. Found: 421.1277. ($C_{22}H_{19}N_3O_6 \cdot 2.0H_2O$) C, H, N.

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Synthesis and Structure–Activity Relationships of New Arylfluoronaphthyridine Antibacterial Agents[1]

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Novel arylfluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids have been prepared and their antibacterial activity evaluated. These derivatives are characterized by having a fluorine atom at the 6-position, substituted amino groups at the 7-position, and substituted phenyl groups at the 1-position. The in vitro antibacterial potency is greatest when the 1-substituent is either *p*-fluorophenyl or *o,p*-difluorophenyl and the 7-substituent is a 3-amino-1-pyrrolidinyl group. 1-(2,4-Difluorophenyl)-6-fluoro-7-(3-amino-1-pyrrolidinyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**38**) was found to possess excellent in vitro potency and in vivo efficacy.

In earlier papers, we reported the syntheses and antibacterial activities of 7-(substituted amino)-6-fluoro-1-aryl-1,4-dihydro-4-oxoquinoline-3-carboxylic acids (**1**)[2] and benzothiazolo[3,2-*a*]quinoline derivatives (**2**).[3] These

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