Thus, when excess acetate is added externally to the DDAB vesicles, acetate exchanges with bromide to produce an outer leaflet that is more highly dissociated from its counterions. Owing to the resulting headgroup–headgroup repulsion, the outer leaflet expands relative to the inner one. Such asymmetry would be expected to increase curvature[12] and, therefore, promote budding and expulsion of small vesicles, as was observed.

The submicroscopic vesicles (and/or micelles) reassemble into giant vesicles, this time with acetate more equally distributed on the two sides of the vesicle walls. The question then arises as to why subsequent fusion is so fast in the face of what certainly must be a severe electrostatic barrier between positively charged membranes. There are two possible answers: (a) hydration repulsion may, for unknown reasons, not manifest itself in our particular system. This seems unlikely because charged bilayer surfaces should, if anything, require particularly strong solvation. (b) The vesicles may fuse because the component amphiphilic molecules are loosely packed within the bilayer assembly. This latter possibility receives support from additional observations: the dioctadecyl analog of DDAB, with T_c = 37 °C, does not exhibit acetate-induced fusion at ambient temperatures where the bilayer exists in the rigid gel state.[13] Moreover, DDAB vesicles, stiffened with 20 mol % cholesterol, fuse very slowly upon acetate injection.

Membrane–membrane interactions are usually analyzed in terms of three additive forces: van der Waals attraction, electrostatic repulsion, and hydration repulsion. Our results suggest that a fourth energy term, a "packing" or "stiffness" factor, must also be taken into account at the very close proximities required for fusion.[14] Indeed, fusion kinetics may be controlled more by the energetics of reassembling and mixing organized molecules[15] than by the need to overcome hydration forces.

Acknowledgment. This work was supported by the National Institutes of Health and Army Research Office.

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New 4 + 1 Radical Annulations. A Formal Total Synthesis of (±)-Camptothecin

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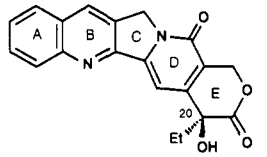
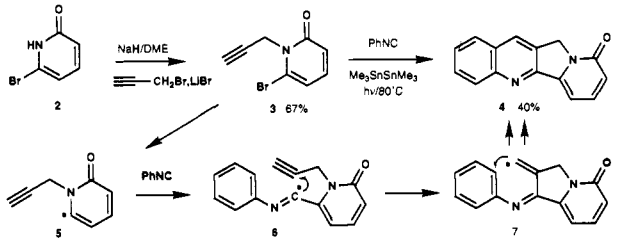
Over the last decade, (20*S*)-camptothecin (**1**)[2] and its close relatives have emerged as some of the most exciting compounds for potential treatment of solid tumors.[3] Very recently, camptothecin has also shown potent anti-retroviral activity at dose levels well tolerated by cells.[4] It may therefore represent a new direction in AIDS chemotherapy. Derivatives of camptothecin have a unique mechanism of action: they kill cells by binding to and stabilizing a complex of DNA and the enzyme topoisomerase I.[5]



camptothecin (1)

These compounds are the most important members of a very small group of compounds[6] known as "topoisomerase I poisons".[7] Camptothecin was synthesized several times during the 1970s,[2,8] and many (though not all) syntheses rely on the Friedlander quinoline synthesis to construct ring B. Given the current interest in camptothecins, new directions in the total synthesis of this family would be welcome. We now report a short, convergent total synthesis of (±)-camptothecin that uses a new 4 + 1 radical annulation[9a] followed by another cyclization[9] to simultaneously assemble rings B and C.

The viability of the key 4 + 1 annulation was first demonstrated in a simple model reaction. Readily available bromopyridone **2**[10] was N-propargylated to give **3** (eq 1). In turn, **3** reacted with phenyl isocyanide under conditions similar to those that we developed for reactions of simple pentynyl iodides.[9a] An 80 °C benzene solution of **3** (1 equiv), phenyl isocyanide (5 equiv), and hexamethylditin (1.5 equiv) was irradiated with a sunlamp for 8 h. After chromatography, we isolated the known tetracycle **4**[11] in 40% yield as a white solid. Equation 1 shows key steps in the proposed mechanism for the conversion of **3** to **4**. Addition of pyridone radical **5** to phenyl isocyanide[12] to give **6** is followed by two radical cyclizations and an oxidative rearomatization.[9,13]



(1)

The formal total synthesis of (±)-camptothecin is shown in eq 2. Nitrile **8** was prepared by standard Doebner condensation of dimethyl acetonedicarboxylate and cyanoacetic acid (70%).[14] Standard saponification (NaOH/EtOH, 95%) gave diacid **9**. Conversion of **9** to bromopyridone **10** was accomplished by modification of a known method to prepare chloropyridones.[14] The

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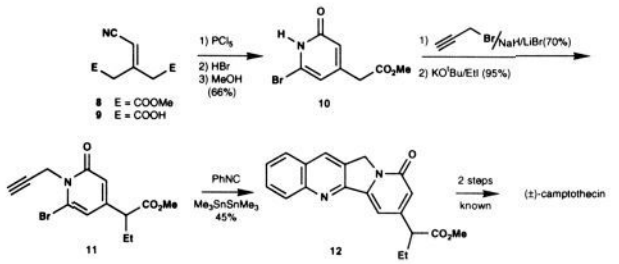
diacid was first treated with PCl_5, and then gaseous HBr (10 equiv) was introduced. After addition of methanol, workup, and purification, we isolated **10** in 66% yield. N-Propargylation (70%) and C-ethylation[15] (95%) then gave the precursor **11** for the 4 + 1 annulation. Reaction of **11** with phenyl isocyanide as described above gave pure **12** in 45% isolated yield. Compound **12** was first prepared by Danishefsky,[16] and it has been a key intermediate in many syntheses of camptothecin.[2] Conversion of **12** to (±)-camptothecin is accomplished in two steps: hydroxymethylation (35%) and oxidation (quantitative).[2,16]



(2)

This synthesis of the key Danishefsky tetracycle **12** requires only six steps starting from dimethyl acetonedicarboxylate, and the overall yield is currently 13%. There is still room for improvement. We plan to use this synthesis as a starting point for further work in the camptothecin area.

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Tridecavanadate, $[V_{13}O_{34}]^{3-}$, a New High-Potential Isopolyvanadate

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There has been considerable recent research activity on polynuclear high-valent vanadium species in biochemistry,[1,2] sol-gel chemistry,[3] layered or intercalated materials and catalysts,[4,5] and sensor technology.[3,6] Very recently several elegant examples of polyvanadates have been reported by the groups of Klemperer and Day,[7,8] Huan and Jacobsen,[9] and Müller.[10,11] Nearly all of these

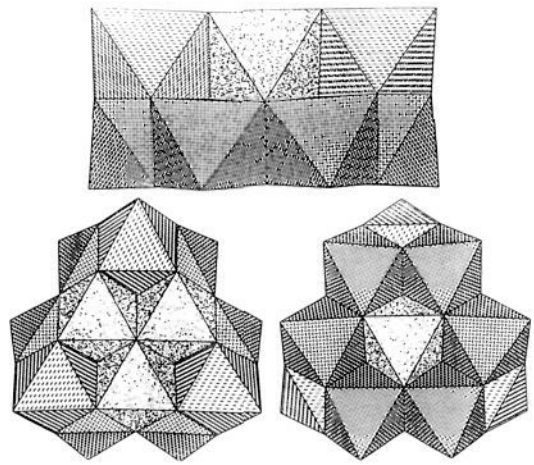

Figure 1. Polyhedral representation of VO_6 components of **1**, oxygens at vertices surrounding the V. Top: side view showing alternating O layers, 2.21 Å between middle and top and bottom parallel planes. Lower left: "top" view showing V(c)O_6 and V(b′)O_6 units with O_{10} plane and three O_9 edges. Lower right: "bottom" view showing V(a)O_6 in the center of six V(b″)O_6 units with O_{12} plane and three O_6 edge faces.

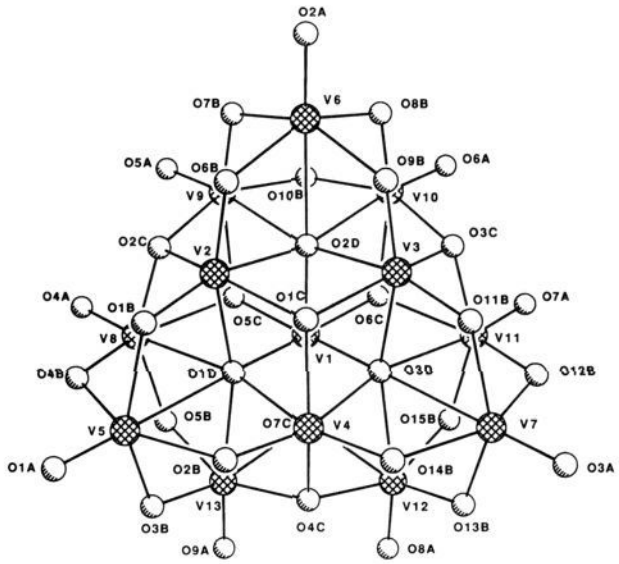

Figure 2. Structure of the $[V_{13}O_{34}]^{3-}$ (**1**) anion, aligned approximately along the triad and showing atom labeling scheme. Selected interatomic distances (min-max, av with typical σ for V···V 0.004, V-O -0.010 Å): V(a), V(1)-μ_6-O 2.04-2.08, 2.045 (4) and V(1)-μ_3-O 1.75-1.77, 1.76 (1); V(b)″, V(8-13)-O_t 1.56-1.60, 1.58 (2) Å, V(8-13)-μ-O 1.78-1.85, 1.81 (2), and V(8-13)-μ_6-O 2.34-2.36, 2.35 (1); V(b′), V(5-7)-O_t 1.55-1.60, 1.58 (3), V(5-7)-μ-O 1.80-1.85, 1.83 (2), and V(5-7)-μ_6-O 2.39-2.42, 2.41 (2); V(c), V(2-4)-μ-O 1.64-1.69, 1.67 (2), V(2-4)-μ_3-O 1.92-1.94, 1.93 (1), and V(2-4)-μ_6-O 2.11-2.15, 2.12 (2); V(a)···V(c) 3.241 (4); V(a)···V(b″) 3.13 (1); V(c)···V(c) 3.09 (1); V(c)···V(b′) 3.091 (8); V(c)···V(b″) 3.17 (1); V(b′)···V(b″) 3.13 (1); V(b′)···V(b″) 3.086 (5).

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