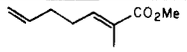
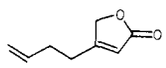
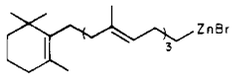
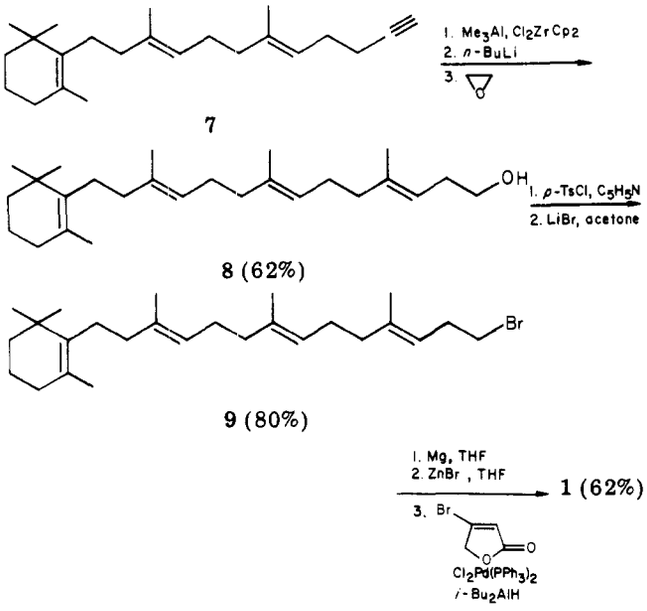
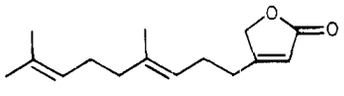
Table I. Pd-Catalyzed Reaction of Homoallylzinc Halides with β-Bromo-Substituted α,β-Unsaturated Carbonyl Derivatives

entry	homoallylzinc halide (RZnX) R	X	alkenyl halide	catalyst[a]	product[b]	% yield[c]
1	3-butenyl	Cl	3	A		62 (82)
2	3-butenyl	Cl	4	A		80 (94)
3	(*E*)-4-methyl-3-nonenyl	Br	4	B	5	69 (94)
4	(*E*)-4,8-dimethyl-3,7-nonadienyl	Cl	4	B	6[d]	55 (82)
5			4	B	1[e]	62

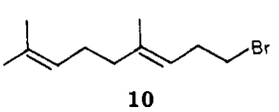
[a] A = $Pd(PPh_3)_4$, B = $Cl_2Pd(PPh_3)_2$ + 2 *i*-Bu_2AlH. [b] The elemental compositions of the products have been established by high-resolution mass spectrometry. All isolated products and intermediates exhibit satisfactory spectral data. [c] The numbers in parentheses are GLC yields. [d] n^{21}_D 1.5006; ^1H NMR ($CDCl_3$, Me_4Si) δ 1.61 (s, 6 H), 1.68 (s, 3 H), 1.95–2.2 (m, with a peak at δ 2.01, 4 H), 2.2–2.5 (m, 4 H), 4.73 (d, J = 1.8 Hz), 4.9–5.3 (m, 2 H), 5.75–5.9 (m, 1 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 16.16, 17.70, 25.69, 25.76, 26.56, 28.76, 39.64, 73.17, 115.66, 122.01, 124.01, 131.53, 137.54, 170.26, 174.06; IR (neat) 1780 (s), 1750 (s), 1630 (m) cm^{-1}. [e] n^{24}_D 1.5159; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.97 (s, 6 H), 1.1–2.5 (m, with peaks at δ 1.58, 1.60 and 2.00, 34 H), 4.69 (d, J = 1.8 Hz, 2 H), 4.95–5.2 (m, 3 H), 5.80 (m, 1 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 16.06, 16.20, 19.62, 19.82, 25.77, 26.56, 26.65, 28.02, 28.67, 28.79, 32.81, 35.00, 39.73, 39.94, 40.36, 73.13, 115.66, 121.86, 123.62, 123.93, 126.89, 135.29, 135.98, 137.25, 137.64, 170.12, 174.01; IR (neat) 1780 (s), 1750 (s), 1640 (w) cm^{-1}.



In a very analogous manner **6** was synthesized in three steps from 2-methyl-2-hepten-6-yne via (*E*)-1-bromo-4,8-dimethyl-3,7-nonadiene (**10**). Here again no significant



6



10

amount (>2%) of the undesirable *Z* isomer is detectable in each step, and the overall procedure is estimated to be 97–98% stereoselective. The experimental results and the physical properties of these butenolides are summarized in Table I.

Acknowledgment is made to the National Institutes of Health, the National Science Foundation, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No. 1, 65717-88-6; 3, 40053-01-8; 4, 56634-50-5; 5, 75476-44-7; 6, 61315-76-2; 7, 74133-12-3; 8, 75476-45-8; 9, 75476-46-9; 10, 69405-35-2; 1-heptyne, 628-71-7; (*E*)-4-methyl-3-nonen-1-ol, 75476-47-0; (*E*)-4-methyl-3-nonen-1-ol tosylate, 75476-48-1; 3-butenylzinc chloride, 74133-07-6; (*E*)-4-methyl-3-nonenylzinc bromide, 75476-49-2; (*E*)-4,8-dimethyl-3,7-nonadienylzinc chloride, 75476-50-5; (*E,E,E*)-4,8,12-trimethyl-14-(2,6,6-trimethyl-1-cyclohexen-1-yl)tetradeca-3,7,11-trienylzinc bromide, 75476-51-6; methyl (*E*)-2-methylhepta-2,6-dienoate, 66052-31-1; 4-(3-butenyl)-2(5*H*)-furanone, 75476-52-7; (*E*)-1-bromo-4-methyl-3-nonene, 75476-53-8.

Supplementary Material Available: Physical and spectral data for methyl (*E*)-2-methylhepta-2,6-dienoate, 4-(3-butenyl)-2(5*H*)-furanone, (*E*)-1-bromo-4-methyl-3-nonene, (*E*)-1-bromo-4,8-dimethyl-3,7-nonadiene, (*E,E,E*)-4,8,12-trimethyl-14-(2,6,6-trimethyl-1-cyclohexen-1-yl)-tetradeca-3,7,11-trien-1-ol, and (*E,E,E*)-1-bromo-4,8,12-trimethyl-14-(2,6,6-trimethyl-1-cyclohexen-1-yl)tetradeca-3,7,11-triene (2 pages). Ordering information is given on any current masthead page.

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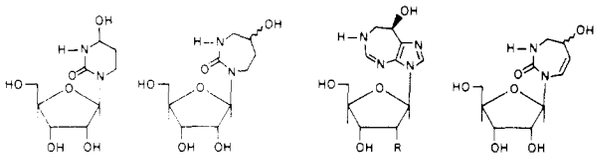
Synthesis of 1,3-Diazepin-2-one Nucleosides as Transition-State Inhibitors of Cytidine Deaminase. 2[1]

Summary: Syntheses of the novel seven-membered-ring (±)-5-hydroxy-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-one (**8**) and its 1-β-D-ribofuranosyl nucleosides **4a** and **4b** have been accomplished by adaptation of the transpositional allylic oxidation procedure following the electrophilic ad-

(1) Presented in part at the 179th National Meeting of the American Chemical Society, Houston, TX, March 1980, Division of Carbohydrate Chemistry, paper no. 14.

dition of ArSeOH to the corresponding starting olefins **5** and **11**.

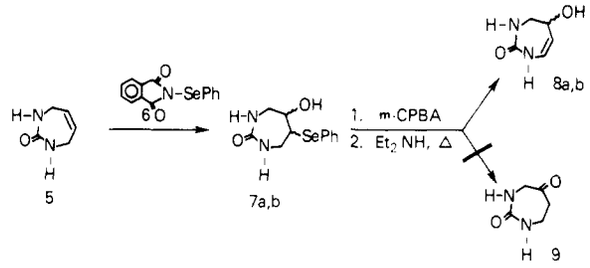
Sir: The inhibition of cytidine deaminase, a catabolic enzyme for the antitumor agent arabinosyl cytidine (Ara-C), continues to be an important objective in cancer chemotherapy.[2] Partial success toward this goal has been achieved by the "transition-state" inhibitor tetrahydrouridine (**1**, THU).[3,4] Recently, a tenfold increase in in vitro inhibitory activity in relation to THU has been demonstrated for one of the diastereoisomers of **2**, which could be regarded as the coformycin (**3a**) counterpart in the pyrimidine series.[5] Coformycin (**3a**) and its 2′-deoxy analogue (**3b**) are the most potent known inhibitors of the analogous enzyme adenosine deaminase and are among the best examples of compounds thought to be active by a "transition-state" inhibitory mechanism.[6,7] Inspection of the molecular structure of coformycin suggested that structure **4** might be the closest and perhaps the most authentic analogue of coformycin in the pyrimidine series. The unusual combination of functionalities in the aglycon portion of this target nucleoside **4** constituted an attractive synthetic goal and is the subject of the present communication.



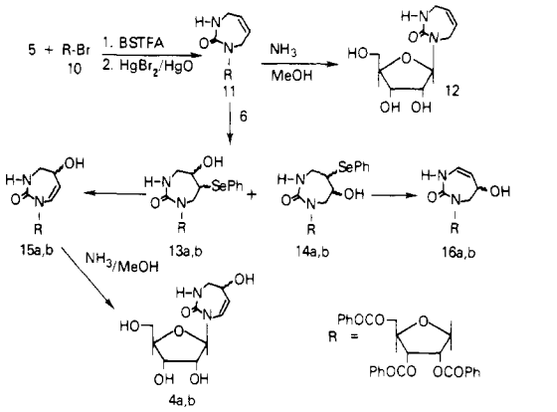
1 **2a,b** **3a**, R = OH; **b**, R = H **4a,b**

The synthesis of the previously unreported aglycon (±)-5-hydroxy-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-one (**8**) was considered a necessary first step, prior to the synthesis of the nucleosides, because the stability of this ring system was unknown. The successful synthesis of **8** was accomplished via the adaptation of a transpositional allylic oxidation procedure following the electrophilic addition of organoselenium reagents (Ar–SeX)[8] to a heterocycle olefin. The substrate olefin selected for this reaction was our previously reported diazepinone **5**.[9] After several trial experiments the reagent of choice was found to be *N*-(phenylselenenyl)phthalimide (**6**)[10] which in a mixture of CH_2Cl_2–CH_3CN–H_2O gave excellent yields (ca. 90%) of the two possible trans enantiomers **7a,b** (Scheme I). The crystalline adduct oxidized instantly at room temperature with either sodium metaperiodate or *m*-chloroperbenzoic acid (*m*-CPBA). The resulting hydroxy selenoxide was stable at room temperature but underwent smooth elimination at 90 °C to provide racemic **8** in 87% yield. The exclusive formation of the allylic alcohol product **8** is

Scheme I



Scheme II



consistent with previous observations of ArSeOH eliminations to form a nonenolic product.[8] Since the N-1 nitrogen and 5-hydroxyl group can both be considered substituents of a carbon α to the phenylselenenyl function in adducts **7a,b**, elimination of ArSeOH could have conceivably taken place in the opposite direction to give the already known 5-oxoperhydrodiazepin-2-one (**9**)[9] (Scheme I). None of this material was detected and the reaction proceeded in a very regiospecific manner,[11] giving only the desired product **8**: mp 152–154 °C;[12] IR (KBr) 3500–2800, 1650 cm^{-1}; NMR (CD_3OD–D_2O) δ 3.1–3.4 (m, 2, CH_2N), 4.17 (m, 1, CHOH), 4.88 (dd, 1, CHOHC**H**=CHN, J = 10, J' = 4 Hz), 5.82 (d, 1, CHOHCH=C**H**N, J = 10 Hz); mass spectrum, m/e (relative intensity) 128 ($M^{+\cdot}$, 26), 110 (M – H_2O, 62).

Encouraged by these results it was decided to investigate a similar oxidative allylic transposition sequence with a suitable nucleoside precursor such as compound **11**. This protected nucleoside was prepared by the new procedure reported earlier[5] for the condensation of **9** and 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**10**). Thus, the persilylated heterocycle **5** was reacted with **10** in the presence of mercury catalysts to afford exclusively the single β-anomer **11** in 55–60% yields. Compound **11** was obtained as a foam: mp 63–64 °C;[12] NMR ($CDCl_3$) δ 3.60–3.80 (m, 4), 4.60 (m, 3), 5.10 (m, 1), 5.60 (m, 2), 5.70 (m, 2), 6.06 (d, 1, H-1′, J = 6 Hz), 7.10–7.60 (m, 9, aryl), 7.80–8.20 (m, 6, aryl). The anomeric assignment was based on considerations of the mechanism of condensation of 2-*O*-benzoylated sugar halides, spectral data, and the very potent cytidine deaminase inhibitory activity displayed by the corresponding deprotected nucleoside **12**.[5]

As shown in Scheme II, compound **11** was allowed to react with the ArSeX reagent **6** at room temperature in

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(10) Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704.
(11) Recently a similar observation has been reported where despite the presence of an α-Cl substituent the elimination proceeded exclusively away from the hydroxyl group. Liotta, D.; Zima, G. *J. Org. Chem.* **1980**, *45*, 2551.
(12) All final target compounds described in the text gave satisfactory elemental analyses within ±0.4% of theoretical values.

a mixture of THF-CH_3CN-H_2O for 3 days in the presence of catalytic amounts of *p*-toluenesulfonic acid. TLC analysis of the reaction mixture showed the expected presence of all four possible trans products resulting from addition to the asymmetric double bond of **11**. The total yield was 74%, with the more polar pair of diastereoisomers (**13a,b**) predominating [R_f 0.32 and 0.46 in ethyl acetate–hexane (3:2)]. This pair of isomers and the less polar pair were separated and resolved into their components by either preparative TLC or high-performance LC. The yields of the diastereoisomers comprising the more polar pair were 29% and 18%, respectively. At this point, the structural differentiation between the two possible regioisomeric sets **13** and **14** was impossible to make. Only after the elimination reaction were we able to assign structures unambiguously as a result of the different positions of the double bonds. It was fortunate that the addition of the ArSeX reagent showed some degree of regioselectivity since the major pair of adducts corresponded to the desired diastereoisomers **13a** and **13b**.[13] Oxidation of **13a** and **13b** with *m*-CPBA at room temperature for 15 min followed by refluxing in $CHCl_3$ (2 h) in the presence of Et_2NH afforded **15a** and **15b**, respectively. Compounds **15a** and **15b** have very similar NMR spectra which conclusively support the assigned structures. Compound **15a** was obtained as a foam: mp 74–80 °C;[12] $[\alpha]^{23}_D$ +17.5° (*c* 0.1, $CHCl_3$); NMR (acetone-d_6) δ 3.00 (br s, 1, OH, D_2O exchanged), 3.25 (m, 2, $NHCH_2CHOH$), 4.00 (m, 1, $NHCH_2CHOH$), 4.75 (m, 3, H-4′, H-5′, H-5′a), 4.98 (dd, 1, $CHOHCH{=}CHN$, J = 10, J' = 5 Hz), 5.86 (m, 2, H-2′, H-3′), 6.12 (d, 1, H-1′, J = 6 Hz), 6.30 (d, 1, $CHOHCH{=}CHN$, J = 10 Hz), 6.70 (br t, 1, $NHCH_2$, J = 5 Hz, D_2O exchanged), 7.20–7.60 (m, 9, aryl), 7.80–8.20 (m, 6, aryl). Compound **15b** was also obtained as a foam: mp 77–82 °C;[12] $[\alpha]^{23}_D$ −71.5° (*c* 0.1, $CHCl_3$); NMR (acetone-d_6) δ 3.10 (br s, 1, OH, D_2O exchanged), 3.30 (m, 2, $NHCH_2CHOH$), 4.20 (m, 1, $NHCH_2CHOH$), 4.80 (m, 3, H-4′, H-5′, H-5′a), 5.00 (dd, 1, $CHOHCH{=}CHN$, J = 10, J' = 2 Hz), 5.90 (m, 2, H-2′, H-3′), 6.20 (d, 1, H-1′, J = 6 Hz), 6.30 (d, 1, $CHOHCH{=}CHN$, J = 10 Hz), 6.80 (br t, 1, $NHCH_2$, J = 5 Hz, D_2O exchanged), 7.20–7.70 (m, 9, aryl), 7.80–8.20 (m, 6, aryl). The well-resolved, first-order nature of these spectra in the downfield region from δ 5 to 7 confirmed the assignment of the structures for this pair of diastereoisomers. In addition, after D_2O exchange, the CH_2 signal of the C-4 carbon of the aglycon was greatly simplified whereas the vinyl hydrogen at C-7 remained unchanged. Decoupling experiments likewise corroborated the assignment. These two diastereoisomers differ only in the absolute configuration of the hydroxyl group at C-5 as evidenced from their different specific rotations and coupling constants ($J'_{5,6}$) in the NMR. Oxidation and thermal elimination of ArSeOH performed on the other diastereoisomeric pair (**14a** and **14b**) gave the expected products (**16a** and **16b**) which showed NMR spectra consistent with the different location of the double bond. Again both spectra were nearly identical and data from only one of the diastereoisomers is given: NMR ($CDCl_3$) δ 2.50 (br s, 1, OH), 3.20–3.40 (m, 2, CH_2N), 4.10 (m, 1, CHOH), 4.60 (m, 3, H-4′, H-5′, H-5′a), 4.90 (dd, 1, $HNCH{=}CHCHOH$, J = 10, J' = 5 Hz), 5.85 (m, 3, $HNCH{=}CHCHOH$, H-2′, H-3′), 6.80 (d, 1, $NHCH{=}$, J = 8 Hz, D_2O exchanged), 7.20–7.50 (m, 9, aryl), 7.70–8.10 (m, 6, aryl). An important difference between the two sets of regioisomers (**15a,b** vs. **16a,b**) is the chemical shift observed for the vinyl hydrogen adjacent to the heterocyclic nitrogen. In diastereoisomers **15a** and **15b**, this signal is significantly lower, absorbing at δ 6.30. This observation can be explained in terms of the magnetic anisotropic effect resulting from the close proximity of the vinyl hydrogen to the furanose ring oxygen in the expected most stable anti configuration of these nucleosides.[14] The corresponding signal in **16a** and **16b** appears at δ 5.85 which compares very well with the resonance of the equivalent proton in the aglycon **8** at δ 5.82.

Deprotection of nucleosides **15a** and **15b** by the standard procedure in methanol saturated with ammonia afforded the corresponding target compounds **4a** and **4b** in ca. 80% yield. Compound **4a** was obtained as a lyophilized powder: mp 75–78 °C;[12] IR (KBr) 1660 cm^{-1}; $[\alpha]^{23}_D$ +62° (*c* 0.1, MeOH); NMR (CD_3OD–D_2O) δ 5.13 (dd, 1, J = 10, J' = 4 Hz), 5.48 (m, 6-Hz wide, 1, H-1′), 6.25 (d, 1, J = 10 Hz); M^+· 620 (penta-Me_3Si derivative). Compound **4b** was also obtained as a lyophilized powder: mp 66–69 °C;[12] IR (KBr) 1660 cm^{-1}; $[\alpha]^{23}_D$ −28.5° (*c* 0.1, MeOH); NMR (CD_3OD–D_2O) δ 5.12 (dd, 1, J = 10, J' = 1 Hz), 5.52 (d, 1, H-1′, J = 6 Hz), 6.20 (d, 1, J = 10 Hz); mass spectrum, *m/e* 620 (M^+·, penta-Me_3Si derivative).

Compound **11** was deblocked in the same manner as **15a** and **15b** to afford the free nucleoside **12**. Preliminary biological testing indicated that all three compounds (**4a**, **4b**, and **12**) were more potent than THU (**1**) as cytidine deaminase inhibitors. A detailed discussion of their activity will be reported elsewhere.

Registry No. **4** (isomer 1), 75430-93-2; **4** (isomer 2), 75421-07-7; **5**, 72331-40-9; **6**, 71098-88-9; **7**, 75421-08-8; **8**, 75421-09-9; **10**, 22860-91-9; **11**, 75421-10-2; **12**, 75421-11-3; **13** (isomer 1), 75421-12-4; **13** (isomer 2), 75444-05-2; **14** (isomer 1), 75421-13-5; **14** (isomer 2), 75444-06-3; **15** (isomer 1), 75421-14-6; **15** (isomer 2), 75421-15-7; **16** (isomer 1), 75421-16-8; **16** (isomer 2), 75421-17-9.

(13) This favorable regioselectivity is perhaps related to a preferential attack by water on the initially formed episelenonium intermediate from the least hindered and most hydrophilic side of the molecule.

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Selenium-Stabilized Carbanions.[1] Acidity of Allyl and Vinyl Sulfides and Selenides

Summary: The rates of deprotonation of vinyl and allyl aryl sulfides with amide bases show that allyl sulfides are kinetically more acidic than allyl selenides, whereas vinyl sulfides are less acidic than vinyl selenides.

Sir: The scattered information available on the acidifying effect of phenylthio and phenylseleno substituents on α-hydrogens indicates that sulfur stabilizes carbanions slightly more effectively than does selenium.[2] In contrast, molecular orbital calculations have predicted that $HSeCH_2^-$ should be approximately 4 kcal/mol more stable than

(1) For previous papers see: (a) H. J. Reich, F. Chow, and S. K. Shah, *J. Am. Chem. Soc.*, **101**, 6638 (1979); (b) H. J. Reich, S. K. Shah, and F. Chow, *ibid.*, **101**, 6648 (1979); (c) H. J. Reich, *J. Org. Chem.*, **40**, 2570 (1975).

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