Practical Asymmetric Synthesis of (*S*)-4-Ethyl-7,8-dihydro-4-hydroxy-1*H*-pyrano[3,4-f]indolizine-3,6,10(4*H*)-trione, a Key Intermediate for the Synthesis of Irinotecan and Other Camptothecin Analogs

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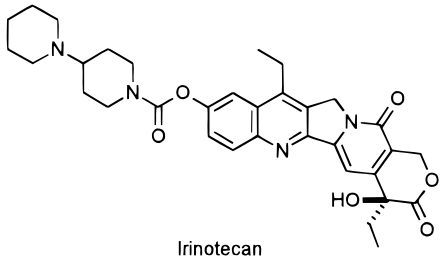
A practical asymmetric synthesis of (*S*) 4-ethyl-7,8-dihydro-4-hydroxy-1*H*-pyrano[3,4-*f*]indolizine-3,6,10(4*H*)-trione (**1**), a versatile intermediate for the synthesis of camptothecin analogs, was developed. Commercially available citrazinic acid is converted in four steps into the 2-chloro-6-methoxypyridine **5**. An ortho-directed metalation followed by reaction with a formamide produces an aldehyde with the required 2,3,4,6-substituted pyridine (**6**) with high regioselectivity. After refunctionalization of the aldehyde, the chloropyridine is converted into an ester by a facile palladium-mediated carbonylation reaction. Wittig reaction and racemic osmylation produce the diol **16** which is resolved by an efficient lipase resolution to an ee > 99%, and a one-pot recycle of the unwanted diol enantiomer was developed. A series of high-yielding oxidation and deprotection steps convert (*S*)-**16** into the pyridone **25**, which is then converted into **1** with an ee > 99.6%.

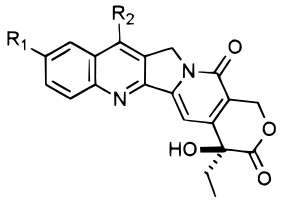
Introduction

Irinotecan[1] (CPT-11) was licensed by Pharmacia & Upjohn from Yakult Honsha and recently approved by the FDA for the treatment of refractory colorectal cancer. Irinotecan is an analog of the natural product camptothecin, whose structure was reported in 1966 by Wall and co-workers.[2] Although camptothecin has potent antitumor activity, it has serious problems with solubility and toxicity, and irinotecan is one of a number of analogs developed to circumvent these problems.[3] Irinotecan functions as the soluble prodrug for the active metabolite SN-38, and both SN-38 and camptothecin function as inhibitors of the enzyme topoisomerase I, which plays an important role in DNA replication. Biological aspects of CPT-11 have recently been reviewed.[4]

Irinotecan has been prepared from natural camptothecin in five chemical steps and about 20% overall yield.[1] Although this synthesis provides a direct route to irinotecan, the reliance on scarce natural camptothecin and other operational problems caused us to evaluate the preparation of irinotecan by total synthesis. Many syntheses of camptothecin have been reported, most dating from the early to mid 1970's. Three reviews cover the older syntheses,[5] which are generally racemic and would be difficult to adapt for large scale synthesis. With the renewed interest in camptothecin analogs several new or improved syntheses have been published, but these approaches would either be impractical for large scale synthesis of enantiomerically pure irinotecan or were unavailable for our use for patent reasons.[6]



Irinotecan



R_1 = H, R_2 = H	Camptothecin
R_1 = OH, R_2 = Et	SN-38

One of the most efficient means of assembling the camptothecin ring system is through a Friedlander condensation,[7] a reaction used in various forms in a number of published camptothecin syntheses. Extensive work has been done by Wall and co-workers and at Daiichi Pharmaceutical to develop a chiral synthesis of camptothecin and analogs using (4*S*)-4-ethyl-7,8-dihydro-4-hydroxy-1*H*-pyrano[3,4-*f*]indolizine-3,6,10(4*H*)-trione (**1**) as a key intermediate (Scheme 1). **1** has been used extensively to produce camptothecin and numerous analogs.[3b,c,6c] A synthesis of racemic **1** was reported by Wall[8] based on chemistry originally developed by Chinese

[⊗] Abstract published in *Advance ACS Abstracts,* August 15, 1997.

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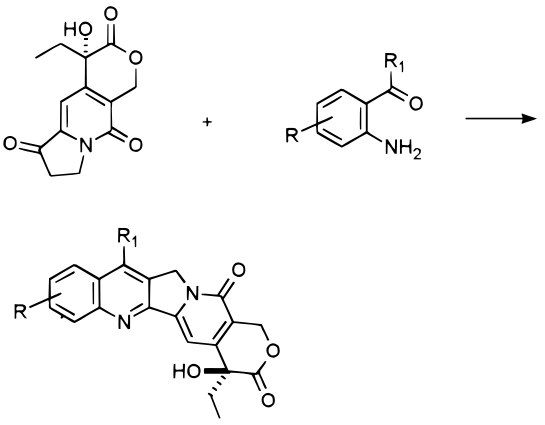
Scheme 1

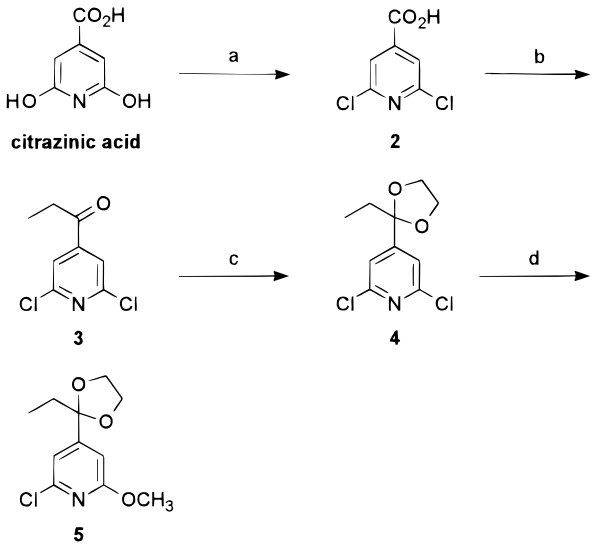


researchers[9] and procedures for the resolution of racemic **1** via the diastereomeric α-methylbenzylamides were published by Wall[6a] and by Tagawa and co-workers at Daiichi.[6b] This synthesis starts with inexpensive materials but several steps present problems, especially for large scale preparations. In addition, the synthesis is limited by the inefficient resolution to prepare enantiomerically enriched material because there are no simple methods for recycling the undesired enantiomer. A second variation of this synthesis uses an alkylation of a chiral amide; this modification overcomes the limitations of the resolution but uses stoichiometric amounts of expensive *N*-tosyl-(*R*)-proline as the chiral auxiliary.[6c] A third modification using a Sharpless asymmetric dihydroxylation has also been reported but gives **1** with an enantiomeric excess of only 84%.[10] Given the continued interest in preparing additional camptothecin analogs and our need for a scaleable total synthesis of irinotecan, we have developed a practical synthesis of the key intermediate **1** with high enantiomeric purity.

Results and Discussion

The starting material for the synthesis (Scheme 2) is citrazinic acid, which is commercially available in bulk.[11] This was converted into 2,6-dichloroisonicotinic acid (**2**) in 78% yield by reaction with phosphorus oxychloride and

Scheme 2[a]



[a] (a) $POCl_3$, Me_4NCl, 120 °C, 78%; (b) EtMgBr, 0 °C, 84%, (c) ethylene glycol, TMSCl, 99%, (d) CH_3ONa, 65 °C, 89%.

1 equiv of tetramethylammonium chloride at 120 °C under atmospheric pressure.[12] In the absence of a quarternary ammonium chloride, product formation occurs only under sealed tube conditions.[13]

Conversion of 2,6-dichloroisonicotinic acid into the ethyl ketone **3** was done in 84% yield by reaction with 3 equiv of ethylmagnesium chloride in THF at −40 °C, quenching the excess Grignard reagent first with methyl formate before an aqueous acidic workup. Use of this protocol essentially eliminates the formation of the tertiary alcohol byproduct. The ketone **3** was then converted into the nicely crystalline ethylene ketal **4** in 99% yield by reaction with ethylene glycol and TMS chloride.[14] Ketal **4** was efficiently desymmetrized by reaction with sodium methoxide in refluxing methanol to give compound **5** in 89% isolated yield as a low melting solid.[15] Under these conditions less than 1% of the 2,6-dimethoxy compound is formed, although it can be made the exclusive product if the reaction is run at higher temperatures and for longer times.

Following the approach used in the Comins' camptothecin synthesis,[6e] introduction of an aldehyde substituent adjacent to the methoxy group was done using an ortho-directed metalation.[16] Cooperative effects in directed metalation reactions are well known and there are a number of examples of metalations of alkoxypyridines,[6e,g,h,17] but there is little precedent for selective reactions with substrates such as **5** having a C-4 substituent. We found that a high degree of site-selectivity

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(11) Citrazinic acid was purchased from Yorkshire Chemical for $60/kg.

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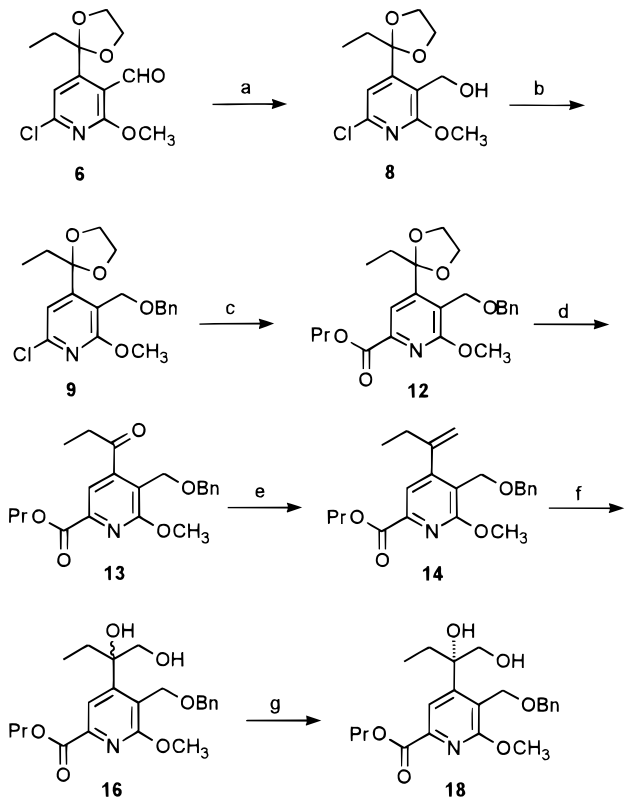
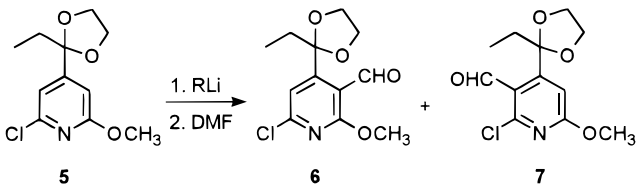
Scheme 3[a]

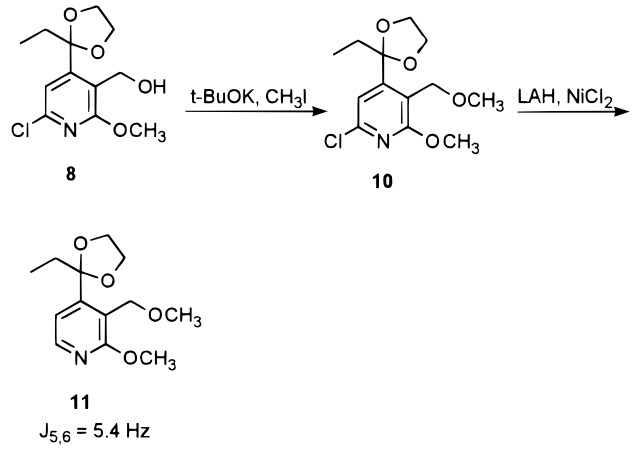


[a] (a) $NaBH_4$, 99%; (b) BnBr, t-BuOK, 99%; (c) CO, $Pd(OAc)_2$, DPPP, DMF, KOAc, n-PrOH, DMF, 90 °C, 89%; (d) 50% TFA, 98%; (e), Ph_3PCH_3Br, KHMDS, DMF, 92%; (f) OsO_4, Me_3NO-$2H_2O$, t-BuOH, 45 °C, 92%; (g) PS-30 catalyst, isopropenyl acetate, MTBE, 38%.

for deprotonation adjacent to either the chloro or methoxy substituent is attainable by appropriate choice of the base and solvent. Deprotonation of **5** with an alkyllithium followed by reaction with DMF yields aldehydes **5** and **6**. Use of nonpolar solvents induces deprotonation adjacent to the methoxy group, and reaction with *n*-butyllithium in heptane at 0 °C gives 95:5 selectivity in favor of **6** after reaction of the anion with DMF. For larger scale reactions, DMF was replaced with the more heptane-soluble *N*-formylpiperidine. With polar solvents or coordinating additives the selectivity is reversed; deprotonation with *sec*-butyllithium in THF at −40 °C gives 90:10 selectivity in favor of **7**. Reactions in all cases were accompanied by 10−20% unreacted starting material and various products arising from butyl substitution at C-2, C-6, or at both positions.



Separation of the desired aldehyde **6** from the regioisomer **7** and other byproducts was done by chromatography on small scale, a separation more easily done after reduction to the alcohol **8** (Scheme 3) with sodium borohydride. Alcohol **8** was obtained in 71% overall yield from **5** (87% corrected for recovered **5**). On larger scale **6** was purified by crystallization from heptane or by formation of the crystalline bisulfite addition product followed by treatment with HCl or NaOH to regenerate the aldehyde, eliminating the need for a chromatography. Reaction of **8** with benzyl bromide and potassium *tert*-butoxide in THF gave benzyl ether **9** in 99% yield. Alcohol **8** was also converted into **10** (methyl iodide/potassium *tert*-butoxide), which was dechlorinated ($NiCl_2$/LAH)[18] to give **11**. The observed coupling constant of 5.4 Hz for the C-5 and C-6 splitting confirms the regiochemical assignment of compounds **6** and **8**.



Palladium-catalyzed carbonylation of the chloropyridine **9** provides an efficient method for C-6 functionalization. Aryl chlorides generally have low reactivity in palladium insertion reactions but insertion complexes of palladium and nickel with 2-chloropyridine have been isolated and simple 2-chloropyridines are known to undergo palladium-catalyzed reactions,[19] although palladium-catalyzed carbonylation reactions of 2-chloropyridines have not been reported. Compound **9** was smoothly carbonylated by reaction with carbon monoxide, palladium acetate (0.25 mol %), 1,3-bis(diphenylphosphino)-propane (DPPP, 0.25 mol %), 1-propanol, and potassium acetate in DMF at 90 °C. The reaction proceeds under low carbon monoxide pressure (15 psi or less) with 1-propanol chosen as the alcohol since its boiling point allows the reaction to be run at atmospheric pressure. Isolated yield of ester **12** after purification was 89%.

Deketalization of **12** with 50% trifluoroacetic acid at room temperature gave the ketone **13** in 98% yield. Conditions of the subsequent Wittig reaction to form **14** required optimization to suppress formation of the diene overreaction product **15**.[20] The optimized base/solvent combination is KHMDS and DMF at 0 °C, which gave **14** in 92% with diene levels less than 3%. On a small scale, the noncrystalline intermediates **9**, **12**, **13**, and **14** were purified by chromatography but on larger scale the crude products were used without purification.

Conversion of the olefin into the racemic diol[21] **16** was done with 1 mol % osmium tetraoxide and 3 equiv of trimethylamine *N*-oxide dihydrate in anhydrous *tert*-butanol at 45 °C.[23] Addition of water beyond that contained in the trimethylamine *N*-oxide dihydrate caused reactions to stall at about 60% completion. Diol **16** was

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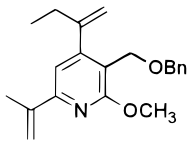

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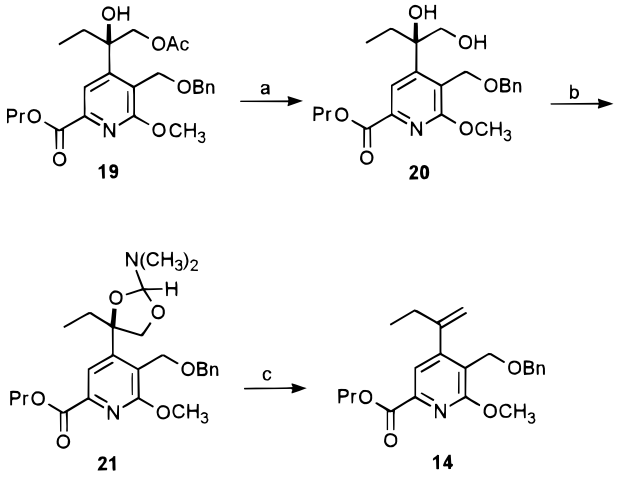
obtained in 78% yield in lab scale runs after crystallization from THF−heptane, with an additional 14% yield of product recoverable from the mother liquors by chromatography. Two large scale (>100 kg) pilot runs for this step gave the product in a total yield of 92%.

Resolution of **16** was done by acetylation with isopropenyl acetate catalyzed by Amano PS-30 lipase immobilized on Celite. The acetylation was taken to 60% conversion, and the (*S*)-diol **18** was separated from the acetylated product **19** by either chromatography or by crystallization; in this case, chromatography gave better recovery and ee of isolated product than crystallization. Yield of (*S*)-diol **18**[24] with ee > 99% as determined by chiral HPLC was 38% (76% of theoretical). The reaction rate significantly increased when the PS-30 was immobilized with Celite 521 (1:1 by weight). For comparison, 20−25% conversion of diol to ester was normally observed after one day at room temperature with immobilized lipase, while commercial PS-30 gave <5% ester formation in the same time. Butyric anhydride, succinic anhydride, vinyl acetate, and isopropenyl acetate were examined as acylating agents. The poorest result was obtained with butyric anhydride (ee_s 79% and ee_p 67%, c = 54%, enantiomeric ratio E[25] = 12). Vinyl acetate and succinic anhydride afforded similar results: vinyl acetate ee_s 93% and ee_p 85% at c = 52%, E = 45, and succinic anhydride ee_s 90% and ee_p 82% at c = 53%, E = 30. Even though the use of succinic anhydride would be advantageous for the separation of the hemisuccinate from the unreacted and desired (*S*)-diol starting material by acid−base extraction, the lipase reaction was too slow for practical usefulness. Isopropenyl acetate and vinyl acetate could be used interchangeably in the reaction.

The best reaction conditions were found to be slurry-to-slurry reaction conditions at room temperature (100 g **16**/250 mL MTBE, equal weight immobilized PS-30 catalyst, 1 equiv isopropenyl acetate). Under these conditions the reaction took 2 days to reach 60% completion; with a homogeneous solution of **16** the reaction took 4 days to reach the same conversion. The lipase reaction could be accelerated by performing the reaction at 40−50 °C without detrimental effect on ee, and the recovered catalyst was reused several times without major loss in activity.

Scheme 4[a]

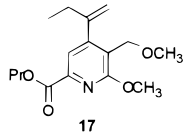


[a] (a) n-PrOH, t-BuOK, CH_2Cl_2; (b) DMF dimethylacetal, p-TSA, THF; (c) Ac_2O, 100 °C, 90% overall.

An efficient procedure for the recycle of the acetylated byproduct **19** from the lipase resolution was developed (Scheme 4). Direct racemization or inversion of the (*R*)-enantiomer is expected to be a difficult process based on the known chemistry of camptothecin and analogs; procedures exist for the inversion of the hydroxyl stereochemistry in related compounds but the yields are low,[6b] and elimination of the hydroxyl group to form **14** directly is not expected to be a facile process.[8a] The acetylated byproducts **19** (primarily *R*) from the lipase resolution were transesterified with 1-propanol and a catalytic amount of potassium *tert*-butoxide at room temperature. The resulting (*R*)-diol mixture **20** was reacted with DMF dimethylacetal to give **21** as a mixture of stereoisomers; heating **21** with acetic anhydride yielded **14**.[26] Overall chemical yield was >90% for the three-step process, which was done in one pot without isolation or purification of the intermediates.

Conversion of the (*S*)-diol **18** into the pyridone **25** was done in four high yielding steps (Scheme 5). The primary alcohol was oxidized to the aldehyde **22** in 95% yield by sodium hypochlorite catalyzed by TEMPO,[27] carefully limiting the amount of sodium hypochlorite used to minimize oxidative cleavage of the aldehyde. Hydrogenation of the benzyl ether gave the lactol **23** as essentially a single diastereomer in 96% yield by crystallization from methanol. Alternatively, **23** can be isolated by crystallization from heptane/THF in 91.7% yield; this crystallization removes impurities that may form in the Tempo oxidation and upgrades the ee from >99% to >99.8% as determined by chiral HPLC assay. A second TEMPO

(21) Preliminary experiments were done with asymmetric dihydroxylations[22] on the dimethyl analog **17**. Reaction with 1 mol % potassium osmate and 1 mol % $DHQD_2$-phthal required 48 h to go to >90% completion and gave diol product with an ee of 68% (Henegar, K. E.; Baughman, T. A., unpublished results). In view of our requirement for an ee > 99% for the final product and time constraints, optimization of the asymmetric dihydroxylation was deferred in favor of a lipase resolution of the racemic diol to establish the enantiomeric purity.



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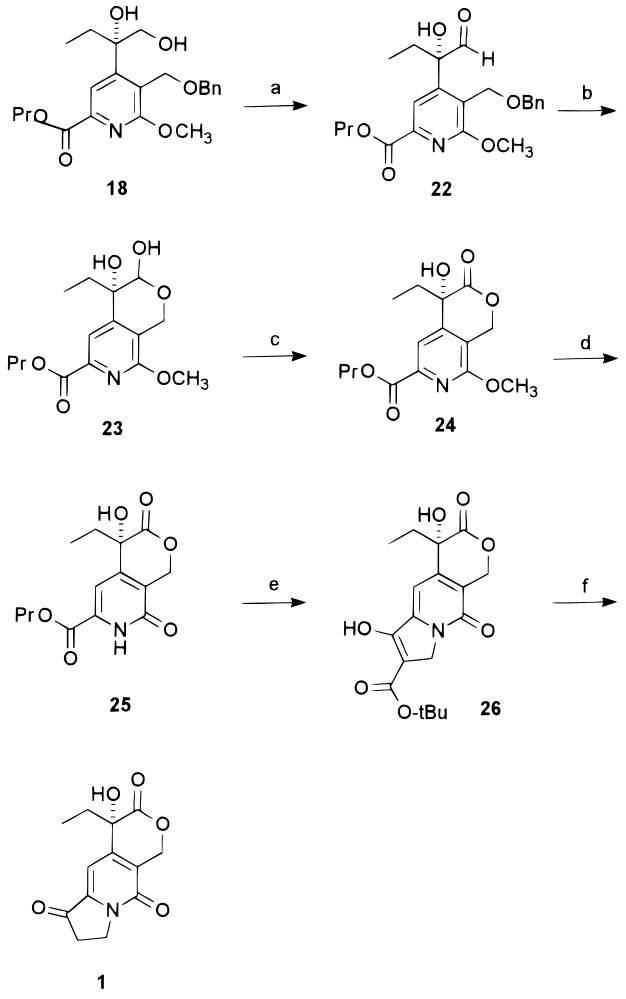
Scheme 5[a]

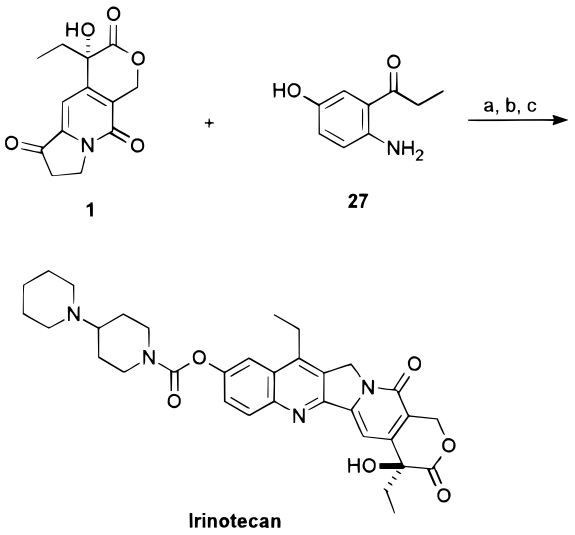


[a] (a) NaOCl, Tempo, 95%; (b) H_2, Pd/C, 92%; (c) NaOCl, Tempo, 95%; (d) TMSCl, NaI, 85%; (e) t-butyl acrylate, Cs_2CO_3, DMSO, 75%; (f) TFA, toluene, 95%.

oxidation converted the lactol into the lactone **24** (95% yield) and reaction of **24** with TMS-I, generated in situ from TMS-Cl and sodium iodide in acetonitrile,[6e,28] gave the pyridone **25** in 89% yield after crystallization from EtOAc−MTBE. Enantiomeric purity of the pyridone was determined by chiral HPLC to be >99.8%.

Annulation of the cyclopentanone ring was done with *tert*-butyl acrylate (10 equiv) and cesium carbonate (2 equiv) in DMSO at 50 °C to give **26**, isolated as the crystalline solvate with toluene (1:1) in 75% yield. The product exists entirely in the enol form. Deesterification and decarboxylation of **26** was done in toluene with TFA as the acidic catalyst to give (*S*)-**1** in 95% yield as a crystalline solid. Purification of **1**, if necessary, can be done by crystallization from methylene chloride−ethyl acetate, but the product is unstable to silica and cannot readily be purified by chromatography. Establishment of absolute stereochemistry of **1** was done by comparison of its measured rotation with the values reported in the literature for material of known stereochemistry (see Experimental Section). Chiral HPLC analysis of **1** showed no detectable *R* enantiomer (ee > 99.6%, limit of detection 0.2%); precursors **23** and **25** had ee > 99.8% (limits of detection 0.1%). Further confirmation of enantiomeric purity was obtained after conversion into irinotecan.

Scheme 6[a]



[a] (a) **27**, AcOH, p-TSA; (b) 4-piperidinopiperidinecarbamyl chloride, pyridine; (c) chromatography, 80.9% overall.

Irinotecan was made from **1** in three steps (Scheme 6). Reaction of **1** with 2-amino-5-hydroxypropiophenone (**27**)[29] yields the intermediate phenol SN-38, not normally isolated and difficult to manipulate due to its poor solubility in most common organic solvents. Conversion of SN-38 into irinotecan was then done using the published procedure[1] by reaction with 4-piperidinopiperidinecarbamyl chloride followed by purification and salt formation to give irinotecan in 70% overall yield from **1**, identical to material obtained from Yakult Honsha. Analysis of this material by chiral HPLC showed the enantiomeric purity to be >99.8% (*R* enantiomer detection limit 0.1%).

Conclusion

The synthesis described produces (*S*)-**1**, a valuable intermediate for the synthesis of camptothecin and analogs, with an ee > 99.6% in 18 chemical steps and 6.4% overall yield on a laboratory scale, uncorrected for recovery of unreacted **5** or recycle of **19**. The synthesis starts with inexpensive, readily available materials and is operationally simple to perform. Enantiomeric purity is established with an efficient lipase resolution and only one chromatography is required. The chemistry described was scaled up successfully with minimal modifications; the initial piloting gave >35 kg of **26** in 6.3% overall yield with eight isolated intermediates.

Experimental Section

Materials were used as received from commercial suppliers. Melting points were determined on an automatic melting point determination instrument. Optical rotations were determined

(28) (a) Olah, G. A.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247−1251. (b) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761−3763. (c) Morita, T.; Okamoto, Y.; Sakurai, H. *J. Chem. Soc., Chem. Commun.* **1978**, 874−875.

(29) Giovannini, E.; Rosales, J.; de Souza, B. *Helv. Chem. Acta* **1971**, *54*, 2111−2113. Material used here was prepared from 2-nitro-5-hydroxybenzaldehyde (five steps) or from *p*-anisidine (one step) (Baughman, T. A.; Hewitt, B. D.; Henegar, K. E., unpublished results).

(30) Tagawa, H.; Terasawa, H.; Ejima, A. Eur. Pat. Appl. 114231, 1986.

with a Rudolph Autopohl III polarimeter using a 10 cm path length cell. Infared spectra were recorded, as noted, in KBr for solid samples (2 mg sample/200 mg KBr) or as thin films for oils. Microanalyses were performed by Structural and Medicinal Chemistry (Pharmacia and Upjohn). MTBE refers to methyl *tert*-butyl ether. All silica used was 230−400 mesh.

2,6-Dichloro-4-pyridinecarboxylic Acid (2). Citrazinic acid (152.0 g, 0.98 mol) and Me_4NCl (107.71 g, 1.02 mol) were suspended in $POCl_3$ (450 g, 273 mL, 2.9 mol) and heated in a 130 °C bath. When the internal temperature reached 75 °C the solids dissolved with a slight exotherm to yield a clear brown solution. The reaction mixture was heated at 130 °C for 18 h and then heated to 145 °C for 2 h. After cooling to rt, the mixture was poured onto 2 kg of ice and stirred for 2 h. The resulting solids were filtered and dried and then stirred with 1.5 L of EtOAc and filtered to remove insoluble material (primarily citrazinic acid). The organic solution was dried over Na_2SO_4 and evaporated to yield 146.9 g (78%) of a light brown solid: mp 203.8−204.7 °C, (lit.[12] mp. 205−207 °C); IR (KBr) 1723 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.80 (s, 2 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 122.9, 144.6, 150.1, 163.7; MS (CI) *m*/*e* 192, 194 ($M^{\cdot+}$), 165, 167, 148, 150, 131, 133, 114, 116.

1-(2,6-Dichloro-4-pyridinyl)-1-propanone (3). Compound **2** (6.6 g, 34 mmol) was mixed with 82 mL of THF and the mixture cooled to −40 °C. Ethylmagnesium chloride in THF (52 mL, 104 mmol) was added over 15 min, keeping the internal reaction temperature less than −30 °C. The resulting dark brown mixture was allowed to warm to 0 °C and stirred at 0 °C for 1 h. The reaction mixture was recooled to −25 °C, and 3.2 mL (52 mmol) of methyl formate was added. After 15 min at −25 °C, 20 mL of 6 M HCl was added and the mixture was allowed to warm to rt. The phases were separated, and the lower aqueous phase was extracted with THF (3 × 10 mL). The combined THF phases were washed twice with a mixture of 15 mL of 1 N NaOH and 15 mL of saturated aqueous NaCl and then once with 15 mL of saturated aqueous NaCl solution. The organic phase was dried over Na_2SO_4 and then concentrated to an oil. Toluene (50 mL) was added, the mixture was concentrated to an oil, and the process was repeated to yield 6.01 g (84%) of a clear brown oil which crystallized under vacuum: mp 61.1−62.4 °C; IR (KBr) 1700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (t, J = 7.1 Hz, 3 H), 2.88 (q, J = 6.6 Hz, 2 H), 7.61 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.5, 32.6, 120.9, 147.7, 151.8, 197.1; MS (EI) *m*/*e* 203, 205 ($M^{\cdot+}$), 174, 176, 146, 148, 110, 85, 76, 60, 50. Anal. Calcd for $C_8H_7Cl_2NO$: C, 47.09; H, 3.46; Cl, 34.75; N, 6.86. Found: C, 46.97; H, 3.39; Cl, 34.39; N, 6.84.

2,6-Dichloro-4-(2-ethyl-1,3-dioxolan-2-yl)pyridine (4). Ketone **3** (90.2 g, 0.44 mol), ethylene glycol (650 mL), and TMSCl (140 mL, 1.1 mol) were stirred at rt. White crystals gradually formed in the mixture. After about 12 h the reaction had gone to completion. The reaction was neutralized by the addition of 1 L of 1 N NaOH solution and extracted with 1:1 EtOAc/heptane (3 × 250 mL). The organic extracts were combined, dried over Na_2SO_4, and evaporated. The crystalline residue was dried under high vacuum to yield 109.71 g (100%) of the product: mp 94.0−95.0 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.80 (t, J = 7.4 Hz, 3 H), 1.78 (q, J = 7.4 Hz, 2 H), 3.72 (t, J = 7.0 Hz, 2 H), 3.99 (t, J = 7.0 Hz, 2 H), 7.27 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.4, 32.8, 65.1, 108.9, 120.3, 150.6, 158.0; MS (EI) *m*/*e* 218, 220 ($M^{\cdot+}$), 174, 176, 110, 101, 85, 76, 57. Anal. Calcd for $C_{10}H_{11}Cl_2NO_2$: C, 48.41; H, 4.47; Cl, 28.58; N, 5.65. Found: C, 48.41; H, 4.55; Cl, 28.55; N, 5.65.

6-Chloro-4-(2-ethyl-1,3-dioxolan-2-yl)-2-methoxypyridine (5). Compound **4** (57.5 g, 0.23 mol) was dissolved in 170 mL of MeOH. NaOMe solution in MeOH (80 mL, 0.35 mol, 25 wt %) was added and the mixture heated to reflux for 20 h. After cooling to rt, 250 mL of water and 200 mL of CH_2Cl_2 were added. The aqueous phase was extracted with CH_2Cl_2 (2 × 200 mL). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated to an amber oil which crystallized upon seeding to yield 50.43 g (89%) of **5** as a light yellow solid: mp 48.1−49.0 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 7.4 Hz, 3 H), 1.85 (q, J = 7.5 Hz, 2 H), 3.78 (t, J = 6.9 Hz, 2 H), 3.93 (s, 3 H), 4.02 (t, J = 7.1 Hz, 2 H), 6.73 (s, 1 H), 6.98 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.6, 32.5, 54.0, 64.8, 106.2, 109.2, 113.8, 148.3, 157.3, 163.9; MS (FAB) *m*/*e* 244, 246 ($[M + H]^+$), 101. HRMS (FAB) *m*/*e* calcd for $C_{11}H_{15}ClNO_3$: ($[M + H]^+$) 244.0740; found: ($[M + H]^+$), 244.0743. Anal. Calcd for $C_{11}H_{14}ClNO_3$: C, 54.22; H, 5.79; Cl, 14.55; N, 5.75. Found: C, 54.30; H, 6.01; Cl, 14.40; N, 5.73.

6-Chloro-4-(2-ethyl-1,3-dioxolan-2-yl)-2-methoxy-3-pyridinecarboxaldehyde (6) and 6-Chloro-4-(2-ethyl-1,3-dioxolan-2-yl)-2-methoxy-3-pyridinemethanol (8). Compound **5** (73.05 g, 0.299 mol) was dissolved in 1400 mL of heptane and cooled to −10 °C. A solution of *n*-BuLi in hexanes (235 mL, 0.588 mol) was added over 10 min, keeping the internal temperature <5 °C. The turbid orange solution was stirred at 0 °C for 30 min after completion of the butyllithium addition and then cooled to −30 °C. *N*-Formylpiperidine (66.0 mL, 0.588 mol) was added, and the mixture was allowed to warm to 0 °C and stirred for 1 h. The deep red mixture was quenched by the addition of 600 mL of 1 N HCl, the phases were separated, and the aqueous phase was extracted with MTBE (2 × 250 mL). A portion of the combined organic phases was concentrated and chromatographed on silica with 4:1 heptane/EtOAc to yield a sample of **6**.

To the combined organic phases were added 250 mL of water, 8.3 g (0.029 mol) of *n*-Bu_4NCl, and 11.3 g (0.29 mol) of $NaBH_4$. The mixture was vigorously stirred at rt for 18 h. Acetone (20 mL) was added, and the mixture was stirred at rt for 30 min. The aqueous phase was removed, and the organic phase was washed once with 500 mL of water. The organic phase was evaporated to an oil and chromatographed on 800 g of silica using 4:1(v/v) hexane/EtOAc to yield 57.30 g (71%) of **8** as a white solid and 15.0 g (20%) of **5**.

6-Chloro-4-(2-ethyl-1,3-dioxolan-2-yl)-2-methoxy-3-pyridinecarboxaldehyde (6): mp 57.6−60.4 °C; IR (KBr) 1709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, J = 9.0 Hz, 3 H), 2.03 (q, J = 9.0 Hz, 2 H), 3.75 (m, 2 H), 4.00 (m, 2 H), 4.00 (s, 3 H), 7.13 (s, 1 H), 10.44 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.3, 33.3, 54.8, 64.8, 109.7, 114.7, 117.2, 150.8, 157.5, 161.7, 190.8; MS (FAB) *m*/*e* 272, 274 ($[M + H]^+$), 254, 101. HRMS (FAB) *m*/*e* calcd for $C_{12}H_{17}ClNO_4$: ($[M + H]^+$) 272.0689; found: ($[M + H]^+$), 272.0695. Anal. Calcd for $C_{12}H_{16}ClNO_4$: C, 53.05; H, 5.19; Cl, 13.05; N, 5.16. Found: C, 53.43; H, 5.31; Cl, 12.76; N, 5.09.

6-Chloro-4-(2-ethyl-1,3-dioxolan-2-yl)-2-methoxy-3-pyridinemethanol (8): mp 46.8−48.8 °C; IR (KBr) 3500 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, J = 7.5 Hz, 3 H), 1.87 (q, J = 7.0 Hz, 2 H), 3.74 (m, 2 H), 3.92 (s, 3 H), 3.97 (m, 2 H), 4.72 (s, 1 H), 7.05 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.5, 33.0, 54.5, 56.7, 65.0, 110.2, 114.5, 119.1, 147.4, 154.5, 163.0; MS (EI) *m*/*e* 273 ($M^{\cdot+}$), 244, 228, 210, 200, 101, 57. Anal. Calcd for $C_{12}H_{16}ClNO_4$: C, 52.66; H, 5.89; Cl, 12.95; N, 5.12. Found: C, 52.74; H, 5.66; Cl, 12.93; N, 5.18.

6-Chloro-4-(2-ethyl-1,3-dioxolan-2-yl)-2-methoxy-3-[(phenylmethoxy)methyl]pyridine (9). Alcohol **8** (503.98 g, 1.841 mol) was dissolved in 1330 mL of THF, and 1200 g of *t*-BuOK solution in THF (2.09 mol, 20 wt %) was added, keeping the internal temperature less than 30 °C. The mixture was stirred for 30 min and then benzyl bromide (230.0 mL, 2.117 mol) was added, keeping the internal temperature less than 30 °C. After completion of the benzyl bromide addition, the mixture was stirred at 20−30 °C for 1 h. Aqueous Me_2NH solution (38 mL, 40 wt %) was added, and the mixture was stirred at 20−30 °C for 30 min. A 276 mL volume of 1 N HCl and 2 L of EtOAc were added, and the phases were separated. The organic phase was washed with water (3 × 1 L) and evaporated to give 663.5 g (99.3%) of **9** as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.75 (t, J = 7.4 Hz, 3 H), 1.82 (q, J = 7.4 Hz, 2 H), 3.61 (m, 2 H), 3.82 (s, 3 H), 3.85 (m, 2 H), 4.48 (s, 2 H), 4.57 (s, 2 H), 6.97 (s, 1 H), 7.23 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.5, 33.0, 54.5, 62.83, 64.7, 73.2, 110.1, 114.8, 116.4, 127.5, 127.8, 128.2, 138.4, 147.9, 155.6, 163.7; MS (EI) *m*/*e* 363 ($M^{\cdot+}$), 272, 254, 228, 210, 101, 91. Anal. Calcd for $C_{19}H_{22}ClNO_4$: C, 62.72; H, 6.09; Cl, 9.74; N, 3.85. Found: C, 62.88; H, 6.12; Cl, 9.72; N, 4.14.

6-Chloro-4-(2-ethyl-1,3-dioxolan-2-yl)-2-methoxy-3-(methoxymethyl)pyridine (10). Alcohol **8** (0.980 g, 3.6 mmol), 2.8 g of *t*-BuOK solution in THF (5 mmol, 20 wt %), and 10 mL of THF were stirred at rt for 10 min. CH_3I (0.31

mL, 5 mmol) was added, causing the immediate formation of a white precipitate. After 10 min, 10 mL of saturated aqueous NH_4Cl solution was added. The aqueous phase was extracted with 10 mL of ether. The organic phases were combined, dried over Na_2SO_4, and evaporated to yield 1.026 g (99%) of **10** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75 (t, J = 7.5 Hz, 3 H), 1.80 (q, J = 7.5 Hz, 2 H), 3.28 (s, 3 H), 3.64 (m, 2 H), 3.82 (m, 3 H), 3.87 (2, 2 H), 4.46, (s, 2 H), 6.96 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.4, 33.0, 54.5, 58.6, 64.7, 64.8, 110.1, 114.8, 116.3, 147.8, 155.5, 163.6; MS (EI) m/e 287 ($M^{\cdot+}$), 258, 242, 214, 184, 101.

4-(2-Ethyl-1,3-dioxolan-2-yl)-2-methoxy-3-(methoxymethyl)pyridine (11). Ether **10** (0.166 g, 0.6 mmol) and 0.18 g (1.6 mmol) of anhydrous $NiCl_2$ were stirred with 5 mL of THF and cooled to −40 °C. LAH solution (2 mL, 2 mmol) in THF was added, causing gas evolution and the immediate formation of a black precipitate. The mixture was stirred and allowed to warm to rt. After 3 h, 10 mL of saturated aqueous NH_4Cl solution was added. The mixture was filtered over Celite to remove black solids. The aqueous phase was extracted with 10 mL of ether, and the combined organic phases were dried over Na_2SO_4. Evaporation yielded 0.127 g (83.6%) of **10** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78 (t, J = 7.5 Hz, 3 H), 1.84 (q, J = 7.4 Hz, 2 H), 3.32 (s, 3 H), 3.62−3.67 (m, 2 H), 3.18−3.91 (m, 2 H), 3.86 (s, 3 H), 4.54 (s, 2 H), 6.94 (d, J = 5.4 Hz, 1 H), 7.95 (d, J = 5.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.5, 33.1, 53.8, 58.6, 64.3, 65.3, 110.3, 115.3, 117.7, 146.0, 152.5, 163.9; MS (EI) m/e 253 ($M^{\cdot+}$), 224, 208, 180, 150, 101.

4-(2-Ethyl-1,3-dioxolan-2-yl)-6-methoxy-5-[(phenylmethoxy)methyl]-2-pyridinecarboxylic Acid, Propyl Ester (12). Compound **9** (66.45 g, 183 mmol), $Pd(OAc)_2$ (2.05 g, 9.13 mmol), DPPP (4.14 g, 10.0 mmol), K_2CO_3 (37.86 g, 274 mmol), *n*-PrOH (665 mL), and DMF (332 mL) were charged to a flask. The flask was purged with nitrogen and then with carbon monoxide. The mixture was vigorously stirred and heated to 90 °C under an atmosphere of carbon monoxide (15 psi) for about 16 h. The reaction was cooled and vented. The solids were removed by filtration through Celite, and the Celite was washed with 350 mL of THF. The combined filtrates and washing were concentrated to a volume of about 400 mL. Water (700 mL) and MTBE (700 mL) were added. The aqueous phase was separated and extracted with 350 mL of MTBE. The combined MTBE solutions were extracted with water (4 × 350 mL), dried over Na_2SO_4, and evaporated. Chromatography on 600 g of silica with 80:20 (v/v) heptane/EtOAc yielded 68.03 g (89%) of **12** as a faintly orange oil: IR (film) 1736 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 7.4 Hz, 3 H), 0.98 (t, J = 7.4 Hz, 3 H), 1.77 (m, 2 H), 1.93 (q, J = 7.4 Hz, 2 H), 3.71 (m, 2 H), 3.94 (m, 2 H), 3.99 (s, 3 H), 4.26 (t, J = 6.7 Hz, 2 H), 4.59 (s, 2 H), 4.74 (s, 2 H), 7.29 (m, 5 H), 7.82 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.5, 10.4, 22.0, 33.1, 54.1, 63.1, 64.7, 67.0, 73.3, 110.3, 117.0, 122.1, 127.5, 128.0, 128.2, 138.4, 144.7, 153.6, 163.9, 165.3; MS (EI) m/e 415 ($M^{\cdot+}$), 386, 324, 306, 280, 262, 101, 91. Anal. Calcd for $C_{23}H_{29}NO_6$: C, 66.49; H, 7.04; N, 3.37. Found: C, 66.65; H, 7.70; N, 3.42.

6-Methoxy-4-(1-oxopropyl)-5-[(phenylmethoxy)methyl]-2-pyridinecarboxylic Acid, Propyl Ester (13). Ketal **12** (68.02 g, 163.7 mmol) was dissolved in 384 mL of 50% aqueous TFA, and the mixture was stirred at rt for 21 h. Water (880 mL) was added, and the mixture was extracted with EtOAc (2 × 500 mL). The organic phases were combined and washed with water (2 × 500 mL) and then neutralized with saturated aqueous $NaHCO_3$ solution. The organic phase was dried over Na_2SO_4 and evaporated to yield 59.86 g (98.4%) of **13** as a light yellow oil: IR (film) 1715 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (m, 6 H), 1.72 (m, 2 H), 2.68 (q, J = 7.2 Hz, 2 H), 3.96 (s, 3 H), 4.23 (t, J = 6.7 Hz, 2 H), 4.42 (s, 2 H), 4.58 (s, 2 H), 7.24 (m, 5 H), 7.48 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.5, 10.4, 22.0, 36.2, 54.1, 63.8, 67.2, 73.6, 115.5, 121.5, 127.9, 128.0, 128.2, 128.4, 137.3, 144.9, 151.0, 161.3, 164.5; MS (FAB) m/e 372 ([M + H]$^+$), 280, 264, 91. HRMS (FAB) m/e calcd for $C_{21}H_{26}CNO_5$: ([M + H]$^+$) 372.1811; found: ([M + H]$^+$), 372.1809. Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77. Found: C, 67.70; H, 6.69; N, 4.03.

6-Methoxy-4-(1-methylenepropyl)-5-[(phenylmethoxy)methyl]-2-pyridinecarboxylic Acid, Propyl Ester (14). Methyltriphenylphosphonium bromide (2.14 g, 6.0 mmol) was dissolved in 15 mL of DMF and stirred at 0 °C. Potassium bis(trimethylsilyl)amide solution in toluene (10 mL, 5.0 mmol) was added, and the yellow solution with suspended white solids was stirred at 0 °C for 10 min. A solution of ketone **13** (1.48 g, 4.0 mmol) in 5 mL of THF was added all at once, giving a deep red color that rapidly faded to brown. The mixture was stirred at 0 °C for 10 min. Additional ylide solution was added until all of the **12** was consumed. The reaction was quenched by the addition of 10 mL of 1 N HCl. MTBE (20 mL) was added, the phases were separated, and the aqueous phase was extracted with MTBE (2 × 20 mL). The combined organic phases were washed with water (3 × 20 mL), dried over Na_2SO_4, and evaporated to a volume of about 15 mL. The solution was chromatographed on 20 g of silica with 4:1 hexane/EtOAc to yield 1.39 g of **14** (92%) as a light yellow oil: IR (film) 1740, 1718 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (m, 6 H), 1.59 (m, 2 H), 2.20 (q, J = 7.4 Hz, 2 H), 3.89 (s, 3 H), 4.12 (t, J = 6.7 Hz, 2 H), 4.33 (s, 2 H), 4.42 (s, 2 H), 4.89 (s, 1 H), 5.06 (s, 1 H), 7.17 (m, 5 H), 7.35 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.4, 12.1, 22.0, 30.2, 53.9, 63.8, 67.0, 73.0, 114.7, 118.7, 121.4, 127.6, 127.9, 128.3, 138.2, 144.5, 147.6, 155.3, 163.1, 165.2; MS (FAB) m/e 370 ([M + H]$^+$), 340, 278, 262, 220, 190, 160, 91. HRMS (FAB) m/e calcd for $C_{22}H_{27}NO_4$: ([M + H]$^+$) 370.2018; found: ([M + H]$^+$), 370.2017. Anal. Calcd for $C_{22}H_{26}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C,71.74; H, 7.28; N, 3.87.

The above chromatography also yielded 0.028 g (2.2%) of the diene **15** as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (t, J = 7.35 Hz, 3 H), 2.21 (s, 3 H), 2.40 (q, J = 7.35 Hz, 2 H), 4.04 (s, 3 H), 4.55 (s, 2 H), 4.62 (s, 2 H), 5.06 (s, 1 H), 5.22 (s, 1 H), 5.27 (s, 1 H), 6.02 (s, 1 H), 6.87 (s, 1 H), 7.31−7.42 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.1, 20.2, 29.4, 30.4, 53.3, 63.9, 72.7, 112.5, 113.6, 115.2, 115.9, 127.4, 127.6, 127.9, 128.2, 138.6, 142.5, 148.7, 154.3, 155.1, 162.0; MS (EI) m/e 323 ($M^{\cdot+}$), 232, 216, 204, 202, 91.

4-[1-Hydroxy-1-(hydroxymethyl)propyl]-6-methoxy-5-[(phenylmethoxy)methyl]-2-pyridinecarboxylic Acid, Propyl Ester (16). Olefin **14** (100.0 g, 0.271 mol), $Me_3NO{-}2H_2O$ (90.24 g, 0.81 mmol), OsO_4 (0.68 g, 2.7 mmol), and *t*-BuOH (300 mL) were charged to a flask. The mixture was heated to 40 °C for 24 h and then cooled to 20−25 °C. Water (300 mL) and sodium bisulfite (110 g) were added, and the mixture was stirred for 30 min at rt. The mixture was extracted with EtOAc (4 × 200 mL). The combined organic phases were stirred with 100 g of magnesol for 1 h, and then the slurry was filtered over 50 g of magnesol. The filtrates were concentrated to an oil. Toluene (200 mL) and heptane (800 mL) were added, and the mixture was allowed to crystallize at −20 °C for 18 h. The solids were filtered, washed with 200 mL heptane, and dried to yield 83.51 g of white solids. Concentration of the mother liquors yielded an additional 3.21 g of white solids. The dark mother liquors were chromatographed on about 500 g of silica with 2:1 heptane/EtOAc to yield 13.75 g of product. Total yield of **16**: 100.47 g, 92%: mp 97.5−101.0 °C; IR (KBr) 3448, 1715 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.74 (t, J = 7.4 Hz, 3 H), 1.03 (t, J = 7.4 Hz, 3 H), 1.80 (m, 4 H), 3.69 (d, J = 11.2 Hz, 1 H), 3.86 (d, J = 11.2 Hz, 1 H), 4.01 (s, 3 H), 4.31 (t, J = 6.7 Hz, 2 H), 4.88 (d, J = 10.7 Hz, 1 H), 4.96 (d, J = 10.7 Hz, 1 H), 7.33 (m, 5 H), 7.64 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.5, 10.4, 22.0, 31.7, 54.2, 62.9, 67.1, 70.9, 72.7, 80.1, 117.8, 122.2, 128.0, 128.4, 137.1, 144.7, 155.8, 163.2, 165.2; MS (FAB) m/e 404, ([M + H]$^+$), 296, 278, 250, 222, 190, 162, 91. HRMS (FAB) m/e calcd for $C_{22}H_{29}NO_6$: ([M + H]$^+$) 404.2073; found: ([M + H]$^+$), 404.2076. Anal. Calcd for $C_{22}H_{29}NO_6$: C, 65.48; H, 7.25; N, 3.47. Found: C, 65.76; H, 7.28; N, 3.49.

(*S*)-4-[1-Hydroxy-1-(hydroxymethyl)propyl]-6-methoxy-5-[(phenylmethoxy)methyl]-2-pyridinecarboxylic Acid, Propyl Ester (17). Racemic diol **16** (100 g, 0.25 mol) and 100 g of PS-30 catalyst (*Pseudomonas cepaica* lipase immobilized on equal weight of Celite 521) were suspended in 2.5 L of MTBE. Isopropenyl acetate (75 mL, 0.68 mol) was added, and

the mixture was stirred at rt for 48 h, when HPLC analysis showed <2% *R* alcohol. MTBE (1 L) was added, and the mixture was heated to 35−40 °C. The catalyst was removed by filtration, washed with 300 mL of MTBE, and saved for reuse. The combined filtrate and washing were evaporated to an oil and redissolved in 200 mL of CH_2Cl_2. The solution was chromatographed on 600 g of silica eluting first with 4:1 heptane/EtOAc and then with 1:1 heptane/EtOAc. Evaporation of the product containing fractions yielded 38 g (76% of theory) of **18** as a white solid (>99% ee by HPLC): mp 99.0−100.1 °C; $[\alpha]^{25}_D = +4.08°$ (*c* 1.0, $CHCl_3$); IR (KBr) 3450, 1716 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.74 (t, $J = 7.4$ Hz, 3 H), 1.03 (t, $J = 7.4$ Hz, 3 H), 1.80 (m, 4 H), 3.69 (d, $J = 11.2$ Hz, 1 H), 3.86 (d, $J = 11.2$ Hz, 1 H), 4.01 (s, 3 H), 4.31 (t, $J = 6.7$ Hz, 2 H), 4.88 (d, $J = 10.7$ Hz, 1 H), 4.96 (d, $J = 10.7$ Hz, 1 H), 7.33 (m, 5 H), 7.64 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.5, 10.4, 22.0, 31.7, 54.2, 62.9, 67.1, 70.9, 72.7, 80.1, 117.8, 122.2, 128.0, 128.4, 137.1, 144.7, 155.8, 163.1, 165.2; MS (FAB) *m*/*e* 404 ($[M + H]^+$), 296, 278, 250, 222, 162, 91. Anal. Calcd for $C_{22}H_{29}NO_6$: C, 65.48; H, 7.25; N, 3.47. Found: C, 65.52; H, 7.35; N, 3.50. Chiral HPLC: Chiralpak AD column (4.6 mm × 25 cm); 90:10 hexane/IPA; 1 mL/min; 295 nm; (*S*)-**19**, 8.1 min; (*R*)-**19**, 8.5 min; (*S*)-**18**, 15.1 min; (*R*)-**18**, 16.7 min.

The above chromatography also yielded 67.75 g (60%) of **monoacetate 19** as a viscous, slightly yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.81 (t, $J = 7.4$ Hz, 3 H), 1.05 (t, $J = 7.4$ Hz, 3 H), 1.81 (s, 3 H) 1.77−2.0 (m, 4 H), 4.04, (s, 3 H), 4.25 (d, $J = 11.3$ Hz, 1 H), 4.33 (t, $J = 6.7$ Hz, 2 H), 4.40 (d, $J = 11.3$ Hz, 1 H), 4.55 (s, 2 H), 5.01 (s, 2 H), 5.26 (s, 1 H), 7.28−7.38 (m, 5 H), 7.56 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.2, 10.3, 20.4, 22.0, 32.2, 54.1, 62.9, 67.1, 71.9, 72.4, 78.5, 117.5, 122.6, 122.8, 127.9, 128.3, 137.3, 144.7, 155.1, 163.1, 165.0, 170.6; MS (CI) *m*/*e* 446 ($[M + H]^+$), 404, 340, 266.

Recycle of 19 To Yield 6-Methoxy-4-(1-methylenepropyl)-5-[(phenylmethoxy)methyl]-2-pyridinecarboxylic Acid, Propyl Ester (14). Monoacetate **19** (100.0 g, 0.224 mol), CH_2Cl_2 (100 mL), *n*-PrOH (200 mL), and *t*-BuOK (0.8 g) were stirred at rt for 4 h. Removal of the acetate was complete at this time. The solution was distilled to dryness under vacuum, toluene (300 mL) was added, and the mixture was distilled to dryness. Toluene (300 mL) was again added, and the mixture was distilled to dryness under vacuum to yield crude **20** as a yellow solid (95.8 g), identified by comparison with **16** by HPLC.

The entire crude diol **20** was dissolved in 400 mL of THF. DMF dimethyl acetal (45 mL, 0.337 mol) and p-TSA−H_2O (2.0 g) were added, and the solution was heated under reflux for 30 min. THF was then distilled under atmospheric pressure until 200 mL of distillate had been collected. DMF dimethyl acetal (10 mL) and THF (200 mL) were then added, and distillation under atmospheric pressure was continued until 200 mL of distillate had been collected. Reaction was complete at this point, and the mixture was distilled under vacuum to yield crude **21** as an oil: (mixture of diastereomers) ^1H NMR (300 MHz, $CDCl_3$) δ 0.81 (q, $J = 7.4$ Hz, 3 H), 1.05 (t, $J = 7.4$ Hz, 3 H), 1.77−1.99 (m, 4 H), 2.34 and 2.47 (s, total of 6 H), 4.07 (s, 3 H), 4.12 (s, 1 H), 4.34 (t, $J = 6.6$ Hz, 2 H), 4.40−4.52 (m, 2 H), 4.65 (s, 2 H) 5.41 and 5.61 (s, total of 1 H), 7.28−7.39 (m, 5 H), 7.92 and 8.00 (s, total of 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.2, 8.2, 10.3, 22.0, 32.8, 34.0, 36.9, 37.0, 54.0, 63.3, 67.0, 73.5, 73.9, 83.3, 84.3, 112.4, 116.6, 117.0, 120.3, 127.8, 128.0, 128.3, 137.7, 144.7, 144.9, 154.4, 155.6, 163.6, 163.8, 165.2.

The entire crude DMF acetal **21** was heated with 200 mL of Ac_2O at 100 °C for 16 h. After cooling to about 50 °C the light yellow solution was added in three portions to 200 mL of water. The mixture was stirred for 30 min, then extracted with toluene (1 × 200 mL and 1 × 100 mL). The combined toluene extracts were washed with 100 mL of saturated aqueous NaCl solution and then stirred with 10 g of silica. The toluene slurry was filtered over 20 g of silica and the silica washed with 100 mL of 95:5 toluene/EtOAc. The combined filtrates and washing were evaporated to yield 80.1 g of a clear honey-colored oil; contained weight of **14** was 64.4 g, 90.1% overall from **19**, as determined by quantitative HPLC weight % assay with chromatographically purified **14** as reference. ^1H NMR analysis showed the main impurity to be toluene.

(*S*)-4-(1-Formyl-1-hydroxypropyl)-6-methoxy-5-[(phenylmethoxy)methyl]-2-pyridinecarboxylic Acid, Propyl Ester (22). (*S*)-Diol **18** (0.565 g, 1.4 mmol), 4-acetoxy-TEMPO (0.006 g, 0.028 mmol), KBr (0.0167 g, 0.14 mmol), and $NaHCO_3$ (0.0153 g, 0.182 mmol) were charged to a flask. CH_2Cl_2 (7 mL) and water (1 mL) were added, and the mixture was cooled to 0 °C. A solution of NaOCl (1.6 mL, 0.95 M) was added via syringe pump over about 40 min. At the end of this addition the reaction was quenched by the addition of 1 mL of 5% (w/v) aqueous sodium metabisulfite solution. The aqueous phase was separated and extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phases were dried over Na_2SO_4 and evaporated to yield 0.601 g (100%) of **22** as a brown syrup: $[\alpha]^{25}_D = +30.8°$ (*c* 0.65, CH_2Cl_2); IR (film) 1719 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, $J = 7.5$ Hz, 3 H), 1.03 (t, $J = 7.5$ Hz, 3 H), 1.83 (m, 2 H), 2.10 (m, 2 H), 4.02 (s, 3H), 4.35 (t, $J = 6.6$ Hz, 2 H), 4.55 (s, 2 H), 4.68 (d, $J = 11.7$ Hz, 1 H), 4.87 (d, $J = 11.7$ Hz, 1 H), 7.35 (m, 5 H), 7.78 (s, 1 H), 9.62 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.2, 10.4, 22.0, 29.7, 54.3, 63.2, 67.2, 73.1, 82.4, 117.4, 122.5, 128.2, 128.5, 136.7, 145.0, 150.5, 162.9, 164.9, 200.1; MS (FAB) *m*/*e* 402 ($[M + H]^+$), 384, 372, 294, 265, 238, 206, 178, 91. HRMS (FAB) *m*/*e* calcd for $C_{22}H_{28}NO_6$: ($[M + H]^+$) 402.1916; found: ($[M + H]^+$), 402.1924. Anal. Calcd for $C_{22}H_{27}NO_6$: C, 65.82; H, 6.78; N, 3.49. Found: C, 65.56; H, 6.72; N, 3.5. Chiralpak AD column (4.6 mm × 25 cm); 90:10 hexane/IPA; 1 mL/min, 295 nm; (*S*)-**22**, 12.3 min; (*R*)-**22**, 13.9 min.

(*S*)-4-Ethyl-3,4-dihydro-3,4-dihydroxy-8-methoxy-1*H*-pyrano[3,4-*c*]pyridine-6-carboxylic Acid, Propyl Ester (23). a. Isolation From Methanol. Aldehyde **22** (2.62 g, 6.6 mol) was dissolved in 30 mL of MeOH and stirred with 10% Pd/C (0.26 g) under an atmosphere of hydrogen (15 psi) at rt. After 96 h the reaction was complete. The catalyst was removed by filtration through Celite and washed with 10 mL of MeOH. Evaporation of the combined filtrate and washing yielded 1.97 g (96%) of **23** as a white solid: mp 126.5−131.1 °C; $[\alpha]^{25}_D = -65.1°$ (*c* 1.0, $CHCl_3$); IR (KBr) 1740, 1716 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, $J = 7.5$ Hz, 3 H), 0.95 (t, $J = 7.4$ Hz, 3 H), 1.73 (m, 4 H), 3.89 (s, 3 H), 4.24 (t, $J = 6.7$ Hz, 2 H), 4.57 (d, $J = 17.2$ Hz, 1 H), 4.73 (d, $J = 17.2$ Hz, 1H), 7.86 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.5, 10.4, 21.9, 31.7, 53.7, 58.3, 67.0, 70.7, 93.3, 116.6, 120.4, 143.5, 149.0, 158.5, 165.3; MS (EI) *m*/*e* 311, ($M^{\cdot+}$), 265, 252, 236, 224, 209, 194, 179, 166, 57. Anal. Calcd for $C_{15}H_{22}NO_6$: C, 57.68; H, 7.10; N, 4.48. Found: C, 57.29; H, 6.91; N, 4.44. Chiralpak AD column (4.6 mm × 25 cm); 90:10 hexane/IPA; flow rate 1 mL/min; 295 nm detector; (*S*)-**23**, 10.2 min; (*R*)-**23**, 19.9 min.

b. Isolation by Crystallization from THF−MTBE. Aldehyde **22** (12.5 kg, 31.17 mol) was dissolved in 60 L of MeOH and stirred with 1.5 kg of 5% Pd/C (50% water wet) under 45 psi hydrogen, maintaining the internal temperature <45 °C. The reaction was complete in 2 h. The catalyst was removed by filtration and washed with 20 L of MeOH. The combined filtrate and washing were distilled under vacuum to a volume of 30 L. Heptane (83 L) and THF (22.1 L) were added, and the mixture was heated to 45 °C for 30 min to dissolve the solids. The solution was cooled to 20−25 °C for 1 h and then to −25 °C. The solids were filtered, washed with 50 L of heptane, and dried at 40 °C. Yield of **23** was 8.89 kg (91.7%) as a white crystalline solid. Properties of this product were identical to those of previously characterized material. Starting material **22** assayed at >99% ee, product **23** assayed at >99.8% ee.

(*S*)-4-Ethyl-3,4-dihydro-4-hydroxy-8-methoxy-3-oxo-1*H*-pyrano[3,4-*c*]pyridine-6-carboxylic Acid, Propyl Ester (24). A solution of lactol **23** (1.94 g, 6.2 mmol) in 37 mL of CH_2Cl_2 was stirred at 0 °C with a solution of TEMPO (0.04 g, 0.25 mmol), $NaHCO_3$ (0.081 g, 0.96 mmol), and KBr (0.088 g, 0.74 mmol) in 3 mL of water. NaOCl solution (12 mL, approximately 12 wt %) was added dropwise over 30 min. Sodium bisulfite (1.0 g) was added to destroy the excess NaOCl. The aqueous phase was extracted with 10 mL of

CH_2Cl_2, and the combined organic phases were washed once with 10 mL of water and dried over Na_2SO_4. The solvent was evaporated to yield 1.90 g of **24** (99%) as a colorless oil that solidified on standing: mp 93.8−94.6 °C; $[\alpha]^{25}_D = +57.6°$ (*c* 0.83, CH_2Cl_2); IR (KBr) 1736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, $J = 7.5$ Hz, 3 H), 0.97 (t, $J = 7.6$ Hz, 3 H), 1.76 (m, 4 H), 4.0 (s, 3 H), 4.25 (t, $J = 6.9$ Hz, 2 H), 5.23 (d, $J = 16.2$ Hz, 1 H), 5.52 (d, $J = 16.2$ Hz, 1 H), 7.85 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.5, 10.3, 21.9, 31.9, 54.1, 65.5, 67.2, 72.7, 114.8, 115.2, 146.0, 148.9, 158.5, 164.5, 173.5; MS (FAB) *m/e* 310, ($[M + H]^+$),280, 250, 222, 178, 57. HRMS (FAB) *m/e* calcd for $C_{15}H_{20}NO_6$: ($[M + H]^+$) 310.1290; found: ($[M + H]^+$), 310.1299. Anal. Calcd for $C_{15}H_{19}NO_6$: C, 58.25; H, 6.19; N, 4.53. Found: C, 58.04; H, 6.09; N, 4.59. Chiralpak AD column (4.6 mm × 25 cm); 90:10 hexane/IPA; 1 mL/min; 295 nm detector; (*S*)-**24**, 17.7 min; (*R*)-**24**, 25.0 min.

(*S*)-4-Ethyl-3,4,7,8-tetrahydro-4-hydroxy-3,8-dioxo-1*H*-pyrano[3,4-*c*]pyridine-6-carboxylic Acid, Propyl Ester (25). Lactone **24** (97.5 g, 0.31 mol) and NaI (94.1 g, 0.62 mol) were dissolved in 730 mL of acetonitrile and stirred at 0 °C. TMSCl (79.7 mL, 0.62 mol) was added, and the mixture was stirred and allowed to warm to rt over 12 h. Additional NaI (9.4 g, 0.062 mol) and TMSCl (8 mL, 0.062 mol) were added and stirring was continued for 6 h. 1 N Hydrochloric acid (88 mL), 38% aqueous sodium bisulfite solution (13 mL), saturated aqueous NaCl solution (195 mL), water (390 mL), and EtOAc (710 mL) were added, and the mixture was stirred for 30 min. The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 310 mL). The combined organic solutions were stirred with 4.4 g of $NaHCO_3$ and 8.8 mL of 38% aqueous sodium metabisulfite solution in 90 mL of water for 15 min. The organic phase was removed and washed with saturated aqueous NaCl solution (2 × 90 mL) and once with water (90 mL). The EtOAc solution was distilled under atmospheric pressure to a volume of about 100 mL. MTBE (100 mL) was added, and the slurry was cooled to 0 °C for 1 h. The solids were filtered, washed with MTBE (2 × 100 mL), and dried on a nitrogen press to yield 81.44 g (89%) of **25** as a light yellow solid: mp 187.6−189 °C; $[\alpha]^{25}_D = +95.55°$ (*c* 1.0, $CHCl_3$); IR (nujol) 1731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (m, 6 H), 1.80 (m, 4 H), 4.36 (t, $J = 6.0$ Hz, 2 H), 5.22 (d, $J = 16.5$ Hz, 1 H), 5.60 (d, $J = 16.5$ Hz, 1 H), 7.40 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.7, 10.3, 21.8, 31.9, 66.1, 68.7, 72.3, 107.1, 124.4, 134.4, 145.0, 159.8, 173.3, 176.6; MS (FAB) *m/e* 296, ($[M + H]^+$), 268, 236, 208, 127. HRMS (FAB) *m/e* calcd for $C_{14}H_{18}NO_6$: ($[M + H]^+$) 296.1134; found: ($[M + H]^+$), 296.1132. Anal. Calcd for $C_{14}H_{17}NO_6$: C, 56.94; H, 5.8; N, 4.74. Found: C, 56.75; H, 5.84; N, 4.81. Chiralcel OD-H column (4.6 mm × 25 cm); 80:20 hexane/EtOH; 1 mL/min; 321 nm detector; (*S*)-**25**, 16.7 min; (*R*)-**25**, 11.7 min.

(*S*)-4-Ethyl-3,4,6,7,8,10-hexahydro-4-hydroxy-3,6,10-trioxo-1*H*-pyrano[3,4-*f*]indolizine-7-carboxylic Acid, 1,1-Dimethylethyl Ester (26). Pyridone **25** (10.0 g, 0.033 mol), Cs_2CO_3 (22.0 g, 0.067 mol), *tert*-butyl acrylate (50 mL, 0.33 mol), and DMSO (160 mL) were stirred at 47−50 °C for 21 h. The mixture was cooled to rt, and 20 mL of concd HCl and 200 mL of water were added. The mixture was extracted four times with a total of 500 mL of 4:1 (v/v) toluene/EtOAc. The combined extracts were washed with water (3 × 100 mL) and then evaporated to an oil. Toluene (200 mL) was added, and the solution was concentrated to yield 11.2 g (74%) of **26** (1:1 toluene solvate) as a light yellow crystalline solid: mp 155.5−157.9 °C; $[\alpha]^{25}_D = +92.88°$ (*c* 1.0, $CHCl_3$); IR (KBr) 3528, 1745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, $J = 7.4$ Hz, 3 H), 1.50 (s, 9 H), 1.71−1.79 (m, 2 H), 2.28 (s, 3 H), 4.59 (s, 2 H), 5.16 (d, $J = 17.8$ Hz, 1 H), 5.61 (d, $J = 17.8$ Hz, 1 H), 6.94 (s, 1 H), 7.0−7.2 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.6, 21.4, 28.2, 31.4, 49.3, 66.1, 72.5, 83.5, 97.8, 105.7, 118.6, 125.2, 128.1, 128.9, 137.8, 143.8, 149.5, 156.8, 159.3, 166.0, 173.6; MS (FAB) *m/e* 364, ($[M + H]^+$), 308, 290, 260, 244, 216, 57. HRMS (FAB) *m/e* calcd for $C_{18}H_{21}NO_7$: ($[M + H]^+$) 364.1396; found: ($[M + H]^+$), 364.1394. Anal. Calcd for $C_{18}H_{21}NO_7 \cdot C_7H_8$: C, 65.92; H, 6.42; N, 3.07. Found: C, 65.63; H, 6.38; N, 3.10. ChromTech AGP column (0.4 mm × 10 cm); 0.05 M pH 5 phosphate buffer; 0.5 mL/min; 355 nm; (*S*)-**26**, 13.6 min; (*R*)-**26**, 25.8 min.

(*S*)-4-Ethyl-4-hydroxy-7,8-dihydro-1*H*-pyrano[3,4-*f*]indolizine-3,6,10(4*H*)-trione (1). Ester **26** toluene solvate (70.3 g, 0.153 mol) was dissolved in 1400 mL of toluene and 140 mL of TFA and heated at 110 °C for 2 h. The solution was cooled and concentrated under vacuum to about 350 mL. EtOAc (1 L) was added, and the mixture was cooled to −20 °C. Filtration yielded 37.92 g (93.4%) of **1** as a light brown crystalline solid: mp 177.1−178.3 °C; (lit.[6a] mp 169−170 °C; lit.[6b] mp 176−177 °C; lit.[6c] mp 170−171 °C; lit.[32] mp 172−174 °C); $[\alpha]^{25}_D = +119.57°$ (*c* 1.0, $CHCl_3$); (lit.[6b] $[\alpha]^{25}_D = +120.6°$ (*c* 0.62, $CHCl_3$); lit.[6c] $[\alpha]^{25}_D = +109.7°$ (*c* 0.76, $CHCl_3$); lit.[32] $[\alpha]^{25}_D = +117.6°$ (*c* 0.56, $CHCl_3$)); $[\alpha]^{25}_D = +104.56°$ (*c* 1.0, 4:1 $CHCl_3$−CH_3OH); (lit.[6a] $[\alpha]^{25}_D = +96°$ (*c* 0.4, 4:1 $CHCl_3$−CH_3OH)); IR (KBr) 3424, 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, $J = 7.5$ Hz, 3 H), 1.80 (q, $J = 6.0$ Hz, 2 H), 2.96 (m, 2 H), 4.36 (t, $J = 6.0$ Hz, 2 H), 5.24 (d, $J = 15.0$ Hz, 1 H), 5.66 (d, $J = 15.0$ Hz, 1 H), 7.27 (s, 1 H); ^1H NMR (300 MHz, DMSO-d_6) δ 0.80 (t, $J = 7.3$ Hz, 3 H), 1.81 (m, 2 H), 2.89 (t, $J = 6.3$ Hz, 2 H), 4.13 (t, $J = 6.3$ Hz, 2 H), 5.34 (d, $J = 17.1$ Hz, 1 H), 5.41 (d, $J = 17.1$ Hz, 1 H), 6.86 (s, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.5, 30.3, 33.7, 42.6, 65.2, 71.9, 98.5, 123.8, 140.2, 149.0, 157.0, 172.0, 197.9; MS (FAB) *m/e* 264, ($[M + H]^+$), 236, 218, 162, 123. Chiralcel OD column (4.6 mm × 25 cm); 65:35 hexane/EtOH + 0.1% TFA; 1 mL/min; 335 nm; (*S*)-**1**, 13.2 min; (*R*)-**1**, 16.2 min.

Warning: Irinotecan and SN-38, like camptothecin and other camptothecin analogs, have cytotoxic properties and are mutagenic. Appropriate precautions must be taken to avoid exposure to irinotecan and to waste streams that are generated. The following procedure was carried out in a class III glove box.

Irinotecan. Ketone **1** (10.0 g, 38.0 mmol), amino ketone **27** (7.0 g, 42 mmol), and *p*-TSA·H_2O (0.2 g) were mixed with 100 mL of toluene and 100 mL of AcOH and heated for 18 h at 95−100 °C. Solids gradually precipitated during the course of the reaction, and the mixture turned black. After 18 h the toluene and AcOH were distilled under reduced pressure to yield a black solid mass.

Pyridine (150 mL) was added to the solid (SN-38), and the mixture was stirred for 15 min at 20−25 °C. A solution of 4-piperidinopiperidinecarbamyl chloride[31] (14.0 g, 60.8 mmol) in 50 mL of CH_2Cl_2 was added. The mixture was stirred at 20−25 °C for 2 h and then distilled to dryness under reduced pressure. Toluene (200 mL) was added, and the mixture was distilled to near dryness under reduced pressure to yield the crude irinotecan base as a black solid.

The unpurified irinotecan was stirred with 200 mL of CH_2Cl_2 and 5 mL of saturated aqueous $NaHCO_3$ solution for 5 min at rt. The phases were allowed to settle, and the CH_2Cl_2 phase was removed. The aqueous phase was extracted with 100 mL of CH_2Cl_2. The CH_2Cl_2 phases were combined and distilled to yield crude solid irinotecan base.

The crude solid irinotecan base was dissolved in 100 mL of 95:5 CH_2Cl_2/MeOH and chromatographed on 300 g of silica, eluting with 95:5 CH_2Cl_2/MeOH. The product containing fractions were combined and distilled to a volume of about 100 mL under atmospheric pressure. Some product crystallization occurred at the end of the distillation. EtOH (150 mL) was added and the slurry allowed to stand at rt for 24 h. The product was filtered, washed with 100 mL of EtOH, and dried to yield 18.03 g (80.9% yield from **1**) of irinotecan base as a pale yellow solid.

Irinotecan base (17.5 g, 29.8 mmol) was suspended in 165 mL of water and heated to 80 °C. A solution of 3 mL of concd HCl (35.8 mmol) and 10 mL of water was added. The irinotecan base dissolved to yield a bright yellow solution that was filtered hot over 5 g of Darco G-60. The filtrate was cooled and allowed to stand for 24 h at rt. The resulting solids were filtered, washed with EtOH (2 × 100 mL), and dried under air to yield 17.2 g (90%, product is the trihydrate) of irinotecan as pale yellow crystals. Spectroscopic (^1H and ^{13}C NMR) and

(31) Prepared from 4-piperidinopiperidine (1. $COCl_2$, toluene, 0 °C; 2. CH_2Cl_2, K_2CO_3).

(32) Tagawa, H.; Terasawa, E. U.S. Pat. 4,778,891.

chromatographic properties (reverse phase HPLC and chiral HPLC) were identical to a sample obtained from Yakult Honsha: mp 259−260 °C, (lit.[1] mp 256.5 °C). Inertsil ODS-2 column (4.6 mm × 25 cm); 70:30 H_2O/CH_3CN + 0.2% TFA; 1 mL/min; 220 nm; **irinotecan**, 5.23 min; **SN-38**, 6.74 min. Chiralpak OD column (4.6 mm × 25 cm); 1:1 hexane/IPA; 1 mL/min; 295 nm detector; (*S*)-**irinotecan**, 16.7 min; (*R*)-**irinotecan**, 11.8 min. Enantiomeric excess of product was >99.8%; chiral HPLC showed no detectable *R* enantiomer, limit of detection 0.1%.

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Supporting Information Available: Copies of NMR spectra for compounds **1**−**6**, **8**−**16**, **18**−**26**, and irinotecan. Chiral HPLC traces for compound **1** (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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