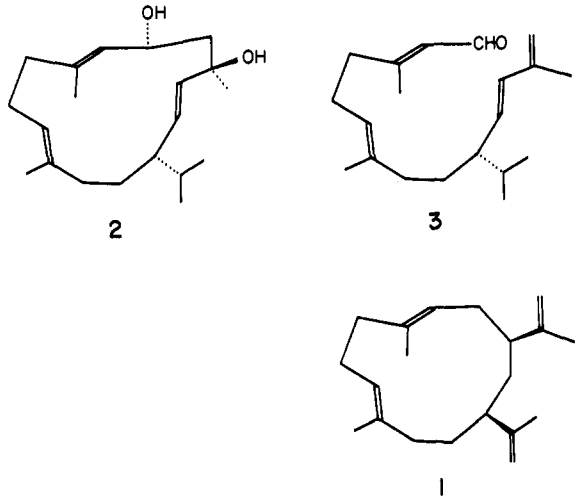

Figure 2. Cubitene and structurally related diterpenoids.

mentation product **3** in tobacco plants[16,17] is intriguing; the joining of C(1) to C(12) in an intermediate related to **3** would give rise to the cubitene skeleton (see Figure 2).

Biosynthetic studies will be necessary to determine whether either of these schemes is correct. The even more basic question of whether termite soldiers synthesize cubitene at all, or whether they simply sequester it (or a closely related precursor) from their food, also remains a topic for future research.

Acknowledgments. We are grateful to Dr. R. M. C. Williams (Centre for Overseas Pest Research) for identification of the termite species, Mr. I. Miura and Professor K. Nakanishi (Columbia University) for the ^{13}C NMR spectrum of cubitene, and Ms. B. A. Solheim (Iowa State University) for collection of the x-ray diffraction data. Partial support of this work by the NIH (Grant No. AI 12020 and Fellowship Awards AI 05076 (G.D.P.) and CA 05646 (D.F.W.)) is acknowledged with pleasure.

Supplementary Material Available: A table of fractional coordinates of cubitene (2 pages). Ordering information is given on any current masthead page.

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Received December 9, 1977

A Stereocontrolled General Synthesis of *C*-Nucleosides[1]

Sir:

C-Nucleosides, having a carbon to carbon ribosidic linkage, constitute the class of compounds that possess important antibiotic properties as well as potent anticancer and antiviral activities.[2] Most of the synthetic approaches reported so far have utilized carbohydrate precursors.[2c] In this communication, we wish to disclose a stereocontrolled entry starting from noncarbohydrate materials.[3] Here the ribose skeleton has been constructed using the polybromo ketone/iron carbonyl reaction[4] as the key method.

The starting material is the bicyclic ketone **1**, which is prepared easily by the $Fe_2(CO)_9$-promoted cyclocoupling reaction of $\alpha,\alpha,\alpha',\alpha'$-tetrabromoacetone and furan followed by Zn/Cu couple reduction.[5] When the unsaturated ketone **1** was allowed to react with 35% H_2O_2 (1.5 equiv) and a catalytic amount of OsO_4 (20:1:1 acetone–ether–*tert*-butyl alcohol, 30–35 °C, 4 h) and then with 70% $HClO_4$ (25 °C, 6 h), the oxygen functions were introduced with perfect stereoselectivity to afford in 65% yield a single acetonide **2**, mp 119–121 °C, having α stereochemistry.[6] Subsequent Baeyer–Villiger oxidation of **2** to the lactone **3**, mp 146–147 °C,[7] was achieved by CF_3CO_3H[8] (2 equiv, room temperature, 1 h) in 92% yield. Thus the ketone **1** was transformed without any complication to **3** that has an adequate *C*-β-glycoside structure.

The optical resolution required for the natural product synthesis was accomplished through cinchonidine salt of the hydrolyzed product **6**, mp ~80 °C, $[\alpha]^{26}_D$ −75 ° (*c* 0.47, C_2H_5OH). Heating of the resolved material with acetic anhydride/pyridine (reflux, 12 h) gave back the optically pure lactone, mp 161–163 °C, $[\alpha]^{26}_D$ +84° (*c* 0.63, $CHCl_3$).

Reaction of the lactone **3** and $[(CH_3)_2N]_2CHOC(CH_3)_3$[9] (excess, DMF, 40–45 °C, 2 h) gave the dimethylaminometh-

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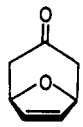

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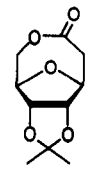

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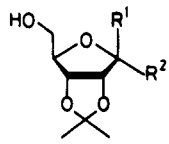
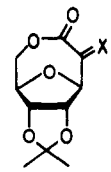
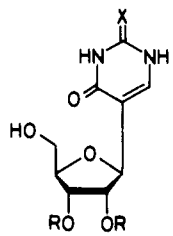


4, $R^1 = CH_2COOCH_3$; $R^2 = H$
5, $R^1 = H$; $R^2 = CH_2COOCH_3$
6, $R^1 = CH_2COOH$; $R^2 = H$

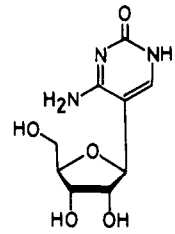


7, X = $CHN(CH_3)_2$
8, X = O

ylene lactone **7**[10] (*Z*/*E*, ~2:1, 64% yield after silica gel chromatography). This compound appeared to serve as a common intermediate for the synthesis of both natural and unnatural pyrimidine *C*-nucleosides. For instance, when a mixture of **7** and urea (4.6 equiv) was exposed to 0.5 N C_2H_5ONa/C_2H_5OH (reflux, 3 h), the uracil derivative **9** was obtained in 60% yield. Removal of the isopropylidene protective group by 1 N HCl (25 °C, 1 h) produced pseudouridine (**10**), identical in all respects with the naturally occurring specimen. In addition, **9** can be readily converted to pseudocytidine (**13**), a natural *C*-nucleoside, through a stereocontrolled, standard method.[11] Condensation of **7** with thiourea (3.5 equiv) with 0.5 N C_2H_5ONa/C_2H_5OH (reflux, 3 h) formed the acetonide **11** (80% yield), hydrolysis of which with 1 N HCl (25 °C, 1 h) gave 2-thiopseudouridine (**12**)[12] (75% yield). In a similar fashion, cyclization with guanidine gave rise to **14** (70% yield). Subsequent acid hydrolysis afforded chemotherapeutically significant pseudoisocytidine (**15**).[12,13] Compounds **12** and **15** were identified by comparison with authentic samples.[12] During these transformations no stereoisomers were produced.



9, R--R = $C(CH_3)_2$; X = O
10, R = H; X = O
11, R--R = $C(CH_3)_2$; X = S
12, R = H; X = S



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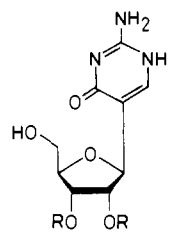
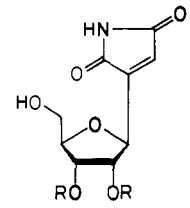


14, R--R = $C(CH_3)_2$
15, R = H



16, R--R = $C(CH_3)_2$
17, R = H

Showdomycin (**17**)[14] was also prepared from the intermediate **7**. Ozonolysis of **7** (ethyl acetate, −78 °C) and reductive workup with $(CH_3)_2S$[15] produced unstable α-keto lactone **8** (IR ($CHCl_3$) 1732 cm^{-1}). Reaction of **8** with $(C_6H_5)_3PCHCONH_2$ (DMF, 50 °C, 1.5 h)[14a,16] followed by removal of the acetonide protective group of resulting **16** with 50% aqueous CF_3COOH (25 °C, 15 min) afforded **17**, identical with the natural authentic sample. The overall yield was 32%.

The directness of this total synthesis is based on the ready availability of the oxa bicyclic ketone **1**. In addition, the use of the rigid bicyclic system allowed efficient stereochemical control throughout the overall transformation that consists of assembling the ribose moiety and elaboration of heterocyclic nuclei having β configuration. It should be added that the ester **4** is stereochemically quite labile under basic conditions[17] and, hence, during introduction of a C_1 unit to the active methylene position by a standard procedure, it isomerizes easily to the more stable α epimer **5** through retro-Michael-type cleavage of the ether linkage. Such undesired stereomutation is precluded by using the lactone **3**.[18,19]

Acknowledgments. We are grateful for the partial financial support from the Ministry of Education, the Japanese Government (Grant in Aid for Scientific Research No. 147022), the Asahi Science Research Grant 1976, the Foundation for the Promotion of Research on Medicinal Resources, and the Naitoh Research Grant for 1976. We are also indebted to Dr. Wataru Nagata of Shionogi Research Laboratory for a generous gift of showdomycin.

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(7) IR ($CHCl_3$) 1737 cm^{-1}; NMR (C_6D_6) δ 1.04 and 1.42 (s, 3 H each, CH_3), 2.16 (dd, J = 14 and 3 Hz, $CH_aH_bC{=}O$), 2.38 (dd, J = 14 and 5.4 Hz, $CH_aH_bC{=}O$), 3.10 (dd, J = 14 and 3 Hz, C(5′)H_aH_b), 3.51 (d, J = 14 Hz, C(5′)H_aH_b), 3.96 (m, C(1′)H and C(4′)H), 4.39 (d, J = 6 Hz, C(2′)H), 4.58 (d, J = 6 Hz, C(3′)H). Ribose numbering is used for this assignment.
(8) Prepared from 90% H_2O_2 and $(CF_3CO)_2O$. We thank Professor Hisashi Yamamoto for indication of this experimental procedure.
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(18) Possibility of the *C*-nucleoside synthesis via the lactone **3** has been suggested previously.[3b] However, its direct formylation is quite difficult and, at least in our hand, no conditions were found which gave the formylated compound (or the derivatives) in a satisfactory yield. The introduction of a C_1 unit, despite lack of stereochemical control, has been done with the ester **4** rather than the lactone **3**.[12]

(19) All stable compounds described herein gave correct elemental and/or mass spectral analysis.

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Stabilities of Carbonium Ions in Solution. 6.[1] Heats of Formation of Simple Alkyl Carbonium Ions in SO_2ClF and Their Relevance to the Nonclassical Ion Question

Sir:

Calorimetric results in Table I present for the first time the enthalpies of forming carbonium ions in solution under stable ion conditions at low temperatures[2-4] through the reaction RX + SbF_5 → $R^+SbF_5X^-$ [5,6] at high dilution in SO_2ClF. The heats of ionization correlate closely with the free energies of activation for solvolysis under limiting conditions and therefore provide important corroboration for the highly successful "carbonium ion theory of organic chemistry".

Until now the stabilities of aliphatic carbonium ions have been inferred primarily from solvolytic rate data. The precise relationship between the energy of formation of the presumed ionic transition state from the precursor and that of the corresponding fully developed ion has always been uncertain. Figure 1 correlates the enthalpies of ionization in SO_2ClF from Table I with the free energies of activation from logarithms of solvolysis rate constants[7]—corrected for isopropyl, *sec*-butyl, and cyclopentyl to remove nucleophilic solvent participation by the method of Schleyer.[8] The high degree of correlation, *and nearly unit slope*, has three important implications. (a) It strongly supports the use of enthalpies of ionization[9] in appropriate cases as a guide to stabilities. (b) It supports Schleyer's[8] treatment of solvolysis data and shows that nearly full charge development has occurred at the solvolysis transition state. (c) It justifies the comparison of carbonium ion stabilities through rate constants (i.e., applications of Hammond's Postulate[10]). Since relative stabilities of carbonium ions in SO_2ClF/SbF_5 parallel closely the gas phase values,[11] they also correspond well to the stabilities expected from theory.[12] This accounts for the great success of the simple carbonium ion theory.[13]

The relevance of Table I to the question of carbonium ion stabilization by σ bridging[14] is also worth noting. The 2-norbornyl ion is a test case since it is considered to be the prototype example of a nonclassical ion and its demand for resonance stabilization in solution should be maximized under stable ion conditions.

Three comparisons of norbornyl and cyclopentyl systems can be made from data on Table I. First, through direct subtraction the difference is ΔH_i: −23.6 + 17.3 = −6.3 kcal/mol. Second, applying logic used recently by Brown and Schleyer[14] to assess the effect of converting a secondary ion to its tertiary homologue by replacing secondary hydrogen with a methyl group we obtain 9.8 kcal/mol for methylcyclopentyl minus cyclopentyl compared with 7.4 kcal/mol for 2-methyl-*exo*-norbornyl minus *exo*-norbornyl.[15,17] This leads to a difference of 2.4 ± 2.0 kcal/mol between the extra driving force for ionization in the 2-norbornyl vs. cyclopentyl systems. Third, a similar comparison of phenyl derivatives yields a difference of 1.6 ± 2.0 kcal/mol for 2-phenyl-2-propyl minus isopropyl

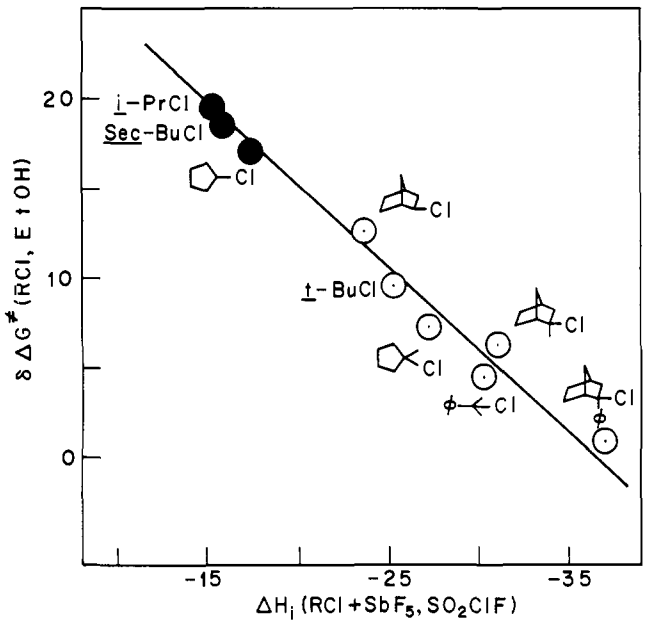

Figure 1. Correlation of heats of ionization of alkyl chlorides vs. differential limiting free energies of solvolysis. Slope = −0.88, coefficient of correlation = 0.987. Solid points corrected for nucleophilic participation by Schleyer's method.[8]

Table I. Calorimetric Heats of Ionization in SO_2ClF[a]

Chlorides	
Isopropyl chloride	−15.3 ± 0.9
sec-Butyl chloride	−15.7 ± 0.8 (−75 °C)
	−30.0 ± 0.8 (−25 °C)[b]
Cyclopentyl chloride	−17.3 ± 0.9
1-Adamantyl chloride	−21.6 ± 0.8
Cyclohexyl chloride	−22.5 ± 0.6[b]
exo-Norbornyl chloride	−23.6 ± 0.8
tert-Butyl chloride	−25.4 ± 0.8
1-Methylcyclopentyl chloride	−27.1 ± 0.6
2-Phenyl-2-propyl chloride	−30.3 ± 0.3
2-Methyl-*exo*-norbornyl chloride	−31.0 ± 1.5
2-Phenyl-*exo*-norbornyl chloride	−37.0 ± 1.2
Fluorides	
Isopropyl fluoride	−16.8 ± 0.6
sec-Butyl fluoride	−17.4 ± 0.7 (−75 °C)
	−32.0 ± 0.8 (−25 °C)[b]
1-Adamantyl fluoride	−22.9 ± 0.9
exo-Norbornyl fluoride	−25.8 ± 0.7
tert-Butyl fluoride	−27.3 ± 0.6

[a] All values are given in kilocalories/mole at −55 °C unless another temperature is shown. The ionization process is accomplished by reaction of RX with SbF_5 at high dilution in SO_2ClF. [b] Ionizes with rearrangement.

= 15.0 kcal/mol vs. 2-phenyl-*exo*-norbornyl minus *exo*-norbornyl.

These varied energy differences might be attributed either to different electronic, steric, or solvation factors in the neutral precursors or in the ions since there is no means at present to separate them.[18] Experiments are in progress which may partially resolve this question.

The large contributions which may arise from initial state energies is exemplified vividly by comparison of the initial state difference between *sec*-butyl chloride and *tert*-butyl chloride (both of which go to *tert*-butyl cation at −25 °C) compared with methylcyclopentyl chloride and cyclohexyl chloride (both of which go to methylcyclopentyl ion at −55 °C). In the former case the tertiary chloride is stabler by 5.1 kcal/mol,[19] while in the latter the secondary is stabler by 4.9 kcal/mol. Thus, there is a 10-kcal/mol inversion of secondary vs. tertiary stabilities for initial states!

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