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Addition of Ester Enolates to *N*-Alkyl-2-fluoropyridinium Salts: Total Synthesis of (±)-20-Deoxycamptothecin and (+)-Camptothecin

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Several 4-substituted dihydropyridones or 2-pyridones have been prepared by nucleophilic addition of α-(methylsulfanyl)ester enolates to *N*-alkyl-2-fluoropyridinium salts, followed by acid hydrolysis or oxidation with concomitant hydrolysis, of the intermediate 2-fluoro-1,4-dihydropyridine adducts, respectively. Addition of the enolate derived from isopropyl α-(methylsulfanyl)butyrate to *N*-(quinolylmethyl)-2-fluoropyridinium triflate **21** followed by DDQ treatment gave pyridone **29**, from which (±)-20-deoxycamptothecin (**31**), a known precursor of camptothecin, was synthesized by a radical cyclization–desulfurization, with subsequent elaboration of the lactone E ring by chemoselective reduction. A similar sequence starting from the enolate of a chiral 2-hydroxybutyric acid derivative (**33**) provides access to natural (+)-camptothecin (**37**).

Introduction

The addition of carbon nucleophiles to pyridinium salts constitutes a classical approach for the formation of C–C bonds in the synthesis of nitrogen compounds embodying a partially or totally reduced pyridine ring.[1] Over the past years, we have been actively studying the reaction of indole-containing enolates with 3-acyl-*N*-alkylpyridinium salts as the initial step of a general and versatile method for the synthesis of indole alkaloids.[2,3] The high reactivity of the resultant 1,4-dihydropyridine adducts[4] has allowed the straightforward construction of complex polycyclic structures, either by acylation of the unsubstituted enamine moiety[5] or via a dihydropyridinium cation generated by protonation[6] or interaction with an electrophile.[5b,7]

We envisaged the use of *N*-alkyl-2-*fluoro*pyridinium salts in the above methodology as a complementary and appealing approach to more functionalized compounds that could also be of use in alkaloid synthesis. Our initial efforts in this field were rewarded when we accomplished a formal synthesis of the indole alkaloid akagerine.[8] We went on to consider the reaction sequence depicted in Scheme 1. If the regioselective addition of an appropriate carbon nucleophile (e.g. an ester enolate) to the 4-position of the ring could be ensured, the intensive functionalization of the initially formed 2-fluoro-1,4-dihydropyridine adducts **A** might give rapid access to dihydro-2-pyridones **B** or 2-pyridones **C**, which bear an α-(alkoxycarbonyl)alkyl substituent at the 4-position, either by hydrolysis of the C–F bond[9] or oxidation with concomitant hydrolysis, respectively. Compounds **B** constitute useful building blocks as they contain two reactive sites (an enamide double bond[10] and a lactam carbonyl group[11]) for further functionalization. On the other hand, 2-pyridones **C** can be recognized as the ring D of the important

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(1) For compilations on this subject, see: (a) Bennasar, M.-L.; Lavilla, R.; Alvarez, M.; Bosch, J. *Heterocycles* **1988**, 27, 789–824. (b) Comins, D. L.; Joseph, S. P. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds; Pergamon: London, UK, 1996; Vol. 5, pp 70–78. (c) Comins, D. L.; Joseph, S. P. In *Advances in Nitrogen Heterocycles*; Moody, C. J., Ed.; JAI Press: London, UK, 1996; Vol. 2, pp 251–294.

(2) For the pioneering use of this reactivity pattern for the construction of indoloquinolizidine alkaloids, see: Wenkert, E. *Pure Appl. Chem*. **1981**, *53*, 1271–1276. (b) Wenkert, E.; Angell, E. C.; Drexler, J.; Moeller, P. D. R.; Pyrek, J. S.; Shi, Y.-J.; Sultana, M.; Vankar, Y. D. *J. Org. Chem*. **1986**, *51*, 2995–3000.

(3) For a review, see: Bosch, J.; Bennasar, M.-L. *Synlett* **1995**, 587–596.

(4) For reviews on the rich chemistry of dihydropyridines, see: (a) Eisner, U.; Kuthan, J. *Chem. Rev*. **1972**, 72, 1–42. (b) Stout, D.; Meyers, A. I. *Chem. Rev*. **1982**, *82*, 223–243. (c) Sausins, A.; Duburs, G. *Heterocycles* **1988**, *27*, 291–314. (d) Lavilla, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141–1156.

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(7) (a) Bennasar, M.-L.; Vidal. B.; Bosch, J. *J. Am. Chem. Soc*. **1993**, *115*, 5340–5341. (b) Bennasar, M.-L.; Vidal. B.; Bosch, J. *J. Chem. Soc., Chem. Commun*. **1995**, 125–126.

(8) Bennasar, M.-L.; Jiménez, J.-M.; Vidal, B.; Sufi, B. A.; Bosch, J. *J. Org. Chem*. **1999**, *64*, 9605–9612.

(9) For the hydrolysis of the C–F bond in 2-fluoropyridines, see: (a) Rocca, P.; Cochennec, C.; Marsais, F.; Thomas-dit-Dumont, L.; Mallet, M.; Godard, A.; Quéguiner, G. *J. Org. Chem*. **1993**, *58*, 7832–7838. (b) Comins, D. L.; Saha, J. K. *Tetrahedron Lett*. **1995**, *36*, 7995–7998.

(10) For *N*-acyliminium chemistry on enamides, see: Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 2, pp 1047–1082.

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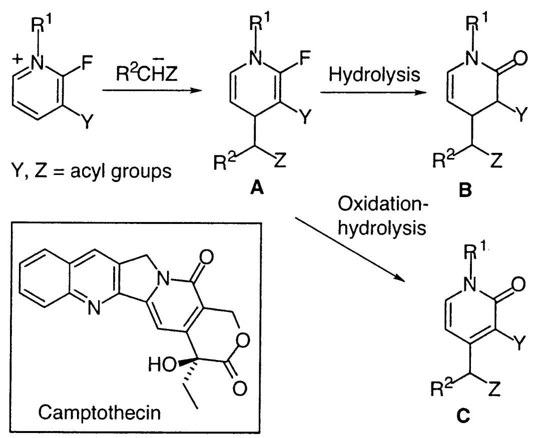
SCHEME 1. 3-Acyl-2-fluoropyridinium Salts: Synthetic Possibilities



pyrroloquinoline alkaloid camptothecin. This paper deals with our work on *N*-alkyl-2-fluoropyridinium salts based on the above concepts, and presents as the most significant results the concise total syntheses of (±)-20-deoxycamptothecin[12] and natural (+)-camptothecin.

Results and Discussion

Synthesis of 4-[α-(Methoxycarbonyl)alkyl]dihydro-2-pyridones. The introduction of functionalized alkyl groups at the 4-position of a pyridine nucleus has received considerable attention and different nucleophilic reagents have been tested.[13] In a previous work,[14] we have shown that α-(methylsulfanyl)ester enolates smoothly undergo addition to 3-acyl-*N*-alkylpyridinium salts, with higher chemoselectivity and C-4 regioselectivity than simple ester enolates.[15] With the final aim of reaching 4-substituted dihydro-2-pyridones, we then decided to study the behavior of sulfanylester enolates toward 3-acetyl-2-fluoropyridinium salts **2a** and **2b**. These salts were efficiently prepared by alkylation of 3-acetyl-2-fluoropyridine (**1**) with methyl or benzyl triflate[16] and immediately treated with the lithium enolates derived from esters **3** and **4** (Scheme 2). After column chromatography of the crude reaction products, the expected

SCHEME 2

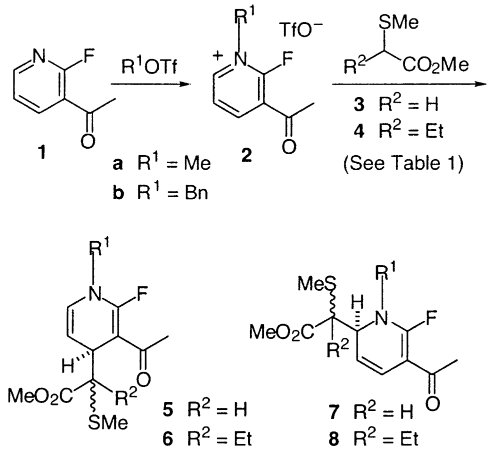


TABLE 1. Reactions of 3-Acetyl-2-fluoropyridinium Salts 2 with Lithium Enolates Derived from Esters 3 and 4

entry	pyridinium salt	ester	products[a] (ratio)	yield (%)
1	**2a**	**3**	**5a** + **7a** (1:1)	60
2	**2a**	**4**	**6a** + **8a** (4:1)	55
3	**2b**	**3**	**5b** + **7b** (5:1)	50
4	**2b**	**4**	**6b**	55

[a] Epimeric mixtures at the ester α carbon.

2-fluorodihydropyridine adducts **5**,**6** or **7**,**8** were obtained in the ratios and yields listed in Table 1.

As can be observed, the addition of the lithium enolate derived from acetic ester **3** to *N*-methylpyridinium triflate **2a** was not regioselective, leading to a nearly equimolecular mixture of 1,4- and 1,2-dihydropyridines **5a** and **7a** in 60% yield (entry 1). More satisfactorily, a 4:1 mixture of dihydropyridines **6a** and **8a** was obtained in similar yield (55%, entry 2) when the enolate derived from butyric ester **4** was used as the nucleophile. On the other hand, *N*-benzylpyridinium triflate **2b** was a more convenient electrophilic substrate as it led to the respective 2-fluoro-1,4-dihydropyridines **5b** (from **3**, entry 3) or **6b** (from **4**, entry 4) as the major or even only product. The regioselectivity of the above reactions seems to depend on steric factors, the desired C-4 attack being favored by the bulkiness of both the substituent at the pyridine nitrogen and the enolate.

The ^{1}H NMR spectra of 2-fluoro-1,4-dihydropyridines **5a**,**b** and **6a**,**b** showed the typical 1,4-dihydropyridine pattern complicated by the ^{1}H−^{19}F coupling (see Experimental Section). As expected, **5a** and **5b** were easily transformed into the respective methyl (2-oxo-1,2,3,4-tetrahydro-4-pyridyl)acetates **9a** and **9b** by acid hydrolysis of the C−F bond with 1 N HCl, followed by desulfurization with *n*-Bu_3SnH−AIBN. The overall yield of both transformations was satisfactory (75−80%, Scheme 3). Similarly, dihydropyridones **10a** and **10b** were obtained in good yield by acid hydrolysis of **6a** and **6b**, respectively (Scheme 3).

We assigned the most stable trans relative configuration to **9a**,**b** and **10a**,**b** after inspecting their ^{1}H NMR spectra. It is worth mentioning that these *β*-dicarbonyl compounds showed a different tautomeric behavior. Thus, whereas **9a**,**b** appeared as a 2:1 mixture of keto and enol forms, the latter with the enol double bond presumably

(11) For the chemistry of lactam-derived vinyl triflates, see: (a) Foti, C. J.; Comins, D. L. *J. Org. Chem.* **1995**, *60*, 2656−2657. (b) Luker, T.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 8131−8140. (c) Occhiato, E.; Trabocchi, A.; Guarna, A. *J. Org. Chem.* **2001**, *66*, 2459−2465.

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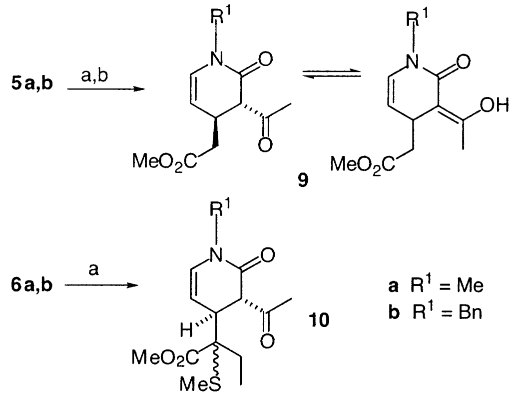
(15) For the addition of these nucleophiles to *N*-alkylpyridinium salts followed by acid-induced cyclization on the indole nucleus, see: Spitzner, D.; Zaubitzer, T.; Shi, Y. J.; Wenkert, E. *J. Org. Chem.* **1988**, *53*, 2274−2278. See also ref 2b.

(16) Alkylation of 2-halopyridines with alkyl halides and tosylates is a difficult process: (a) Dobbs, A. P.; Jones, K.; Veal, K. T. *Tetrahedron Lett.* **1997**, *38*, 5383−5386. (b) Vega, J. A.; Vaquero, J. J.; Alvarez-Builla, J.; Ezquerra, J.; Hamdouchi, C. *Tetrahedron* **1999**, *55*, 2317−2326.

SCHEME 3[a]



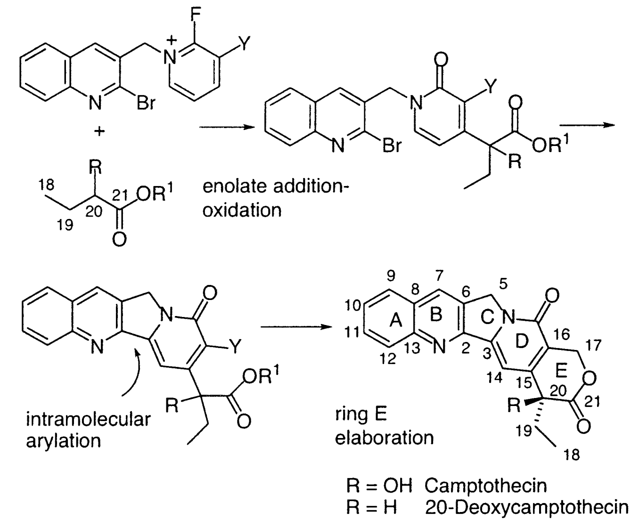
[a] Key: (a) 1 N HCl, THF, rt, 3 h; (b) *n*-Bu_3SnH-AIBN, C_6H_6, reflux, 2 h.

in a *Z* configuration, **10a**,**b** were exclusively in the keto form. It seems reasonable to assume that the predominance of the keto form increases with the size of the substituent at the 4-position of the ring, due to A1,3 strain in the enol form with the methyl group at the sp^2 carbon.

Synthesis of Camptothecins. Camptothecin and 20-deoxycamptothecin[17] are pentacyclic alkaloids with a pyrrolo[3,4-*b*]quinoline nucleus fused to a 2-pyridone ring. First isolated by Wall et al. in 1966 from *Camptotheca acuminata*,[18] camptothecin is an important lead compound among the anticancer natural products, the identified intracellular target for the drug being topoisomerase I.[19] This interesting cytotoxic activity has made camptothecin and its structural derivatives attractive objectives for chemical synthesis.[20,21]

Our approach to camptothecins is based on the convergent construction of a suitably substituted and functionalized tetracyclic ABCD derivative from an *N*-(quinolylmethyl)-2-fluoropyridinium salt and the closure of the lactone E ring at the final synthetic step (Scheme 4). Thus, the regioselective addition of the enolate of a butyric acid derivative (the $C_{18}-C_{21}$ fragment) to this 2-fluoropyridinium salt, followed by oxidation of the intermediate 2-fluoro-1,4-dihydropyridine with concomitant hydrolysis of the C−F bond, would lead to a 4-substituted-2-pyridone. Then, the quinoline and pyridone rings would be connected by a radical cyclization taking advantage of a bromine atom present at the 2-position of the quinoline nucleus (Comins procedure).[9b,21d,e,n] The one-carbon substituent (Y) at the β-position of the starting pyridinium salt would be subsequently converted to the C-17 oxymethylene group of the alkaloid.

SCHEME 4. Synthetic Approach to Camptothecins



To test the feasibility of our proposal for the construction of the 2-pyridone moiety we undertook a brief study of the nucleophilic addition−2-fluorodihydropyridine oxidation sequence starting from model *N*-benzyl-2-fluoropyridinium salts **12**, which bear a variety of one-carbon substituents at the β-position (Scheme 5, Table 2). The good C-4 regioselectivity exhibited by α-(methylsulfanyl)-butyrate **4** toward 2-fluoropyridinium salts **1** made its use in this sequence particularly attractive. As in the above 3-acetyl series, 2-fluoropyridinium salts **12** were easily prepared by benzyl triflate alkylation of the respective pyridines **11**, which, with the exception of commercially available **11c**, were obtained by ortholithiation of 2-fluoropyridine followed by reaction with a suitable electrophile.[22]

We first focused our attention on 2-fluoropyridinium triflates **12a** and **12b**, whose substitution pattern would allow access to the C-17 oxymethylene group of camptothecin by reduction. Satisfactorily, only the desired C-4 adduct **14a** (mixture of epimers) was isolated from the reaction of ester **4** with 2-fluoro-3-(methoxycarbonyl)-pyridinium triflate **12a** (entry 1). In contrast, only trace amounts of 1,4-dihydropyridine **14b** were obtained from 3-formylpyridinium triflate **12b** (entry 2), probably due

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(19) Fan, Y.; Weinstein, J. N.; Kohn, K. W.; Shi, L. M.; Pommier, Y. *J. Med. Chem.* **1998**, *41*, 2216−2226 and references therein.

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(21) For more recent syntheses of camptothecin, see: (a) Shen, W.; Coburn, G. A.; Bornmann, W. G.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 611−617. (b) Rama Rao, A. V.; Yadav, J. S.; Valluri, M. *Tetrahedron Lett.* **1994**, *35*, 3613−3616. (c) Fang, F. G.; Xie, S.; Lowery, M. W. *J. Org. Chem.* **1994**, *59*, 6142−6143. (d) Comins, D. L.; Hong, H.; Saha, J. K.; Jianhua, G. *J. Org. Chem.* **1994**, *59*, 5120−5121. (e) Comins, D. L.; Hoang, H.; Jianhua, G. *Tetrahedron Lett.* **1994**, *35*, 5331−5334. (f) Jew, S.; Ok, K.; Kim, H.; Kim, M. G.; Kim, J. M.; Hah, J. M.; Cho, Y. *Tetrahedron: Asymmetry* **1995**, *6*, 1245−1248. (g) Fortunak, J. M. D.; Kitteringham, J.; Mastrocola, A. R.; Mellinger, M.; Sisti, N. J.; Wood, J. L.; Zhuang, Z.-P. *Tetrahedron Lett.* **1996**, *37*, 5683−5686. (h) Murata, N.; Sugihara, T.; Kondo, Y.; Sakamoto, T. *Synlett* **1997**, 298−300. (i) Ciufolini, M. A.; Roschangar, F. *Tetrahedron* **1997**, *53*, 11049−11060. (j) Chavan, S. P.; Venkatraman, M. S. *Tetrahedron Lett.* **1998**, *39*, 6745−6748. (k) Josien, H.; Ko, S.-B.; Bom, D.; Curran, D. P. *Chem. Eur. J.* **1998**, *4*, 67−83. (l) Tagami, K.; Nakazawa, N.; Sano, S.; Nagao, Y. *Heterocycles* **2000**, *53*, 771−775. (m) Brown, R. T.; Jianli, L.; Santos, C. A. M. *Tetrahedron Lett.* **2000**, *41*, 859−862. (n) Comins, D. L.; Nolan, J. M. *Org. Lett.* **2001**, *3*, 4255−4257. (o) Yabu, K.; Masumoto, S.; Kanai, M.; Curran, D. P.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 2923−2926.

(22) For a recent review on the ortho-metalation of pyridines and quinolines, see: Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4059−4090.

SCHEME 5. Model Studies

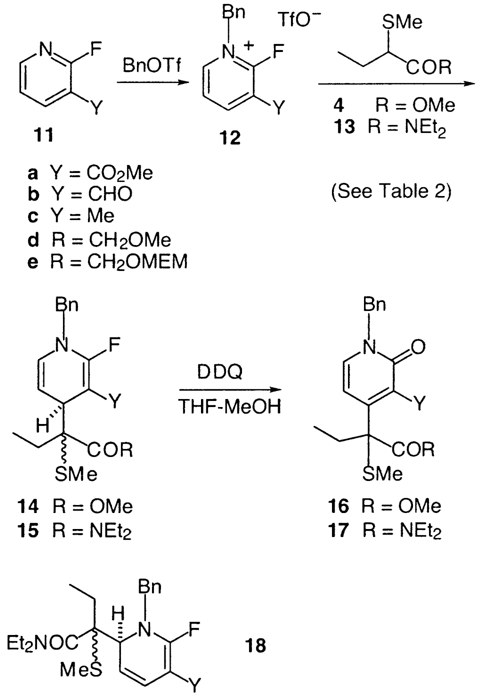


TABLE 2. Reactions of 2-Fluoropyridinium Salts 12a−e with Lithium Enolates Derived from 4 and 13 Followed by Oxidation

entry	pyridinium salt	Li-enolate derived from	adduct	pyridone (overall yield, %)[a]
1	**12a**	**4**	**14a**	**16a** (65)
2	**12b**	**4**	**14b** (trace)	
3	**12a**	**13**	**15a** + **18a** (4:1)	**17a** (50)
4	**12c**	**4**	**14c**	**16c** (30)
5	**12d**	**4**		complex mixtures
6	**12e**	**4**		complex mixtures

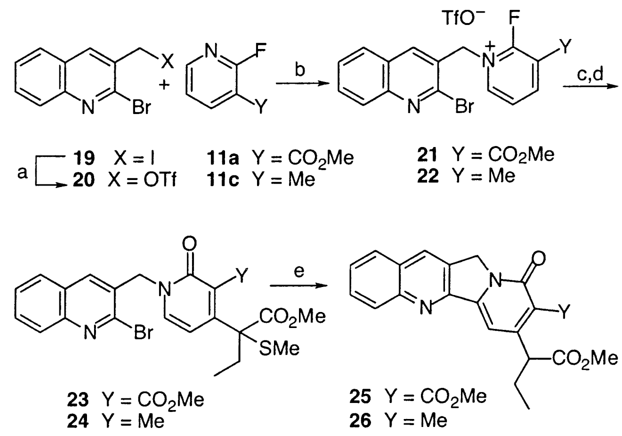
[a] From the corresponding pyridine **11**.

to the low chemoselectivity of the nucleophilic addition. As expected, treatment of **14a** with DDQ in THF−MeOH resulted in oxidation with concomitant hydrolysis of the C−F bond to give pyridone **16a** in 65% overall yield from 2-fluoropyridine **11a**.

We also considered using the enolate derived from α-(methylsulfanyl)butyramide **13** in order to subsequently reach 2-pyridones with a different functionalization for the lactonization step. As can be observed in entry 3, its reaction with 2-fluoropyridinium salt **12a** was less regioselective, leading to a 4:1 mixture of C-4 and C-6 adducts, **15a** and **18a**. DDQ treatment of **15a** gave pyridone **17a** in 50% overall yield from **11a**.

The behavior of pyridinium triflates **12c**−**e**, lacking the characteristic β-acyl substituent, was also investigated. We were pleased to observe that 2-fluoro-3-methylpyridinium triflate **12c** was electrophilic enough to participate in the addition−oxidation sequence with ester **4** to give pyridone **16c** (through **14c**, not isolated) in 30% overall yield from **11c**. Unfortunately, we were not able to extend the chemistry outlined above to pyridinium triflates **12d** or **12e**, which carry protected hydroxymethyl groups with the same oxidation level as C-17 of camptothecin.

SCHEME 6. Construction of the Pyrrolo[3,4-*b*]quinoline System[a]



[a] Key: (a) AgOTf, CH_2Cl_2, rt, 30 min; (b) CH_2Cl_2, rt, 30 min; (c) ester **4**, LDA, THF, −78 °C, then −30 °C, 1.5 h; (d) DDQ, THF−MeOH, rt, 4 h; (e) TTMSS (2 equiv), AIBN, C_6H_6, reflux, 4 h.

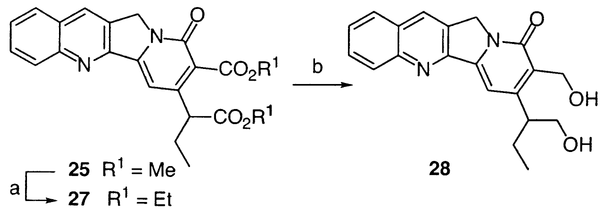
The application of the above strategy to the construction of the pyrrolo[3,4-*b*]quinoline system of camptothecins required starting from pyridinium salts **21** or **22**, which incorporate the 2-bromo-3-quinolylmethyl fragment needed for the closure of the five-membered C ring. These salts were obtained by alkylation of 2-fluoropyridines **11a** or **11c** with triflate **20**, prepared from 2-bromo-3-(iodomethyl)quinoline (**19**). The resulting pyridinium triflates **21** and **22** were allowed to react as in the above *N*-benzyl series with the enolate derived from methyl ester **4** and then with DDQ to provide pyridones **23** and **24** in 50% and 30% overall yield from **11a** and **11c**, respectively. Our first attempts to assemble the desired tetracyclic system by radical cyclization using the *n*-Bu_3SnH−AIBN conditions reported by Comins[21e] resulted in premature reductive dehalogenation. However, satisfactorily, treatment of **23** and **24** with the poorer hydrogen atom donor tris(trimethylsilyl)silane (TTMSS)[23]−AIBN brought about both a radical arylation[24] and desulfurization to give the key tetracycles **25** and **26** in 70% and 65% yield (Scheme 6).

Completion of the pentacyclic system of camptothecin from diester **25** required the seemingly simple task of chemoselectively reducing the conjugate rather than the aliphatic ester so that lactonization to 20-deoxycamptothecin could occur. This reductive route had already been reported from the diethyl ester analogue **27** by treatment with DIBAL (no details given).[21j] However, in our hands, the sequential treatment of **25** with DIBAL−CH_2Cl_2 at −78 °C or DIBAL−THF at −40 °C and $NaBH_4$ gave diol **28** as the only isolable product in 80% yield (Scheme 7). Neither were we able to induce this transformation from diethyl ester **27**, prepared in 90% yield by transesterification of **25**. Diol **28** was also formed as the major product in 75% yield.

Given the difficulties encountered in the chemoselective reduction of tetracycles **25** or **27**, we decided to tackle

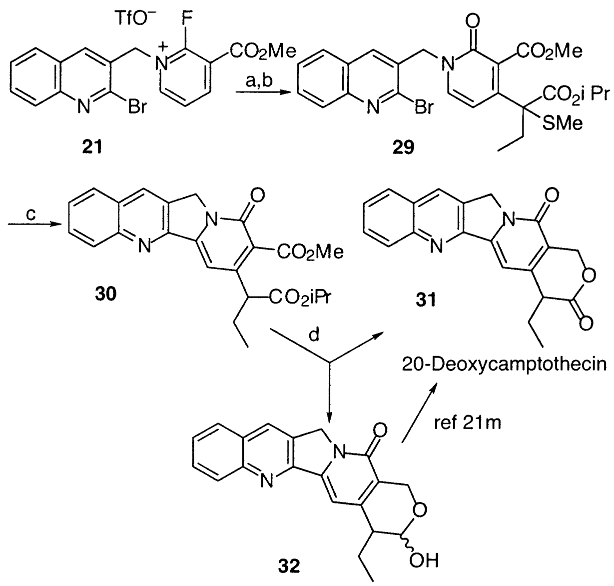
(23) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188−194.
(24) For the radical arylation of 2-pyridones, see: (a) Nadin, R.; Harrison, T. *Tetrahedron Lett.* **1999**, *40*, 4073−4076. (b) Orito, K.; Satoh, Y.; Nishizawa, H.; Harada, R.; Tokuda, M. *Org. Lett.* **2000**, *2*, 2535−2537. (c) See also ref 21e.

SCHEME 7[a]



[a] Reagents and conditions: (a) KF, EtOH, reflux, 40 h; (b) DIBAL−CH_2Cl_2, CH_2Cl_2, −78 °C or DIBAL−THF, THF, −40 °C, then $NaBH_4$.

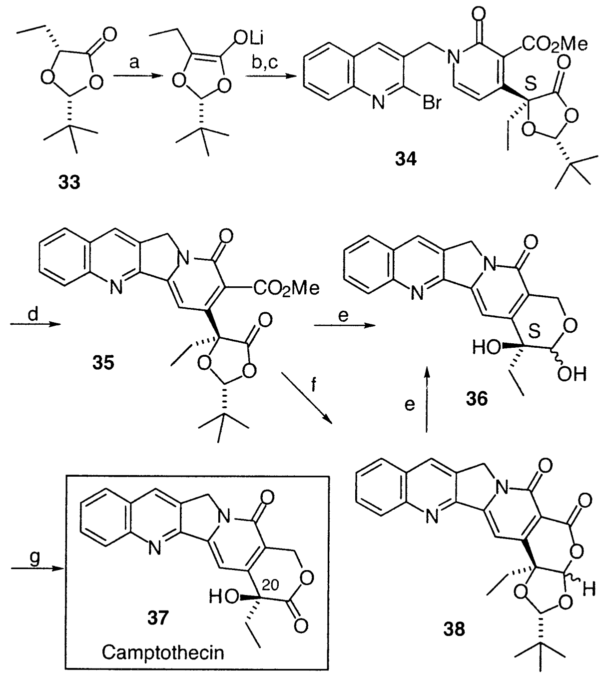
SCHEME 8. Synthesis of (±)-20-Deoxycamptothecin[a]



[a] Key: (a) isopropyl α-(methylsulfanyl)butyrate, LDA, THF, −78 °C, then −30 °C, 1.5 h; (b) DDQ, 2:1 THF−MeOH, rt, 12 h; (c) TTMSS (2 equiv), AIBN, C_6H_6, reflux, 4 h; (d) DIBAL−hexane (3 equiv), DME, −70 °C, 15 min, then $NaBH_4$, *i*PrOH, rt, 30 min.

the problem by differentiating the two ester groups as in the pioneering Winterfeldt synthesis of camptothecin from a closely related tetracyclic substrate.[25] Thus, we turned our attention to tetracycle **30** (Scheme 8), which was prepared by reaction of pyridinium triflate **21** with the enolate derived from isopropyl α-(methylsulfanyl)-butyrate, followed by DDQ oxidation (50% overall yield from **11a**) and subsequent radical cyclization (70% yield). Gratifyingly, treatment of **30** with DIBAL−hexanes in DME at −70 °C and then with $NaBH_4$ in 2-propanol afforded a 1:1 mixture of the target lactone **31** (20-deoxycamptothecin) and lactol **32** (65% yield), which were easily separated by column chromatography. The conversion of lactol **32** into **31** (65% yield) by PCC treatment has recently been reported.[21m] NMR data of synthetic **31** were identical with those described for this product.[21a] Considering that (±)-20-deoxycamptothecin (**31**) has previously been converted by hydroxylation at C-20 to either racemic[21a,25] or natural (+)-camptothecin[21l] the

SCHEME 9. Synthesis of (+)-Camptothecin[a]



[a] Key: (a) LDA, THF, −78 °C, 30 min; (b) **21**, −30 °C, 1.5 h; (c) DDQ, 2:1 THF−MeOH, rt, 4 h; (d) TTMSS (2 equiv), AIBN, C_6H_6, reflux, 4 h; (e) DIBAL−CH_2Cl_2, −78 to −30 °C, 45 min; (f) DIBAL−CH_2Cl_2, −78 °C, 30 min; (g) I_2, $CaCO_3$, 10:1 MeOH−H_2O, rt, 4 days.

synthesis reported here constitutes a formal synthesis of this natural product.

The success of the above synthesis motivated us to pursue a more ambitious goal, the total synthesis of natural (+)-camptothecin, taking advantage of the same methodology but using the enolate of a chiral 2-*hydroxy*-butyric acid derivative in the nucleophilic addition step to the 2-fluoropyridinium ring.[26]

The enolate of (2*R*,5*R*)-2-*tert*-butyl-5-ethyl-1,3-dioxolan-4-one (**33**),[27] derived from (*R*)-2-hydroxybutyric acid, was the nucleophile of choice as it had proven to react with electrophiles (allyl bromide[27] and an α,*β*-unsaturated diester[21g]) in a highly diastereoselective manner from the opposite side to the *tert*-butyl group. We expected that this enolate would react in the same way with 2-fluoropyridinium salt **21** to give, after the oxidation step, a 2-pyridone incorporating the stereogenic center with the desired configuration (20*S*). The remainder of the synthesis would closely parallel the racemic synthesis, the hydroxyacid moiety[28] being reestablished at the final lactonization step (Scheme 9).[21g]

We were pleased to find that the addition of the lithium enolate of **33** to 2-fluoropyridinium triflate **21** followed by DDQ oxidation gave pyridone **34** as a single diastereomer (NMR), whose configuration at the C-5 of the dioxolanone ring was tentatively assigned as *S* taking into account the above precedents. The overall yield of

(25) (a) Winterfeldt, E.; Korth, T.; Pike, D.; Boch, M. *Angew. Chem., Int. Ed.* **1972**, *11*, 289−290. (b) Krohn, K.; Winterfeldt, E. *Chem. Ber.* **1975**, *108*, 3030−3042.

(26) For the use of chiral nucleophiles toward *N*-alkyl-3-acylpyridinium salts, see: (a) Amann, R.; Arnold, K.; Spitzner, D.; Majer, Z.; Snatzke, G. *Liebigs Ann.* **1996**, 349−355. (b) See also ref 6e.

(27) Krohn, K.; Hamann, I. *Liebigs Ann.* **1988**, 949−953.

(28) For the development of this concept ("self-reproduction of chirality"), see: Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313−1324.

this key transformation was lower (20% from **11a**) than that observed in the above racemic series. Some variations of the reaction conditions (temperature, time, base) were examined, but they did not significantly alter the yield. Nevertheless, we went on with the next step of the synthesis, i.e., the intramolecular arylation of **34**. This was accomplished by treatment with TTMSS−AIBN, providing the desired tetracycle **35** in 65% yield.

The remaining challenge at this point was to find the right conditions for the lactonization step, which would now involve the chemoselective reduction of the conjugated methoxycarbonyl rather than the dioxolanone carbonyl group to give a hydroxymethyl derivative, and the subsequent intramolecular transesterification with loss of pivalaldehyde. In fact, we did not expect many difficulties since it had been reported that the sequential treatment of the 10-methoxy derivative of **35** with DIBAL in CH_2Cl_2 (no conditions given), $NaBH_4$, and aqueous NaOH produced (*S*)-10-methoxycamptothecin in 70% yield.[21g] To our surprise, when tetracycle **35** was treated with DIBAL in CH_2Cl_2 at −78 °C for 30 min and then with $NaBH_4$ we cleanly obtained a single product (65% yield), which was identified as hexacycle **38** after a careful inspection of the mono- and bidimensional (HSQC and HMBC) NMR spectra. The formation of hexacycle **38** was striking as it involved the initial reduction of the lactone carbonyl group and the subsequent relactonization of the initially formed lactol with the *intact* methoxycarbonyl group.

However, α-hydroxylactol **36**, a dihydroderivative of camptothecin, was the main product (45%) when the reduction of **35** with DIBAL in CH_2Cl_2 was effected at a higher temperature (−30 °C). Lactol **36** was also obtained when hexacycle **38** was subjected to similar reduction conditions, thus confirming that the latter was an intermediate in the transformation of **35** to **36**. The formation of **36** must therefore involve the double reduction of the C-17 carbonyl group, followed by hemiacetalization with loss of pivalaldehyde. Finally, as expected, α-hydroxylactol **36** could be converted in 60% yield into (+)-camptothecin (**37**) by oxidation with iodine in the presence of $CaCO_3$.[29] Our synthetic (+)-camptothecin, $[\alpha]^{22}_D$ +25 (*c* 0.2, 4:1 $CHCl_3$−MeOH) (lit.[18] $[\alpha]^{22}_D$ +31 (4:1 $CHCl_3$−MeOH)), showed NMR spectra and chromatographic behavior identical with an authentic material.

In summary, we have shown that the nucleophilic addition of ester enolates to 2-fluoropyridinium salts followed by suitable manipulation of the resultant 2-fluoro-1,4-dihydropyridine adducts provides a rapid synthetic entry to highly functionalized and substituted dihydro-2-pyridones or 2-pyridones. The effectiveness of the strategy is illustrated in the concise total synthesis of (±)-camptothecin and natural (+)-camptothecin.

Experimental Section

General Procedures. Reactions courses and product mixtures were routinely monitored by TLC on silica gel (precoated F_{254} Merck plates). Drying of organic extracts during the workup of reactions was performed over anhydrous Na_2SO_4. Evaporation of the solvents was accomplished under reduced pressure with a rotatory evaporator. Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 0.04−0.06 mm). Melting points are uncorrected. Unless otherwise indicated, NMR spectra were recorded in $CDCl_3$ solution at 300 (^1H) or 75.4 MHz (^{13}C), using TMS as internal reference. Microanalyses and HRMS were performed by Centro de Investigación y Desarrollo (CSIC), Barcelona.

3-Acetyl-2-fluoro-1-methylpyridinium Trifluoromethanesulfonate (2a). CF_3SO_2Me (0.27 mL, 2.5 mmol) was added to 3-acetyl-2-fluoropyridine (**1**)[30] (0.23 g, 1.65 mmol) at room temperature under Ar. The resulting mixture was diluted with dry CH_2Cl_2 (3 mL) and stirred at room temperature for 10 min. The white precipitate was filtered and washed with anhydrous Et_2O to give pyridinium triflate **2a**, which was immediately used in the next reaction.

3-Acetyl-1-benzyl-2-fluoropyridinium Trifluoromethanesulfonate (2b). Benzyl bromide (0.26 mL, 2.16 mmol) was added to a suspension of CF_3SO_2Ag (0.55 g, 2.16 mmol) in dry Et_2O (2 mL) at room temperature under Ar. A yellow-green precipitate (AgBr) was formed. The reaction mixture was filtered over pyridine **1** (0.2 g, 1.44 mmol) and the resulting suspension was stirred at room temperature for 10 min. The solvent was removed under an Ar stream to give a white gum, which was immediately used in the next reaction.

Reaction of Pyridinium Triflate 2a with the Enolate Derived from 3. LDA 1.5 M in cyclohexane (1.33 mL, 2 mmol) was added under Ar to a solution of acetate **3** (0.22 mL, 2 mmol) in THF (15 mL) cooled at −78 °C, and the resulting mixture was stirred at −78 °C for 30 min. A suspension of pyridinium triflate **2a** (prepared from 1.65 mmol of **1**) in THF (5 mL) was added, and the mixture was stirred at −30 °C for 1.5 h. The reaction mixture was poured into H_2O and extracted with Et_2O. The organic extracts were concentrated and the resulting residue was chromatographed (7:3 hexanes−AcOEt) to give a 1:1 mixture of fluorodihydropyridines **5a** and **7a** (270 mg, 60%). An additional chromatograph (CH_2Cl_2) allowed the isolation of pure **methyl 3-acetyl-2-fluoro-1-methyl-α-(methylsulfanyl)-1,4-dihydropyridine-4-acetate** (**5a**, epimeric mixture). Less polar epimer: mp 95 °C (Et_2O−hexanes); ^1H NMR δ 2.14 (s, 3H), 2.36 (d, J = 7.3 Hz, 3H), 3.09 (d, J = 2.5 Hz, 3H), 3.45 (d, J = 3 Hz, 1H), 3.74 (s, 3H), 4.32 (ddd, J = 5.4, 3, 1.6 Hz, 1H), 5.10 (ddd, J = 7.6, 5.4, 1.8 Hz, 1H), 5.88 (dd, J = 7.6, 5 Hz, 1H); ^{13}C NMR δ 16.2 (CH_3), 30.7 (CH_3), 34.3 (CH_3), 37.4 (CH), 52.0 (CH_3), 55.1 (CH), 90.5 (C), 105.8 (CH), 129.9 (CH), 161.2 (C, J = 262.5 Hz), 172.4 (C), 193.0 (C). Anal. Calcd for $C_{12}H_{16}FNSO_3\cdot{}^1/_4H_2O$: C, 51.88; H, 5.98; N, 5.04. Found: C, 51.66; H, 6.30; N, 5.10.

Reaction of Pyridinium Triflate 2a with the Enolate Derived from 4. Operating as above, from pyridinium triflate **2a** (prepared from 1.65 mmol of **1**) and ester **4** (0.36 mL, 2.5 mmol) a 4:1 mixture of fluorodihydropyridines **6a** and **8a** (273 mg, 55%) was obtained. An additional column chromatograph (CH_2Cl_2) allowed the isolation of pure **methyl 3-acetyl-α-ethyl-2-fluoro-1-methyl-α-(methylsulfanyl)-1,4-dihydropyridine-4-acetate** (**6a**, 3:2 epimeric mixture): ^1H NMR δ 0.90 and 0.92 (2t, J = 7.3 Hz, 3H), 1.50, 1.65, 1.85, and 2.03 (4m, 2H), 2.04 and 2.17 (2s, 3H), 2.36 and 2.40 (2d, J = 7.3 Hz, 3H), 3.11 and 3.13 (2d, J = 2.4 Hz, 3H), 3.64 and 3.68 (2s, 3H), 4.27 and 4.35 (dd, J = 8.7 or 8.3, 6.1 Hz, 1H), 5.07 and 5.31 (ddd, J = 8.3 or 8.7, 7.3, 1.8 Hz, 1H), 5.91 and 6.00 (2dd, J = 7.3, 4.3 Hz, 1H); ^{13}C NMR δ 9.1, 9.5 (CH_3), 11.3, 13.0 (CH_3), 23.6, 24.5 (CH_2), 30.5, 30.6 (CH_3), 34.1, 34.2 (CH_3), 39.8, 40.1 (CH), 51.9, 52.3 (CH_3), 63.0, 66.3 (C), 90.1, 90.5 (C), 105.5, 106.9 (CH), 129.3, 130.1 (CH), 159.5, 160.0 (J = 270 Hz, C), 172.5, 172.8 (C), 193.6, 193.8 (C). Anal. Calcd for $C_{14}H_{20}FNSO_3\cdot{}^3/_2H_2O$: C, 53.65; H, 6.86; N, 4.47. Found: C, 53.52; H, 6.93; N, 4.79.

Reaction of Pyridinium Triflate 2b with the Enolate Derived from 3. Operating as above, from pyridinium triflate **2b** (prepared from 1.44 mmol of **1**) and acetate **3** (0.19 mL,

(29) For similar transformations on tetracyclic DE substructures of camptothecin, see refs 21c and 21k.

(30) Güngör, T.; Marsais, F.; Queguiner, G. *J. Organomet. Chem.* **1981**, *215*, 139−150.

1.73 mmol) a 5:1 mixture of fluorodihydropyridines **5b** and **7b** (251 mg, 50%) was obtained. An additional column chromatograph (1:9 hexanes−CH_2Cl_2) allowed the isolation of pure **methyl 3-acetyl-1-benzyl-2-fluoro-α-(methylsulfanyl)-1,4-dihydropyridine-4-acetate** (**5b**, 4:3 mixture of epimers): ^{1}H NMR δ 2.09 and 2.12 (2s, 3H), 2.36 and 2.38 (d, J = 7.4 or 7.1 Hz, 3H), 3.29 and 3.48 (d, J = 6.3 or 3 Hz, 1H), 3.60 and 3.73 (2s, 3H), 4.19 and 4.34 (2m, 2H), 4.53 and 4.60 (2d, J = 15.7 Hz, 2H), 5.14 (m, 1H), 5.95 (m, 1H), 7.20−7.50 (m, 5H); ^{13}C NMR δ 14.6, 16.2 (CH_3), 30.7 (CH_3), 36.4, 37.6 (CH), 50.8, 50.9 (CH_2), 51.8, 52.0 (CH_3), 53.9, 54.9 (CH), 90.8, 90.9 (C), 106.4, 106.7 (CH), 127.2, 128.1, 129.0 (CH), 128.0, 128.8 (CH), 135.5, 135.6 (C), 159.5, 160.0 (J = 270 or 267 Hz, C), 171.1, 172.3 (C), 193.3, 193.6 (C). Anal. Calcd for $C_{18}H_{20}FNSO_3{\cdot}1H_2O$: C, 59.67; H, 5.96; N, 3.87. Found: C, 59.67; H, 6.12; N, 3.83.

Methyl 3-Acetyl-1-benzyl-α-ethyl-2-fluoro-α-(methylsulfanyl)-1,4-dihydropyiridine-4-acetate (6b). Operating as above, from pyridinium triflate **2b** (prepared from 1.44 mmol of **1**) and ester **4** (0.25 mL, 1.73 mmol) 2-fluoro-1,4-dihydropyridine **6b** (1:1 epimeric mixture) was obtained after flash chromatography (8:2 hexanes−AcOEt): 298 mg (55%); ^{1}H NMR δ 0.73 and 0.83 (2t, J = 7.5 Hz, 3H), 1.22, 1.54, 1.81 and 1.95 (4m, 2H), 1.93 and 2.12 (2s, 3H), 2.30 and 2.37 (2d, J = 7.5 Hz, 3H), 3.49 and 3.58 (2s, 3H), 4.25 and 4.33 (dd, J = 8.7 or 8.1, 6 Hz, 1H), 4.47−4.63 (m, 2H), 5.03 and 5.19 (ddd, J = 7.2, 6, and 1.5 or 1.8 Hz, 1H), 5.95 and 6.07 (2dd, J = 7.2, 4.5 Hz, 1H), 7.20−7.40 (m, 5H); ^{13}C NMR δ 8.8, 9.3 (CH_3), 11.5, 12.8 (CH_3), 23.5, 24.3 (CH_2), 30.5, 30.8 (CH_3), 39.8, 40.2 (CH), 50.5, 50.6 (CH_2), 51.7, 52.1 (CH_3), 61.9, 65.4 (C), 89.7, 89.8 (C), 105.6, 106.6 (CH), 127.4, 127.9, 128.6 (CH), 135.1, 135.2 (C), 158.9 and 160.0 (J = 265 or 270 Hz, C), 172.1, 172.6 (C), 193.4, 194.0 (C). Anal. Calcd for $C_{20}H_{24}FNO_3S{\cdot}1H_2O$: C, 61.60; H, 6.56; N, 3.59. Found: C, 61.60; H, 6.34; N, 3.85.

Methyl 3-Acetyl-1-methyl-2-oxo-1,2,3,4-tetrahydropyridine-4-acetate (9a). A solution of 2-fluoro-1,4-dihydropyridine **5a** (0.21 g, 0.76 mmol) in THF (10 mL) and 1 N aqueous HCl (10 mL) was stirred at room temperature for 3 h. The reaction mixture was poured into a saturated Na_2CO_3 solution and extracted with Et_2O. Concentration of the dried extracts gave a residue that was dissolved in dry benzene (10 mL). The resulting solution was heated at reflux, and AIBN (catalytic) and Bu_3SnH (0.22 mL, 0.8 mmol) were added. After the mixture was refluxed for 1 h, Bu_3SnH (0.22 mL, 0.8 mmol) and AIBN (catalytic) were again added and the mixture was stirred for 1 h. The reaction mixture was poured into H_2O and extracted with Et_2O. After concentration of the organic extracts, the crude product was chromatographed (6:4 hexanes−AcOEt) to give **9a** (2:1 mixture of keto−enol tautomers): 0.14 g (80%); ^{1}H NMR δ (keto form) 2.31 (s, 3H), 2.39 (m, 2H), 3.07 (s, 3H), 3.33 (m, 1H), 3.50 (d, J = 5.5 Hz, 1H), 3.68 (s, 3H), 5.13 (ddd, J = 7.8, 4.8, 1 Hz, 1H), 5.97 (dd, J = 7.8, 1 Hz, 1H); ^{1}H NMR δ (enol form, most significant signals) 2.01 (s, 3H), 3.09 (s, 3H), 3.68 (masked, 1H), 5.91 (d, J = 7.8 Hz, 1H), 14.23 (s, 1H); ^{13}C NMR (keto form) δ 29.3 (CH_3), 30.6, (CH), 34.3 (CH_3), 37.3 (CH_2), 51.6 (CH_3), 59.7 (CH), 108.0 (CH), 129.9 (CH), 171.5 (C), 172.2 (C), 202.8 (C); ^{13}C NMR (enol form) δ 18.1 (CH_3), 32.0 (CH), 33.8 (CH_3), 42.8 (CH_2), 51.8 (CH_3), 98.3 (C), 107.3 (CH), 129.2 (CH), 165.5 (C), 169.0 (C), 172.2 (C); HRMS calcd for $C_{11}H_{15}NO_4$ 226.1080 (M + 1), found 226.1079.

Methyl 3-Acetyl-1-benzyl-2-oxo-1,2,3,4-tetrahydropyridine-4-acetate (9b). Operating as above, from 2-fluoro-1,4-dihydropyridine **5b** (100 mg, 0.29 mmol) tetrahydropyridine **9b** (2:1 mixture of keto−enol tautomers) was obtained after flash chromatography (7:3 hexanes−AcOEt): 60 mg (75%); ^{1}H NMR (keto form) δ 2.31 (s, 3H), 2.39 (m, 2H), 3.34 (m, 1H), 3.60 (d, J = 5 Hz, 1H), 3.66 (s, 3H), 4.63 and 4.73 (2d, J = 15 Hz, 2H), 5.14 (dd, J = 7.8 and 5.4 Hz, 1H), 6.00 (d, J = 7.8 Hz, 1H), 7.20−7.40 (m, 5H); ^{1}H NMR (enol form, most significant signals) δ 2.04 (s, 3H), 3.67 (s, 3H), 3.67 (masked, 1H), 5.95 (d, J = 7.8 Hz, 1H); ^{13}C NMR (keto form) δ 29.3 (CH_3), 30.6 (CH), 37.1 (CH_2), 51.8 (CH_2, CH_3), 59.9 (CH), 108.4 (CH), 127.4, 127.7, 128.7 (6 CH), 136.8 (C), 171.7 (C), 171.5 (C), 202.6 (C); ^{13}C NMR (enol form, most significant signals) δ 18.3 (CH_3), 32.0 (CH), 42.9 (CH_2), 51.7 (CH_2, CH_3), 98.2 (C), 107.8 (CH), 165.2 (C).

Methyl 3-Acetyl-α-ethyl-1-methyl-α-(methylsulfanyl)-2-oxo-1,2,3,4-tetrahydropyridine-4-acetate (10a). A solution of 2-fluoro-1,4-dihydropyridine **6a** (150 mg, 0.49 mmol) in THF (10 mL) and HCl 1 N (10 mL) was stirred at room temperature for 3 h. The reaction mixture was partitioned between saturated aqueous Na_2CO_3 and Et_2O, and extracted with Et_2O. The organic extracts were dried and concentrated and the resulting residue was chromatographed (7:3 hexanes−AcOEt) to give **10a** (1:1 epimeric mixture, 119 mg, 80%). An additional chromatography (CH_2Cl_2) allowed the isolation of the less polar epimer: ^{1}H NMR δ 0.97 (t, J = 7.4 Hz, 3H), 1.73 (m, 1H), 1.87 (m, 1H), 2.07 (s, 3H), 2.34 (s, 3H), 3.08 (s, 3H), 3.57 (d, J = 5.9 Hz, 1H), 3.75 (s, 3H), 4.01 (s, 1H), 4.97 (ddd, J = 7.9, 5.9, 1.4 Hz, 1H), 6.05 (d, J = 7.9 Hz, 1H); ^{13}C NMR δ 9.5 (CH_3), 12.6 (CH_3), 26.1 (CH_2), 28.5 (CH_3), 34.2 (CH_3), 38.0 (CH), 52.2 (CH_3), 57.5 (CH), 58.5 (C), 103.9 (CH), 131.6 (CH), 165.3 (C), 172.2 (C), 202.4 (C). Anal. Calcd for $C_{14}H_{21}NSO_4{\cdot}{}^2/_3H_2O$: C, 53.99; H, 7.23; N, 4.50. Found: C, 54.00; H, 7.17; N, 4.36.

Methyl 3-Acetyl-1-benzyl-α-ethyl-α-(methylsulfanyl)-2-oxo-1,2,3,4-tetrahydropyridine-4-acetate (10b). Operating as above, tetrahydropyridine **10b** (1:1 epimeric mixture) was obtained from 2-fluoro-1,4-dihydropyridine **6b** (0.25 g, 0.66 mmol): 0.21 g (85%); ^{1}H NMR δ 0.90 and 0.98 (2t, J = 7.2 Hz, 3H), 1.70 (m, 2H), 1.97 and 2.03 (2s, 3H), 2.32 and 2.33 (2s, 3H), 3.38 (d, J = 5.4 Hz, 1H), 3.56 and 3.72 (2s, 3H), 4.07 (s, 1H), 4.47−4.93 (2m, 2H), 4.96 and 5.05 (ddd, J = 8.1, 5.7 or 5.4, 1.2 or 1.5 Hz, 1H), 6.09 and 6.10 (2 dd, J = 8.1, 1.2 Hz, 1H), 7.10−7.20 (m, 5H); ^{13}C NMR δ 8.7, 8.2 (CH_3), 11.7, 11.2 (CH_3), 25.3, 24.2 (CH_2), 27.8 (CH_3), 37.4, 37.9 (CH), 48.8, 48.7 (CH_2), 51.4, 51.2 (CH_3), 56.8, 57.5 (CH), 57.7, 58.7 (C), 103.3, 102.6 (CH), 127.0, 127.4, 127.8 (5 CH), 129.4, 129.0 (CH), 135.3 (C), 164.3, 163.8 (C), 171.4, 170.8 (C), 201.6 (C).

Methyl 2-Fluoro-3-pyridinecarboxylate (11a). n-BuLi (1.6 M in hexane, 6.9 mL, 11 mmol) was added under Ar to a solution of diisopropylamine (1.6 mL, 11 mmol) in THF (10 mL) cooled at −78 °C, and the mixture was stirred at −78 °C for 30 min. Then, a solution of 2-fluoropyridine (0.86 mL, 10 mmol) in THF (50 mL) was added, and the mixture was stirred at the same temperature for 4 h. Methyl chloroformate (0.93 mL, 12 mmol) was added and, after being stirred at −78 °C for 1 h, the mixture was allowed to rise to room temperature. The reaction mixture was poured into H_2O and extracted with Et_2O. The ethereal extracts were dried and concentrated. Flash chromatography (9:1 hexanes−Et_2O) of the residue gave **11a**: 1.2 g (78%); ^{1}H NMR δ 3.97 (s, 3H), 7.35 (m, 1H), 8.40 (m, 2H); ^{13}C NMR δ 52.3 (CH_3), 113.2 (C), 121.2 (CH), 142.8 (CH), 151.2 (CH), 161.0 (J = 244 Hz, C), 163.1 (C). Anal. Calcd for $C_7H_6FNO_2$: C, 54.20; H, 3.90; N, 9.03. Found: C, 53.88; H, 3.97; N, 8.90.

2-Fluoro-3-formylpyridine (11b). Pyridine **11b** was prepared from 2-fluoropyridine following a previously reported procedure.[31]

2-Fluoro-3-(methoxymethyl)pyridine (11d). 2-Fluoro-3-(hydroxymethyl)pyridine[31a] (0.2 g, 1.6 mmol) in THF (2.5 mL) was added dropwise (over 30 min) to a solution of MeI (0.4 mL, 6.4 mmol) in THF (0.5 mL) in the presence of NaH (55% in mineral oil, 105 mg, 2.4 mmol). When the addition was finished, the reaction mixture was poured into H_2O and extracted with Et_2O. The ethereal extracts were dried and concentrated. Flash chromatography (9:1 hexanes−AcOEt) gave **11d**: 68 mg (30%); ^{1}H NMR δ 3.45 (s, 3H), 4.50 (s, 2H), 7.20 (m, 1H), 7.86 (m, 1H), 8.14 (d, J = 4.8 Hz, 1H).

2-Fluoro-3-[(2-methoxyethoxy)methyl]pyridine (11e). DMAP (20 mg, 0.16 mmol), diisopropylethylamine (0.28 mL,

(31) (a) Ashimori, A.; Ono, T.; Uchida, T.; Ohtaki, Y.; Fukaya, C.; Watanabe, M.; Yokoyama, K. *Chem. Pharm. Bull.* **1990**, *38*, 2446−2458. (b) Mallet, M. *J. Organomet. Chem*. **1991**, *406*, 49−56.

1.6 mmol), and 2-(methoxyethoxy)methyl chloride (0.2 mL, 1.6 mmol) were added to a solution of 2-fluoro-3-(hydroxymethyl)-pyridine[31a] (0.2 g, 1.6 mmol) in dry CH_2Cl_2 (2 mL), and the resulting mixture was stirred at room temperature overnight. The usual workup and flash chromatography (75:25 hexanes−Et_2O) gave **11e**: 220 mg (64%); ^{1}H NMR δ 3.40 (s, 3H), 3.60 and 3.73 (2m, 4H), 7.22 (m, 1H), 7.87 (m, 1H), 8.20 (d, J = 4.8 Hz, 1H), 4.68 (s, 2H), 4.85 (s, 2H), 7.20 (m, 1H), 7.85 (m, 1H), 8.15 (d, J = 4.8 Hz, 1H).

General Procedure for the Preparation of 2-Fluoropyridinium Triflates 12a−e. Pyridinium triflates **12a**−**e** were prepared from pyridines **11a**−**e** and benzyl triflate, following the procedure described for **2b**, and immediately used in the next reaction.

Methyl 1-Benzyl-α-ethyl-3-(methoxycarbonyl)-α-(methylsulfanyl)-2-oxo-1,2-dihydropyridine-4-acetate (16a). Pyridinium triflate **12a** (prepared from 0.97 mmol of **11a**) was allowed to react with the enolate derived from ester **4** (0.17 mL, 1.2 mmol) as described for the preparation of 2-fluorodihydropyridines **5a** and **6a**. Workup and flash chromatography (85:15 hexanes−AcOEt) gave 2-fluoro-1,4-dihydropyridine **14a** (epimeric mixture): 248 mg; ^{1}H NMR δ 0.81 and 0.91 (2t, J = 7.5 Hz, 3H), 1.35, 1.60, 1.90, and 2.08 (4m, 2H), 1.98 and 2.14 (2s, 3H), 3.58, 3.64, 3.70, and 3.74 (4s, 6H), 4.22 (m, 1H), 4.46, 4.47, 4.53, and 4.58 (4d, J = 15.3 Hz, 2H), 4.99 and 5.08 (2m, 1H), 5.98 and 6.08 (2dd, J = 7.3 and 4.3 Hz, 1H), 7.20−7.40 (m, 5H). To a solution of dihydropyridine **14a** (248 mg, 0.64 mmol) in THF (40 mL) and MeOH (2 mL) was added DDQ (182 mg, 0.78 mmol) and the mixture was stirred at room temperature for 5 h. The reaction mixture was poured into H_2O and extracted with Et_2O. Concentration of the ethereal extracts followed by flash chromatography (55:45 hexanes−AcOEt) gave pyridone **16a**: 248 mg (65%); ^{1}H NMR δ 0.89 (t, J = 7 Hz, 3H), 1.96 (s, 3H), 2.19 and 2.30 (2m, 2H), 3.75 and 3.84 (2s, 6H), 5.11 and 5.13 (2d, J = 12 Hz, 2H), 6.60 (d, J = 6.8 Hz, 1H), 7.28 (d, J = 6.8 Hz, 1H), 7.30−7.36 (m, 5H); ^{13}C NMR δ 9.3 (CH_3), 13.9 (CH_3), 29.7 (CH_2), 52.3 (CH_3), 52.3 (CH_2), 59.9 (C), 107.2 (CH), 124.8 (C), 128.0 (CH), 128.5 (CH), 128.8 (CH), 135.0 (C), 136.1 (CH), 148.8 (C), 160.1 (C), 166.5 (2C); HMRS calcd for $C_{20}H_{23}NO_5S$ 389.1296, found 389.1286.

***N,N*-Diethyl-1-benzyl-α-ethyl-3-(methoxycarbonyl)-α-(methylsulfanyl)-2-oxo-1,2-dihydropyridine-4-acetamide (17a)**. Amide **13** (0.17 mL, 1.2 mmol) in anhydrous THF (10 mL) was allowed to react with LDA (1.2 mmol) at −78 °C for 30 min and then with pyridinium triflate **12a** (prepared from 0.97 mmol of **11a**) as above. Workup and flash chromatography (8:2 hexanes−AcOEt) of the residue gave 280 mg of a 4:1 mixture of 2-fluorodihydropyridines **15a** and **18a**. An additional chromatography (CH_2Cl_2) allowed the isolation of pure **15a** (epimeric mixture): ^{1}H NMR δ 0.84 and 0.92 (2t, J = 7.5 Hz, 3H), 1.20 (m, 4H), 1.55 (m, 1H), 1.88 and 1.91 (2s, 3H), 3.40 (br s, 4H), 3.69 and 3.74 (2s, 3H), 4.34−4.63 (m, 3H), 5.04 and 5.18 (2t, J = 6.4 or 6.7 Hz, 1H), 5.99 (m, 1H), 7.20−7.40 (m, 5H). 2-Fluorodihydropyridine **15a** (0.21 g, 0.50 mmol) in THF (10 mL) and MeOH (3 mL) was allowed to react with DDQ (136 mg, 0.6 mmol) as above. Workup and flash chromatography (6:4 hexanes−AcOEt) gave pyridone **17a**: 208 mg (50%); ^{1}H NMR δ 0.92 (t, J = 7.5 Hz, 6H), 1.12 (t, 3H), 1.90 (s, 3H), 2.18 (m, 2H), 3.12 and 3.50 (2m, 4H), 3.88 (s, 3H), 5.06 and 5.14 (2d, J = 14.4 Hz, 2H), 6.27 (d, J = 7.5 Hz, 1H), 7.19 (d, J = 7.5 Hz, 1H), 7.26−7.40 (m, 5H); ^{13}C NMR δ 8.8 (CH_3), 11.9 (CH_3), 12.4 (CH_3), 12.6 (CH_3), 30.8 (CH_2), 41.1 (CH_2), 42.3 (CH_2), 51.9 (CH_2), 52.6 (CH_3), 106.3 (CH), 123.9 (C), 128.0 (CH), 128.5 (CH), 128.8 (CH), 135.0 (C), 135.9 (CH), 148.7 (C), 160.0 (C), 166.3 (C), 167.7 (C); HMRS calcd for $C_{23}H_{30}N_2O_4S$ 430.1933, found 430.1926.

Methyl-1-benzyl-α-ethyl-3-methyl-α-(methylsulfanyl)-2-oxo-1,2-dihydropyridine-4-acetate (16c). Pyridinium triflate **12c** (prepared from 1.35 mmol of **11c**) was allowed to react with the enolate derived from **4** (0.23 mL, 1.6 mmol) as described for the preparation of **5a** and **6a**. Anhydrous MeOH (2 mL) and DDQ (0.37 g, 1.6 mmol) were added at −30 °C, and the mixture was stirred at room temperature for 4 h. Extractive workup (Et_2O) and flash chromatography (85:15 hexanes−AcOEt) of the crude product gave pyridone **16c**: 140 mg (30%); ^{1}H NMR δ 0.84 (t, J = 7.5 Hz, 3H), 1.97 (s, 3H), 2.00 (s, 3H), 2.10 (q, J = 7.5 Hz, 2H), 3.75 (s, 3H), 5.10 and 5.17 (2d, J = 14.5 Hz, 2H), 6.60 (d, J = 7.5 Hz, 1H), 7.17 (d, J = 7.5 Hz, 1H), 7.27−7.36 (m, 5H); ^{13}C NMR δ 8.8 (CH_3), 13.4 (CH_3), 14.3 (CH_3), 28.5 (CH_2), 52.4 (CH_2), 52.4 (CH_2), 59.3 (C), 106.5 (CH), 127.9 (C), 128.0 (CH), 128.5 (CH), 128.8 (CH), 135.0 (C), 132.3 (CH), 145.4 (C), 162.8 (C), 171.4 (C). Anal. Calcd for $C_{19}H_{23}NSO_3$: C, 66.06; H, 6.71; N, 4.05. Found: C, 65.65; H, 6.55; N, 4.55.

2-Bromo-3-(iodomethyl)quinoline (19). 2-Bromo-3-(bromomethyl)quinoline[32] (1 g, 3.3 mmol) in dry acetone (10 mL) was treated vith NaI (1 g, 6.6 mmol), and the resulting mixture was stirred at room temperature overnight. The solvent was removed and the residue was partitioned between H_2O and Et_2O and extracted with Et_2O. The organic extracts were concentrated and the resultant residue was chromatographed (9:1 hexanes−AcOEt) to give quinoline **19**: 1 g (92%); ^{1}H NMR δ 4.68 (s, 2H), 7.58 (t, J = 8.1 Hz, 1H), 7.73 (t, J = 8.1 Hz, 1H), 7.83 (d, J = 8,1 Hz, 1H), 8.03 (d, J = 8.1 Hz, 1H), 8.20 (s, 1H); ^{13}C NMR δ 2.7 (CH_2), 126.0 (CH), 126.2 (CH), 126.8 (C), 127.0 (CH), 129.4 (CH), 131.7 (C), 136.1 (CH), 141.6 (C), 146.1 (C).

1-[(2-Bromo-3-quinolyl)methyl]-2-fluoro-3-(methoxycarbonyl)pyridinium Triflate (21). Quinoline **19** (0.18 g, 0.5 mmol) in dry CH_2Cl_2 (2 mL) was added under Ar to a solution of CF_3SO_2Ag (130 mg, 0.5 mmol) in dry CH_2Cl_2 (0.5 mL). After the solution was stirred at room temperature for 30 min, a yellow precipitate formed (AgI). The reaction mixture was filtered over 2-fluoropyridine **11a** (66 mg, 0.43 mmol) and the resulting suspension was concentrated to 1 mL approximately under an Ar stream and then stirred for 30 min. The solvent was removed under Ar to give a gum, which was washed with dry Et_2O and immediately used in the next reaction.

1-[(2-Bromo-3-quinolyl)methyl]-2-fluoro-3-methylpyridinium Triflate (22). Operating as above, pyridinium triflate **22** was obtained from quinoline **19** (0.18 g, 0.51 mmol) and 2-fluoro-3-methylpyridine **11c** (48 mg, 0.43 mmol).

Methyl 1-[(2-Bromo-3-quinolyl)methyl]-α-ethyl-3-(methoxycarbonyl)-α-(methylsulfanyl)-2-oxo-1,2-dihydropyridine-4-acetate (23). Pyridinium triflate **21** (prepared from 0.43 mmol of pyridine **11a**) was allowed to react with the enolate derived from ester **4** (0.07 mL, 0.5 mmol) as described for the preparation of **5a** and **6a**. After extractive workup (Et_2O) and flash chromatography (8:2 hexanes−AcOEt) a solid (115 mg) was obtained. To a solution of the above solid in THF−MeOH (2:1, 7 mL) was added DDQ (56 mg, 0.24 mmol), and this mixture was stirred at room temperature for 4 h. Extractive workup and flash chromatography (1:1 hexanes−AcOEt) gave pyridone **23**: 112 mg (50%); ^{1}H NMR δ 0.92 (t, J = 7.5 Hz, 3H), 1.98 (s, 3H), 2.16 and 2.32 (2m, 2H), 3.76 and 3.84 (2s, 6H), 5.37 (s, 2H), 6.71 (d, J = 7.2 Hz, 1H), 7.60 (t, J = 7 Hz, 1H), 7.70 (d, J = 7.2 Hz, 1H), 7.76 (t, J = 7 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H), 8.01 (d, J = 8.1 Hz, 1H), 8.23 (s, 1H); ^{13}C NMR δ 9.2 (CH_3), 13.7 (CH_3), 29.7 (CH_2), 52.2 (2 CH_3), 52.3 (CH_2), 59.8 (C), 107.6 (CH), 124.7 (C), 126.8 (C), 127.4 (CH), 127.6 (CH), 127.7 (C), 128.2 (CH), 128.6 (C), 131.0 (CH), 137.2 (CH), 139.6 (CH), 142.0 (C), 147.5 (C), 149.8 (C), 160.2 (C), 169.7 (C).

Methyl 2-[(2-Bromo-3-quinolyl)methyl]-α-ethyl-3-methyl-α-(methylsulfanyl)-2-oxo-1,2-dihydropyridine-4-acetate (24). Operating as in the preparation of pyridone **16c**, pyridone **24** was obtained from pyridinium triflate **22** (prepared from 0.43 mmol of pyridine **11c**), ester **4** (0.07 mL, 0.51 mmol), and DDQ (117 mg, 0.51 mmol) after flash chromatography (3:2 hexanes−AcOEt): 60 mg (30%); ^{1}H NMR δ 0.88 (t,

(32) Comins, D. L.; Baevsky, M. F.; Hong, H. *J. Am. Chem. Soc.* **1992**, *114*, 10971−10972.

J = 7.5 Hz, 3H), 2.00 (s, 3H), 2.02 (s, 3H), 2.17 (masked, 2H), 3.78 (s, 3H), 5.37 (s, 2H), 6.70 (d, J = 7.5 Hz, 1H), 7.45 (d, J = 7.5 Hz, 1H), 7.57 (t, J = 8.1 Hz, 1H), 7.73 (t, J = 8.4 Hz, 1H), 7.80 (d, J = 7.5 Hz, 1H), 8.03 (d, J = 8.7 Hz, 1H), 8.10 (s, 1H); ^{13}C NMR δ 8.8 (CH_3), 13.5 (CH_3), 28.5 (CH_2), 14.3 (CH_3), 52.2 (CH_2), 52.4 (CH_3), 59.3 (C), 106.9 (CH), 127.0 (C), 127.3 (CH), 127.7 (CH), 128.1 (CH), 128.3 (C), 129.3 (C), 130.6 (CH), 133.0 (CH), 138.6 (CH), 142.4 (C), 146.2 (C), 147.7 (C), 162.9 (C), 171.4 (C). Anal. Calcd for $C_{22}H_{23}BrN_2O_3S\cdot{}^1/_2H_2O$: C, 54.55; H, 4.99; N, 5.78. Found: C, 54.37; H, 4.53; N, 6.02.

Methyl α-Ethyl-3-(methoxycarbonyl)-4-oxo-4,6-dihydroindolizino[1,2-*b*]quinoline-2-acetate (25). AIBN (catalytic) and TTMSS (0.03 mL, 0.09 mmol) were added to a heated (reflux) solution of pyridone **23** (46 mg, 0.09 mmol) in dry benzene (10 mL). After 2 h at reflux, AIBN (catalytic) and TTMSS (0.03 mL, 0.09 mmol) were added, and the mixture was stirred at the same temperature for 2 h. The reaction mixture was poured into H_2O and extracted with Et_2O. Concentration of the organic extracts and flash chromatography (9:1 AcOEt−MeOH) of the crude product gave tetracycle **25**: 25 mg (70%); ^{1}H NMR δ 0.97 (t, J = 7.2 Hz, 3H), 1.95 and 2.23 (2 m, 2H), 3.71 (s, 3H), 3.79 (t, J = 7.5 Hz, 1H), 3.99 (s, 3H), 5.28 (s, 2H), 7.41 (s, 1H), 7.67 (t, J = 7.2 Hz, 1H), 7.83 (t, J = 7 Hz, 1H), 7.94 (d, J = 8.1 Hz, 1H), 8.23 (d, J = 8.4 Hz, 1 H), 8.39 (s, 1H); ^{13}C NMR (most significant signals) 12.0 (CH_3), 25.6 (CH_2), 49.4 (CH), 50.2 (CH_2), 52.4 (CH_3), 52.7 (CH_3), 99.6 (CH), 128.1 (2CH), 129.7 (CH), 130.5 (CH), 131.0 (CH), 172.2 (C).

Methyl α-Ethyl-3-methyl-4-oxo-4,6-dihydroindolizino-[1,2-*b*]quinoline-2-acetate (26). Operating as above, tetracycle **26** was obtained from pyridone **24** (42 mg, 0.09 mmol), AIBN (catalytic), and TTMSS (2 × 0.03 mL, 0.18 mmol), after flash chromatography (98:2 AcOEt−MeOH): 20 mg (65%); ^{1}H NMR δ 0.95 (t, J = 7.5 Hz, 3H), 1.92 and 2.22 (2 m, 2H), 2.36 (s, 3H), 3.70 (s, 3H), 3.87 (t, J = 7.6 Hz, 1H), 5.25 (s, 2H), 7.33 (s, 1H), 7.61 (t, J = 8.1 Hz, 1H), 7.80 (t, J = 8.4 Hz, 1H), 7.89 (d, J = 8.1 Hz, 1H), 8.20 (d, J = 8.4 Hz, 1H), 8.32 (s, 1H); ^{13}C NMR δ 11.9 (CH_3), 12.7 (CH_3), 25.1 (CH_2), 49.4 (CH), 49.9 (CH_2), 52.2 (CH_3), 100.1 (CH), 127.3 (CH), 127.9 (C), 127.8 (CH), 128.0 (C), 128.5 (C), 129.5 (CH), 130.1 (CH), 130.7 (CH), 142.4 (C), 147.4 (C), 148.7 (C), 153.2 (C), 161.4 (C), 172.9 (C); HRMS calcd for $C_{21}H_{20}N_2O_3$ 348.1473, found 348.1474. Anal. Calcd for $C_{21}H_{20}N_2O_3\cdot1.5H_2O$: C, 66.96; H, 6.19; N, 7.44. Found: C, 66.68; H, 5.80; N, 7.70.

Diethyl Ester (27). KF (70 mg, 1.2 mmol) was added to a solution of tetracycle **25** (25 mg, 0.06 mmol) in dry EtOH (5 mL) and the mixture was heated (reflux) for 40 h. The solvent was removed and the residue was partitioned between H_2O and AcOEt, then extracted with AcOEt. The organic extracts were dried and concentrated, and the resulting residue was chromatographed (99:1 AcOEt−MeOH) to give tetracycle **27**:[21j] 23 mg (90%); ^{1}H NMR δ 0.97, 1.24, and 1.43 (3 t, J = 7.2 Hz, 9H), 1.95 (m, 1H), 2.22 (m, 2H), 3.75 (t, J = 7.6 Hz, 1H), 4.16 (m, 2H), 4.48 (q, J = 7.2 Hz, 2H), 5.30 (s, 2H, 5-H), 7.44 (s, 1H), 7.57 (t, J = 7.6 Hz, 1H), 7.81 (t, J = 7.8 Hz, 1H), 7.92 (d, J = 8.2 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H), 8.38 (s, 1H).

Diol 28. A: To a solution of tetracycle **25** (25 mg, 0.06 mmol) in dry CH_2Cl_2 (0.5 mL) cooled at −78 °C was added DIBAL (1 M in CH_2Cl_2 0.18 mL, 0.18 mmol) under Ar, and the mixture was stirred at −78 °C for 2 h. $NaBH_4$ (spatula) and dry MeOH (1 mL) were added, and the mixture was stirred at room temperature for 30 min. The reaction mixture was poured into H_2O and extracted with CH_2Cl_2. Concentration of the organic extracts and flash chromatography (98:2 $CHCl_3$−MeOH) of the crude product gave **28**: 16 mg (80%); ^{1}H NMR δ 0.89 (t, J = 7.5 Hz, 3H), 1.75 (m, 2H), 3.30 (m, 1H), 3.80 (dd, J = 10.5 and 9.6 Hz, 1H), 3.98 (dd, J = 10.5 and 4.8 Hz, 1H), 4.67 and 5.03 (2d, J = 12.6 Hz, 2H), 5.17 (s, 2H), 7.28 (s, 1H), 7.57 (t, J = 7.8 Hz, 1H), 7.78 (m, 2H), 8.12 (d, J = 8.4 Hz, 1H), 8.26 (s, 1H); ^{13}C NMR δ 12.0 (CH_3), 24.0 (CH_2), 45.8 (CH), 49.9 (CH_2), 56.5 (CH_2), 66.0 (CH_2), 99.5 (CH), 127.6 (CH), 127.8 (C), 128.0 (CH), 128.6 (C), 129.3 (CH), 130.3 (CH, C), 130.9 (CH), 144.4 (C), 148.5 (C), 152.6 (C), 154.7 (C), 161.1 (C); HRMS calcd for $C_{20}H_{20}N_2O_3$ 336.1473, found 336.1474.

B: To a solution of tetracycle **25** (25 mg, 0.06 mmol) in THF (0.5 mL) cooled at −78 °C was added DIBAL (1 M in THF, 0.18 mL, 0.18 mmol) under Ar, and the mixture was stirred at −78 °C for 1.5 h. The reaction mixture was allowed to rise to −40 °C and stirred for 10 min. $NaBH_4$ (spatula) and H_2O (1 mL) were added and the mixture was stirred at room temperature for 30 min. Workup and flash chromatography as above gave diol **28**: 16 mg (80%).

C: Operating as in the above method A, diol **28** was obtained from tetracycle **27** (20 mg, 0.05 mmol), DIBAL (1 M in CH_2Cl_2 0.18 mL, 0.18 mmol), and $NaBH_4$ (catalytic amount): 13 mg, (75%).

Isopropyl 1-[(2-Bromo-3-quinolyl)methyl]-α-ethyl-3-(methoxycarbonyl)-α-(methylsulfanyl)-2-oxo-1,2-dihydropyridine-4-acetate (29). Isopropyl 2-(methylsulfanyl)-buyrate (90 mg, 0.51 mmol) in THF (20 mL) was allowed to react with LDA (0.5 mmol) at −78 °C for 30 min and then with pyridinium triflate **21** (prepared from 0.43 mmol of 2-fluoropyridine **11a**) and DDQ as described for the preparation of pyridone **23**. After flash chromatography (1:1 hexanes−AcOEt) of the crude product pyridone **29** was obtained: 117 mg (50%); ^{1}H NMR δ 0.91 (t, J = 7.8 Hz, 3H), 1.27 and 1.31 (2d, J = 6.3 Hz, 6H), 1.98 (s, 3H), 2.15 and 2.30 (2m, 2H), 3.84 (s, 3H), 5.06 (m, J = 6.3 Hz, 1H), 5.38 (s, 2H), 6.56 (d, J = 7.5 Hz, 1H), 7.58 (t, J = 7 Hz, 1H), 7.60 (d, J = 7.5 Hz, 1H), 7.74 (t, J = 7 Hz, 1H), 7.81 (d, J = 8.1 Hz, 1H), 8.01 (d, J = 8.4 Hz, 1H), 8.22 (s, 1H); ^{13}C NMR δ 9.5 (CH_3), 13.9 (CH_3), 21.2 (CH_3), 21.6 (CH_3), 29.7 (CH_2), 51.9 (CH_2), 52.3 (CH_3), 60.2 (C), 69.4 (CH), 107.6 (CH), 125.4 (C), 127.0 (C), 127.4 (CH), 127.9 (CH), 128.0 (CH), 128.5 (C), 130.9 (CH), 136.5 (CH), 139.6 (CH), 142.3 (C), 147.8 (C), 149.3 (C), 160.2 (C), 166.4 (C), 168.4 (C); HRMS calcd for $C_{25}H_{27}BrN_2O_5S$ 546.0824, found 546.0793. Anal. Calcd for $C_{25}H_{27}BrN_2O_5S\cdot1.5H_2O$: C, 52.19; H, 5.27; N, 4.87. Found: C, 52.19; H, 5.21; N, 4.94.

Isopropyl α-Ethyl-3-(methoxycarbonyl)-4-oxo-4,5-dihydroindolizino[1,2-*b*]quinoline-2-acetate (30). Operating as in the preparation of tetracycles **25** or **26**, tetracycle **30** was obtained from pyridone **29** (46 mg, 0.09 mmol) after flash chromatography (9:1 AcOEt−MeOH): 25 mg (70%); ^{1}H NMR δ 0.98 (t, J = 7.2 Hz, 3H), 1.18 and 1.26 (2d, J = 6.3 Hz, 6H), 1.95 and 2.20 (2m, 2H), 3.72 (t, J = 7.5 Hz, 1H), 3.99 (s, 3H), 5.03 (m, J = 6.3 Hz, 1H), 5.28 (s, 2H), 7.45 (s, 1H), 7.66 (t, J = 7 Hz, 1H), 7.83 (t, J = 7 Hz, 1H), 7.93 (d, J = 8 Hz, 1H), 8.22 (d, J = 8.2 Hz, 1H), 8.38 (s, 1H); ^{13}C NMR δ 12.0 (CH_3), 21.6 (CH_3), 21.8 (CH_3), 25.6 (CH_2), 50.1 (CH), 50.3 (CH_2), 52.6 (CH_3), 68.8 (CH), 99.7 (CH), 124.7 (C), 127.9 (CH), 128.0 (CH), 128.8 (2C), 129.8 (CH), 130.5 (CH), 130.9 (CH), 146.4 (C), 148.9 (C), 151.3 (C), 152.3 (C), 158.3 (C), 166.5 (C), 171.3 (C); HRMS calcd for $C_{24}H_{24}N_2O_5$ 420.1685, found 420.1688.

Reduction of Diester 30. A solution of diester **30** (15 mg, 0.03 mmol) in DME (2 mL) was added to a cooled (−70 °C) solution of DIBAL (1 M in hexane, 0.1 mL, 0.1 mmol) in DME (2 mL), and the resulting solution was stirred at −70 °C for 15 min. The reaction mixture was poured into H_2O and extracted with CH_2Cl_2. The organic extracts were concentrated to give a residue, which was disolved in dry 2-propanol (1 mL). $NaBH_4$ (spatula) was added and the mixture was stirred at room temperature for 30 min. After extractive workup (CH_2Cl_2) and flash chromatography (AcOEt−MeOH) of the crude product the following compounds were isolated:

(±)-20-Deoxycamptothecin (31):[21a] elution with 99:1 AcOEt−MeOH, 3.8 mg (32%); ^{1}H NMR δ 1.09 (t, J = 7.4 Hz, 3H), 2.09 (m, 2H), 3.62 (t, J = 6.6 Hz, 1H), 5.29 (s, 2H), 5.39 (d, J = 16.3 Hz, 1H), 5.57 (d, J = 16.3 Hz, 1H), 7.19 (s, 1H), 7.66 (dt, J = 7.5 and 1 Hz, 1H), 7.83 (dt, J = 6.9 and 1.4 Hz, 1H), 7.93 (d, J = 7 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H), 8.39 (s, 1H).

Lactol 32:[21m] elution with 85:15 AcOEt−MeOH, 3.9 mg (33%); ^{1}H NMR δ 1.05 (t, J = 7.4 Hz, 3H), 1.80 (m, 2H), 2.68 (t, J = 6.6 Hz, 1H), 2.84 (s, 1H), 4.82 (s, 2H), 5.24 (s, 2H), 5.40

(s, 1H), 7.20 (s, 1H), 7.63 (t, $J = 7{,}5$ Hz, 1H), 7.80 (t, $J = 7$ Hz, 1H), 7.91 (d, $J = 8.1$ Hz, 1H), 8.20 (d, $J = 9$ Hz, 1H), 8.34 (s, 1H).

Methyl 1-[(2-Bromo-3-quinolyl)methyl]-4-[(2*R*,5*S*)-2-*tert*-butyl-5-ethyl-4-oxo-1,3-dioxolan-5-yl]-2-oxo-1,2-dihydropyridine-3-carboxylate (34). Dioxolanone **33**[27,33] (0.1 g, 0.58 mmol) in THF (13 mL) cooled at −78 °C was allowed to react with LDA (0.6 mmol) under Ar at −78 °C for 30 min and then with pyridinium triflate **21** (prepared from 0.54 mmol of 2-fluoropyridine **11a**) and DDQ as described for the preparation of pyridone **23**. After extractive workup (Et_2O) and flash chromatography (6:4 hexanes−AcOEt) of the crude product pyridone **34** was obtained: 59 mg (20%); $[\alpha]^{22}_D$ −59 (*c* 0.6, $CHCl_3$); ^{1}H NMR δ 0.94 (masked, 3H), 0.99 (s, 9H), 2.09 and 2.16 (2m, 2H), 3.87 (s, 3H), 5.16 (s, 1H), 5.28 and 5.39 (2d, $J = 14.7$ Hz, 2H), 6.53 (d, $J = 7.8$ Hz, 1H), 7.58 (t, $J = 7$ Hz, 1H), 7.64 (d, $J = 7.2$ Hz, 1H), 7.75 (t, $J = 7$ Hz, 1H), 7.84 (d, $J = 8$ Hz, 1H), 8.01 (d, $J = 8$ Hz, 1H), 8.26 (s, 1H, 4-H); ^{13}C NMR δ 8.4 (CH_3), 23.6 ($3CH_3$), 31.7 (CH_2), 34.7 (C), 52.3 (CH_2), 52.6 (CH_3), 83.3 (C), 103.1 (CH), 108.2 (CH), 123.9 (C), 127.1 (C), 127.5 (CH), 128.0 (CH), 128.2 (CH), 131.1 (CH), 138.2 (CH), 139.9 (CH), 142.4 (C), 146.3 (C), 147.9 (C), 159.8 (C), 166.4 (C), 170.9 (C); HRMS calcd for $C_{26}H_{27}N_2O_6Br$ 542.1052, found 542.1034.

Methyl 2-[(2*R*,5*S*)-2-*tert*-Butyl-5-ethyl-4-oxo-1,3-dioxolan-5-yl]-4-oxo-4,6-dihydroindolizino[1,2-*b*]quinoline-3-carboxylate (35). A solution of pyridone **34** (66 mg, 0.12 mmol) in dry benzene (10 mL) was allowed to react with TTMSS (2 × 0.04 mL, 0.24 mmol) and AIBN (catalytic) as described for the preparation of tetracycle **25**. After extractive workup and flash chromatography (4:6 hexanes−AcOEt) of the crude product tetracycle **35** was obtained: 34 mg (60%); $[\alpha]^{22}_D$ −191 (*c* 1, $CHCl_3$); ^{1}H NMR δ 1.02 (s, 9H), 1.08 (t, $J = 7.2$ Hz, 3H), 2.22 and 2.34 (2m, 2H), 3.93 (s, 3H), 5.22 and 5.27 (2s, 3H), 7.61 (s, 1H), 7.66 (t, $J = 7.2$ Hz, 1H), 7.83 (t, $J = 8$ Hz, 1H), 7.94 (d, $J = 8.4$ Hz, 1H), 8.24 (d, $J = 8.4$ Hz, 1H), 8.37 (s, 1H); ^{13}C NMR δ 8.5 (CH_3), 23.7 ($3CH_3$), 31.9 (CH_2), 34.7 (C), 50.2 (CH_2), 52.6 (CH_3), 83.3 (C), 97.8 (CH), 108.1 (CH), 122.9 (C), 128.0 (CH), 128.1 (CH, C), 128.6 (C), 130.0 (CH), 130.5 (CH), 130.9 (CH), 146.3 (C), 147.3 (C), 148.9 (C), 151.7 (C), 158.5 (C), 166.6 (C), 171.0 (C); HRMS calcd for $C_{26}H_{26}N_2O_6$ 462.1790, found 462.1794.

Hexacycle 38. DIBAL (1 M in CH_2Cl_2, 0.1 mL, 0.1 mmol) was added under Ar to a solution of tetracycle **35** (32 mg, 0.07 mmol) in dry CH_2Cl_2 (0.6 mL) cooled at −78 °C. After the solution was stirred at −78 °C for 15 min, DIBAL (1 M in CH_2Cl_2, 0.1 mL, 0.1 mmol) was added again, and the reaction mixture was stirred at −78 °C for 15 min. Dry MeOH (1 mL) and $NaBH_4$ (spatula) were added and the mixture was stirred at 0 °C for 30 min. The reaction mixture was quenched with 2 N NaOH. After the solution was stirred for 30 min, glacial acetic acid was added until neutralization and the mixture was stirred for 30 min. The solvent was removed and the resultant residue was chromatographed (99:1 $CHCl_3$−MeOH) to give hexacycle **38**: 20 mg (65%); $[\alpha]^{22}_D$ −60 (*c* 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, biogenetic numbering, assignments aided by HSQC and HMBC) δ 0.92 (s, 9H), 1.00 (t, $J = 7.5$ Hz, 3H, 18-H), 2.15 and 2.25 (2m, 2H, 19-H), 4.61 (s, 1H), 5.36 and 5.12 (2d, $J = 15$ Hz, 2H, 5-H), 5.66 (s, 1H, 21-H), 7.47 (s, 1H, 14-H), 7.70 (t, $J = 7.5$ Hz, 1H, 10-H), 7.90 (t, $J = 7.5$ Hz, 1H, 11-H), 8.05 (d, $J = 7.5$ Hz, 1H, 9-H), 8.35 (d, $J = 7.5$ Hz, 1H, 12-H), 8.48 (s, 1H, 7-H); ^{13}C NMR (assignments aided by HSQC and HMBC) δ 7.5 (C-18), 23.8 ($3CH_3$), 29.4 (C-19), 34.6 (C), 50.9 (C-5), 77.7 (C-20), 96.6 (C-14), 101.0 (C-21), 109.1 (CH), 112.0 (C-16), 128.2 (C-9), 128.5 (C-10), 128.6 (C-6), 129.4 (C-8), 129.8 (C-12), 130.9 (C-11), 131.6 (C-7), 149.0 (C-13), 151.7 (C-3), 151.8 (C-2), 156.8 (C-15), 157.2 (N−CO), 157.5 (C-17); HMRS calcd for $C_{25}H_{24}N_2O_5$ 432.1685, found 432.1674.

(−)-*O*,21-Dihydrocamptothecin (36). DIBAL (1 M in CH_2Cl_2, 0.2 mL, 0.2 mmol) was added to a solution of tetracycle **35** (32 mg, 0.07 mmol) in dry CH_2Cl_2 (0.6 mL) cooled at −78 °C, and the mixture was allowed to rise to −30 °C (45 min). Dry MeOH (1 mL) and $NaBH_4$ (catalytic) were added, and the mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched with 2 N NaOH. After the solution was stirred at room temperature for 30 min, 2 N HCl was added to bring the pH to 4−5, and the mixture was stirred for 30 min. The reaction mixture was extracted with 99:1 $CHCl_3$−MeOH. Concentration of the organic extracts and flash chromatography (99:1 $CHCl_3$−MeOH) of the residue afforded α-hydroxylactol **36**: 11 mg (45%); $[\alpha]^{22}_D$ −29 (*c* 0.2, $CHCl_3$−CH_3OH 4:1); ^{1}H NMR (DMSO-d_6) δ 0.89 (t, $J = 7.2$ Hz, 3H), 1.72 (q, $J = 7.2$ Hz, 2H), 4.49 and 4.60 (2d, $J = 17$ Hz, 2H), 4.96 (s, 1H), 4.99 (br, 1H), 5.22 (s, 2H), 6.75 (br, 1H), 7.36 (s, 1H), 7.67 (t, $J = 7.5$ Hz, 1H), 7.84 (t, $J = 7.5$ Hz, 1H), 8.12 (2d, 2H), 8.64 (s, 1H); ^{13}C NMR δ (DMSO-d_6) 7.8 (CH_3), 32.5 (CH_2), 49.7 (CH_2), 58.4 (CH_2), 70.3 (C), 92.7 (CH), 98.6 (CH), 123.1 (C), 127.3 (CH), 127.8 (C), 128.4 (CH), 128.9 (CH), 129.4 (C),130.1 (CH), 131.3 (CH), 142.8 (C), 147.9 (C), 150.1 (C), 153.0 (C), 157.3 (C).

(+)-Camptothecin (37). To a solution of α-hydroxylactol **36** (7 mg, 0.02 mmol) in MeOH−H_2O (0.5 mL, 10:1) were added iodine (0.46 g, 0.18 mmol) and $CaCO_3$ (4 mg, 0.04 mmol), and the mixture was stirred at room temperature for 4 days. The reaction mixture was carefully washed with H_2O (5 mL) and extracted with 99:1 $CHCl_3$−MeOH. Concentration of the organic extracts and flash chromatography (98:2 $CHCl_3$−MeOH) of the crude product gave (+)-camptothecin (**37**): 4 mg (60%); $[\alpha]^{22}_D$ +25 (*c* 0.2, $CHCl_3$−CH_3OH 4:1) (lit.[18] $[\alpha]^{22}_D$ +31 ($CHCl_3$:CH_3OH 4:1)).

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Supporting Information Available: NMR spectra of compounds **9a**, **9b**, **10b**, **11d**, **11e**, **16a**, **17a**, **19**, **23**, **25**, **28**, **30**−**32**, and **34**−**38**. This material is available free of charge via the Internet at http://pubs.acs.org.

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