geometrically far removed on the potential energy surface from the boat form (II), as is shown in Figure 1. Much extrapolation is then needed to determine the energy of the boat form, and the results therefore depend strongly on the nature of the model used. A quartic model for the potential energy surface may be satisfactory for four- and five-membered rings,[14] which have low barriers, but we believe that it is too restrictive and therefore unsatisfactory for describing the *entire* ring inversion energy surface in cyclohexene, even though it may be excellent in the vicinity of the half-chair. On the other hand, a less restrictive model would probably have too many adjustable parameters for the available data, so that a meaningful ring inversion energy surface is unlikely to be obtainable purely from an analysis of infrared frequencies. The present results also cast doubts on the energy surfaces for ring inversion in heterocyclic analogs of cyclohexene determined by Laane and co-workers from infrared data,[4] as the torsional constraints in all these molecules are similar; the calculated inversion barriers are also substantially higher than those obtained by MM2 calculations and by dynamic NMR.[4]

Acknowledgment. We are grateful to the National Science Foundation for support of this research. Computations were supported by a Joint Study grant from the IBM Corporation and the UCLA Office of Academic Computing on an IBM ES/9000 Model 900 computer.

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A 10-Step, Asymmetric Synthesis of (*S*)-Camptothecin

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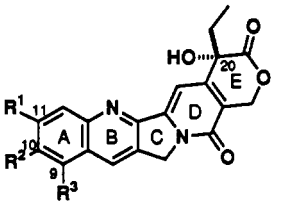
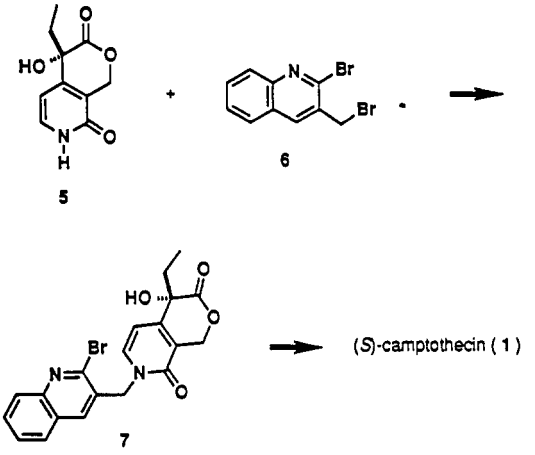
(*S*)-Camptothecin (**1**), a pentacyclic alkaloid isolated from *Camptotheca acuminata* by Wall and co-workers in 1966, continues to be one of the most important lead compounds among the anticancer natural products.[1] A number of promising analogs have been prepared that show improved solubility, low overall toxicity, and impressive in vivo activity against certain solid tumors.[2] Some of the more active derivatives include 9-aminocamptothecin[2a] (**2**), 10,11-(methylenedioxy)camptothecin[2a,3] (**3**), and (20*S*)-9-[(dimethylamino)methyl]-10-hydroxycamptothecin[2b] (**4**). Analog **4** is currently undergoing phase I clinical trials in cancer patients. The camptothecins' mode of action has been demonstrated to involve inhibition of DNA relaxation through interference with topoisomerase I function.[4] This novel activity and a recent report of potent anti-retroviral activity[5] for (*S*)-camptothecin have reenergized interest in this family of alkaloids.



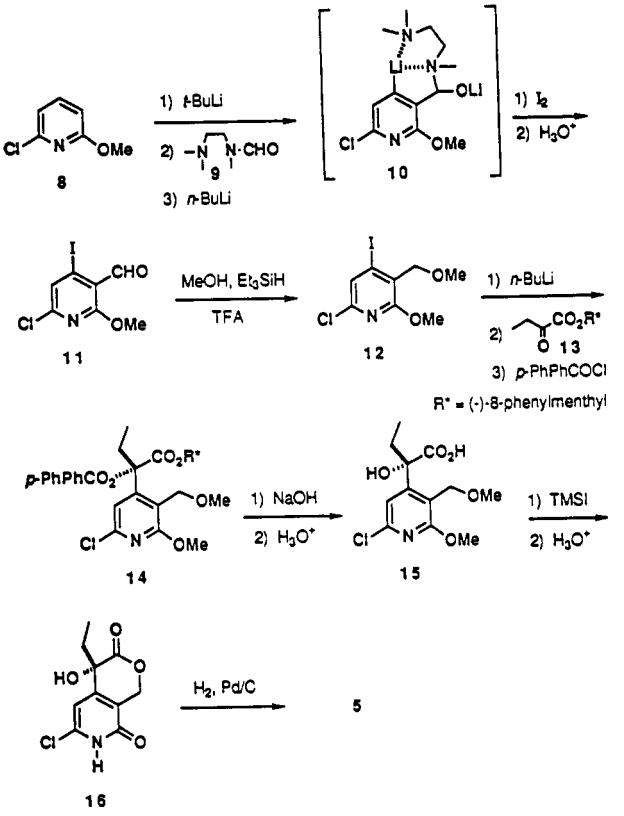
1, R^1, R^2, R^3 = H (*S*)-camptothecin
2, R^1, R^2 = H, R^3 = NH_2
3, R^1, R^2 = -OCH_2O-, R^3 = H
4, R^1 = H, R^2 = OH, R^3 = CH_2NMe_2

Although much beautiful synthetic work has been reported in this area,[1,6] most of the syntheses are racemic and not attractive

Scheme I



Scheme II



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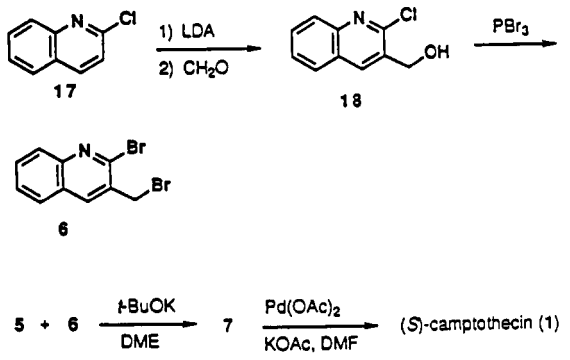
Scheme III



for large-scale preparation of active derivatives. Furthermore, only the (*S*) enantiomer of **1** exhibits biological activity, which limits the usefulness of racemic syntheses. To date three enantioselective syntheses of **1** have been reported,[7] two of which involve a resolution.[7a,b] Given the emerging medicinal value of the camptothecins, a practical asymmetric synthesis amenable to analog preparation is needed. We now report such a process that uses α-amino alkoxide directed lithiation and the Heck reaction in key steps.

The synthetic plan called for preparing enantiopure D and E rings **5** and bromoquinoline **6**, combining the two fragments through N-alkylation to provide intermediate **7**, and concluding with a C-ring cyclization to give **1** (Scheme I).

The hydroxylactone **5**[8] was prepared enantioselectively in six steps starting from commercially available 2-chloro-6-methoxypyridine (**8**) as shown in Scheme II. Directed lithiation (*t*-BuLi, THF, -78 °C, 1 h) and trapping with formamide **9**[9] gave an α-amino alkoxide in situ. Addition of *n*-butyllithium (-23 °C, 2 h) effected α-amino alkoxide directed lithiation[10] to give dianion **10**, which on reaction with iodine provided a 78% yield of aldehyde **11**, mp 129-130 °C. Methyl ether **12**, mp 74-75 °C, was prepared in 92% yield from **11** in one step on treatment with MeOH, triethylsilane, and TFA.[11] Lithium halogen exchange (THF, -78 °C, 1 min) and addition of α-keto ester **13**, prepared from α-ketobutyric acid and (-)-8-phenylmenthol, afforded the addition product as a lithium alkoxide in situ.[12] Trapping with 4-phenylbenzoyl chloride (room temperature, 36 h) provided a solid product (87% de), which on recrystallization from petroleum ether gave diastereomerically pure **14** as a white crystalline solid, mp 100-103 °C, in 60% yield. Saponification of diester **14** with 2 N NaOH/EtOH provided a 76% yield of hydroxy acid **15** as a colorless oil. Prior to acidification, extraction of the saponification reaction mixture with ether gave a near-quantitative recovery of the chiral auxiliary, (-)-8-phenylmenthol. Without purification, **15** was treated with TMSCl/NaI (CH_3CN, Dabco, reflux, 5 h) followed by hydrolysis with 6 N HCl (100 °C, 4 h). Workup provided hydroxylactone **16** in 77% yield as an off-white solid [mp 219-220 °C; $[\alpha]^{23}_D$ +58.5° (*c* 0.85, MeOH)]. Catalytic hydrogenation (Pd/C, NaOAc, MeOH) effected the removal of the C-6 chloro group to give the desired intermediate **5** [mp 233-234 °C; $[\alpha]^{23}_D$ +105.2° (*c* 1.0, MeOH)] in 95% yield.

The bromoquinoline **6** was prepared in two steps from 2-chloroquinoline (**17**) (Aldrich). Lithiation[13] at C-3 with LDA and trapping with formaldehyde gave the alcohol **18** (Scheme III). Bromination of **18** with PBr_3 provided the desired dibromo compound **6**[14] in high yield. Intermediates **5** and **6** were joined through N-alkylation using *t*-BuOK/DME (reflux, 48 h) to give an 87% yield of the tetracyclic intermediate **7** [mp 115-116 °C; $[\alpha]^{23}_D$ +48.7° (*c* 1.0, $CHCl_3$)]. The C ring was closed using a Heck reaction[15] ($Pd(OAc)_2$, $Bu_4N^+Br^-$, KOAc, DMF, 90 °C, 3 h), which provided a 59% yield of (*S*)-camptothecin (**1**) [mp 272-275 °C; $[\alpha]^{23}_D$ +42.3° (*c* 0.36, $CHCl_3$/MeOH, 4:1)] [lit.[7a] mp 275-278 °C dec; lit.[7c] $[\alpha]_D$ +42.0° (*c* 0.51, $CHCl_3$/MeOH, 4:1)]. Our synthetic (*S*)-camptothecin was identical in every respect with authentic material.[16]

This synthesis was carried out in 10 steps from commercially available materials.[17] The overall yield of **1** from pyridine **8** and bromoquinoline **6** was 12%. Work is in progress on the enantioselective synthesis of other members of the camptothecin family.

Acknowledgment. We gratefully acknowledge support of this work by Glaxo, Inc.

Supplementary Material Available: Listings giving full spectroscopic and analytical characterizations of **5**, **7**, **10-14**, and **16** (7 pages). Ordering information is given on any current masthead page.

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Stereoselective Addition of (Triphenylsilyl)magnesium Bromide to Chiral 1-Acyl-4-methoxypyridinium Salts. Synthesis and Reactions of Enantiopure 1-Acyl-2-(triphenylsilyl)-2,3-dihydro-4-pyridones

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Reaction of chiral 1-acylpyridinium salt **1**, prepared in situ from 4-methoxy-3-(triisopropylsilyl)pyridine[1a] and the chloroformate of (-)-8-phenylmenthol,[2] with aliphatic Grignard reagents gives 2,3-dihydro-4-pyridones **2** in high yield and 81-92% de (eq 1).[1]

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