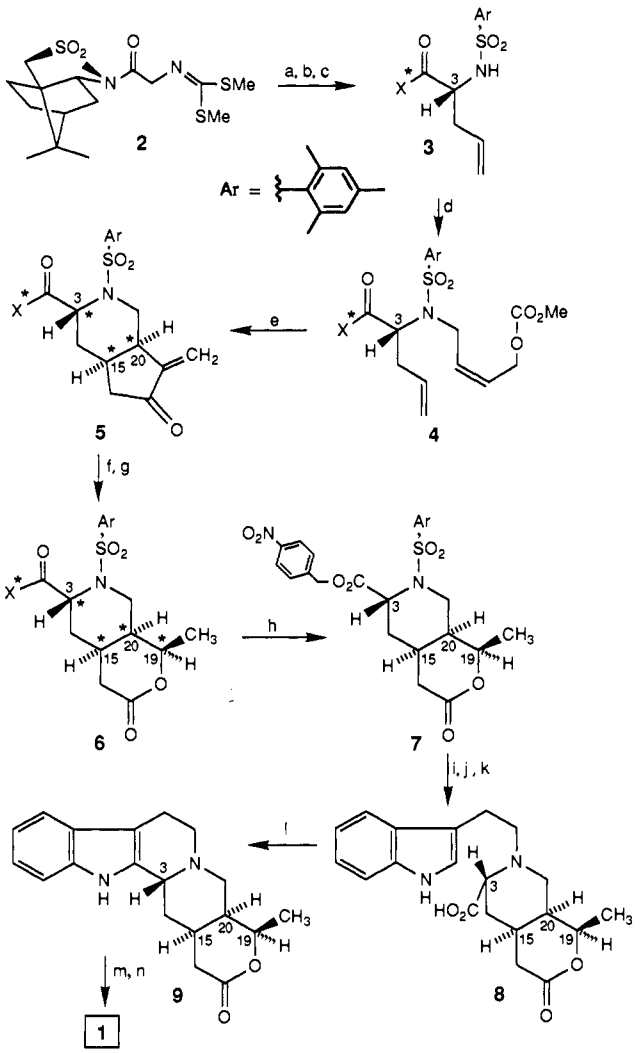
Scheme I[a]



[a] (a) Allyl iodide (1.2 equiv), Bu_4NHSO_4 (1.2 equiv), LiOH (50 equiv), CH_2Cl_2/H_2O (19:1), ultrasound, −7 °C (bath), 6 min. (b) HCl (0.5 N), THF/H_2O (1:1), room temperature, 4 h. (c) Mesitylenesulfonyl chloride (1.5 equiv), pyridine (3.5 equiv), CH_2Cl_2, reflux, 24 h. (d) (*Z*)-1-Bromo-4-[(methoxycarbonyl)oxy]-2-butene (1.2 equiv), NaH (1 equiv), DMF, 0 °C, 12 h. (e) $Pd(dba)_2$ (0.1 equiv), PBu_3 (0.3 equiv), CO (1 atm), AcOH, 80 °C, 3 h. (f) Pd/C (0.1 equiv), H_2 (1 atm), EtOAc, room temperature, 18 h. (g) MCPBA (80%, 1.5 equiv), $NaHCO_3$ (10 equiv), CH_2Cl_2, room temperature, 18 h. (h) *p*-Nitrobenzyl alcohol (1.3 equiv), *n*-BuLi (1 equiv), THF/hexane (25:1), −30 °C, 0.5 h, then addition of **6**, −30 °C → −10 °C, 6 h. (i) Pyridine/70% HF (excess), anisole (2 equiv), room temperature, 8 h. (j) Tryptophyl bromide (1.2 equiv), $NaHCO_3$ (10 equiv), MeCN, 80 °C, 6 h; then addition of further tryptophyl bromide (0.4 equiv), 80 °C, 5 h. (k) Pd/C (0.05 equiv), H_2 (1 atm), EtOH, room temperature, 0.5 h. (l) $PhPOCl_2$ (excess), 105 °C, 4 min, then addition of 1 N aqueous HCl, 70 °C, 10 min. (m) NaHMDS (10 equiv), THF, −78 °C, 2 h, then addition of methyl formate (40 equiv), −78 °C, 1 h, then →0 °C, 4 h. (n) Saturated HCl/MeOH, CH_2Cl_2 (1:9), 120 °C (sealed tube), 24 h, then *p*-TsOH (5 equiv), CH_2Cl_2, reflux, 15 h.

In summary, (+)-3-isorauniticine has been synthesized via a sequence of 14 steps, which highlights once more the preparative utility of sultam-directed asymmetric alkylations[6,15] and of transition-metal-catalyzed carbometalation/carbonylation reactions.[4,5,10,16]

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Supplementary Material Available: Reaction scheme, preparations, and analysis data, including mp, IR, ^{13}C NMR, and MS (9 pages). Ordering information is given on any current masthead page.

Silicon-Mediated Reductive Coupling of Aldehydes and Allylic Alcohols. A Stereoselective Synthesis of Tunicaminyluracil

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We report the development of a method for carbon–carbon bond formation between the olefinic terminus of an allylic alcohol and the carbonyl carbon of an aldehyde.[1] This coupling reaction forms the basis of a highly convergent synthesis of tunicaminyluracil (**1**),[2] the undecose core of the tunicamycin antibiotics (tunicamycin C, shown below, is exemplary),[3] from simple carbohydrate-derived precursors.

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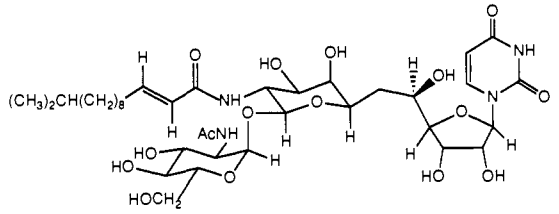
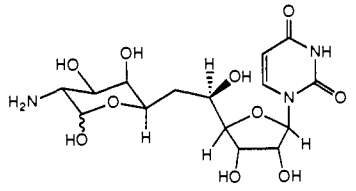
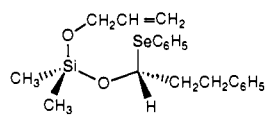


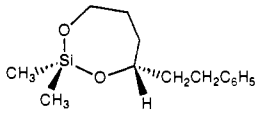
Tunicamycin C



Tunicaminyluracil (1)



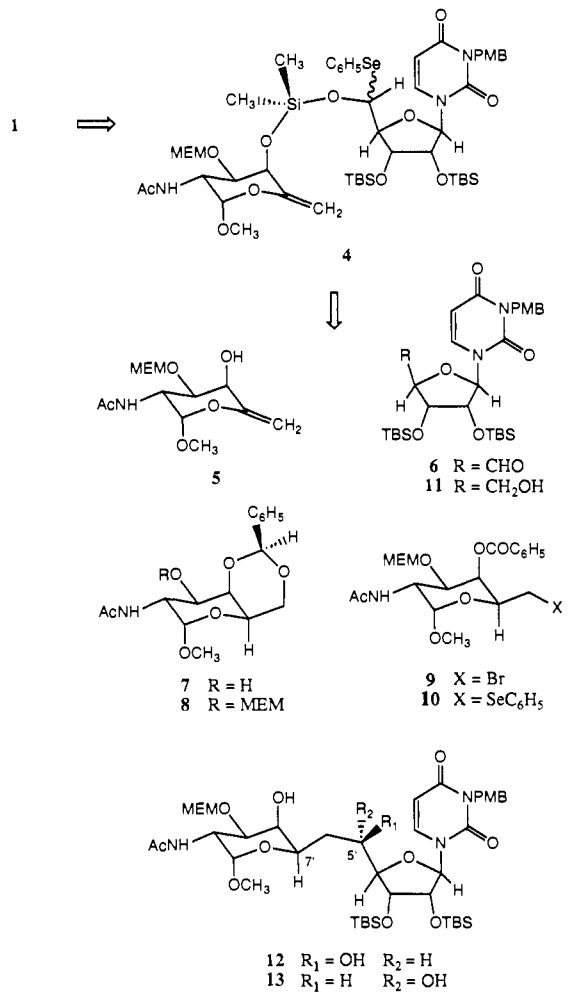
2



3

Preliminary experiments have established an efficient protocol for the formation of *O*-(allyloxy)dimethylsilyl hemiselenoacetals (e.g., **2**) from equimolar quantities of an aldehyde and an allylic alcohol. For example, addition of a mixture of hydrocinnamaldehyde and benzeneselenol (1 equiv) in pyridine to a solution of dimethyldichlorosilane (5–10 equiv) in pyridine at 23 °C, removal of excess dimethyldichlorosilane in vacuo, and addition of allyl alcohol (1 equiv) affords, after filtration and concentration, the coupling product **2** in 93% yield (>90% purity).[4] Dropwise addition of tributyltin hydride (2.6 equiv) and azobisisobutyronitrile to a solution of crude **2** (3 mM) in toluene at 60 °C leads to the formation of cyclic siloxane **3** (60–70%), the product of 7-endo-trig radical closure, as well as minor amounts of noncyclized reduction product (~15%).[5-7] Within the context of retrosynthetic analysis of the tunicamycins, this coupling reaction provides an exceptionally powerful solution to synthetic simplification, i.e., **1** ⇒ **4** ⇒ **5** + **6** (Scheme I).[8] Analysis of the hypothetical cyclization of **4** as compared with, e.g., **2** suggests that this substrate may be near optimally disposed for cyclization. This interpretation rests on the presumed greater exothermicity of the closure reaction (as manifested in the transition state), as well as the entropic advantage gained from cyclization of a conformationally constrained substrate. Two stereochemical concerns in this sequence are the sense of attack on the aldehyde-derived radical (C5′ stereochemistry) and the outcome of hydrogen atom abstraction at C7′ (see structure **12**). The latter is predicted to result in the required 7′*R* stereochemistry, given the strain associated with equatorial C–H bond formation in this ring system and the well-established preference for anomeric radicals to react to form axial bonds.[9] The stereochemistry at C5′, by contrast, proves to be a much more subtle issue, as described below.

Scheme I



Alcohol **5** and aldehyde **6** are available in gram quantities from simple, commercially available carbohydrate precursors. The crystalline benzylidene-protected α-methyl glycoside **7** is prepared in one step (55% yield, mp 165–166.5 °C) from *N*-acetyl-D-galactosamine and serves as the starting material for synthesis

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of **5**.[10,11] Use of the benzylidene protecting group is essential, as it serves as a masked form of the sensitive enol ether functionality present in **5**. Protection of **7** as its (2-methoxyethoxy)methyl (MEM) ether (**8**, 75%, mp 53.5–54.0 °C) and reaction of **8** with *N*-bromosuccinimide in carbon tetrachloride at reflux[12] affords the bromide **9** (87%, mp 57.0–57.5 °C), which undergoes smooth displacement with benzeneselenol and triethylamine to form the phenyl selenide **10** (96%, mp 44.0 °C). Oxidation/elimination of selenide **10** affords the benzoyl ester of **5** (99%, mp 44.0–44.5 °C),[13] which upon mild transesterification with potassium carbonate in methanol at 23 °C provides **5** (92%, mp 102.5 °C). The coupling partner **6** (mp 73–74 °C) is prepared by Swern oxidation of **11**,[14] available in high yield from uridine by a series of standard protection–deprotection steps.[15] As efforts to purify the labile aldehyde **6** lead to its deterioration, coupling reactions are performed directly on the crude material employing, in this case, a 2-fold excess of the aldehyde. Thus, crude **6** and alcohol **5** are transformed, as described above, to the crystalline coupling product **4** in 92% yield after purification by flash chromatography (1:1 mixture of diastereomers). For purposes of characterization, the diastereomers can be separated by careful column chromatography (mp 57–59 °C and 59.5–61 °C, respectively). Free-radical cyclization of diastereomers **4** under a variety of conditions proceeds smoothly to provide, after siloxane hydrolysis with potassium fluoride in methanol, the diols **12** and **13**. Cyclization of **4** in toluene at reflux leads predominantly to the undesired diol **13** (**12**:**13** = 1:3). At lower reaction temperatures, made possible with triethylborane initiation,[16] the selectivity toward formation of **13** increases (**12**:**13** = 1:6 at 0 °C, 74% combined yield). A variety of modified silicon linkers are similarly found to favor formation of **13** [$(CH_3O)_2Si$, 1:3; $(CH_2)_3Si$, 1:5; $(CH_3)_2SiOSi(CH_3)_2$, <5:95]. Though various C5′-epimerization schemes can be imagined, further experimentation reveals a striking solvent effect in the cyclization of **4**, leading to an inversion in selectivity. Reactions conducted in methanol, ethanol, 2-propanol, or acetonitrile preferentially form the diol **12** (**12**:**13** ~ 3–4:1).[17] As reactions in alcoholic media produce unacceptable levels of reduction product, acetonitrile has proven to be the optimum solvent. In a typical experiment (Bu_3SnH, Et_3B initiation, CH_3CN, −10 to 23 °C), **12** (mp 98.5–101 °C) is obtained in 62% yield after siloxane hydrolysis and radial chromatography. Diastereomer **13** (18%) and alcohol **5** (13%) are isolated in separate fractions. The identity of synthetic **12** is confirmed upon deprotection (ceric ammonium nitrate; 3 N HCl) and HPLC comparison with authentic tunicaminyluracil. In addition, synthetic and natural tunicaminyluracil[1d] are separately transformed to the α-peracetate derivatives, shown to be identical in all respects, including optical rotation.

In conclusion, an efficient method for carbon–carbon bond formation between an aldehyde and an allylic alcohol is described, forming the basis for a synthesis of the protected tunicaminyluracil derivative **12** or its C7′-epimer **13**. With regard to the latter application, a notable feature of this methodology is its almost certain compatibility with the problematic *N*-acetylglucosamine glycosidic linkage, thus allowing for a highly convergent synthesis of the tunicamycin antibiotics by late-stage carbon–carbon bond formation.

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Supplementary Material Available: High-resolution ^1H NMR, IR, and mass spectral data of all synthetic intermediates and synthetic and authentic tunicaminyluracil α-peracetate, ^{13}C NMR spectra of the latter, and HPLC comparisons of synthetic and authentic tunicaminyluracil and tunicaminyluracil α-peracetate (33 pages). Ordering information is given on any current masthead page.

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(17) The origin of this unusual solvent effect is under investigation.

Helix Formation in Apocytochrome b_5: The Role of a Neutral Histidine at the N-Cap Position

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In the last few years, NMR investigations have revealed that many proteins display discrete conformers under native conditions.[1] Little is known about the occurrence of conformational equilibria when a structural component such as a prosthetic group or a cofactor is removed. In what follows, we demonstrate that the deletion of heme–protein interactions in cytochrome b_5 increases the population of a nonnative conformer in the C-terminal region of the protein. The partial destabilization allows us to study one of the factors responsible for the formation of a helix and conclude that a single main chain/side chain hydrogen bond plays a key role in attaining the holoprotein secondary structure. The hydrogen bond involves a neutral imidazole group at the helix N-terminal boundary (N-cap position)[2] and satisfies the backbone amide H-bond requirement of the third residue in the helix.

The water-soluble fragment of cytochrome b_5 is a 98-residue protein containing a single heme group[3] which confers some rigidity and stability to the protein[4] and influences its fold.[5] We use the apoprotein of rat liver cytochrome b_5[6] as a model molecule for probing precursor states of the holoprotein and the relationship between sequence and structure. We have shown by NMR spectroscopy that the structural effects of heme removal are localized; apocytochrome b_5 retains native holoprotein features in the region remote from the heme binding site (β-sheet and helices I and VI).[7,8] Here we describe unique dynamic properties involving His 80, a residue located 20 Å from the heme site at the start of helix VI.

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