Scheme I

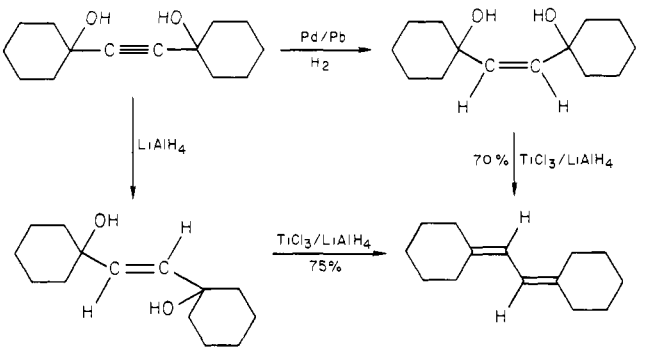
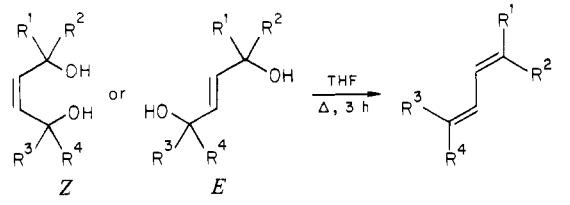


Table I. Reduction of (*E*)- and (*Z*)-2-Ene-1,4-diols to 1,3-Dienes



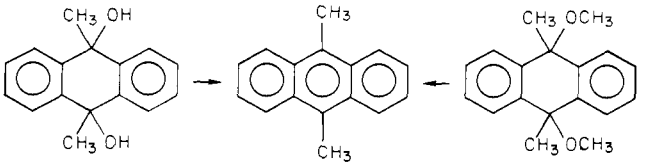
R^1	R^2	R^3	R^4	isomer	molar ratio $TiCl_3$: diol	diene[a] yield, %
$-(CH_2)_5-$		$-(CH_2)_5-$		*Z*	4:1	70
$-(CH_2)_5-$		$-(CH_2)_5-$		*E*	4:1	75
CH_3	CH_3	CH_3	CH_3	*Z*	4:1	62[b]
CH_3	CH_3	CH_3	CH_3	*E*	4:1	78
Ph	Ph	Ph	Ph	*Z*	4:1	42[b,c]
Ph	Ph	Ph	Ph	*E*	3:1	83
Ph	H	Ph	H	*Z*	2.5:1	75[d]

[a] Identity of all products was established by IR, ^{1}H-NMR spectra, and comparison with reported data. [b] On the basis of the ^{1}H NMR spectrum, all other yields are isolated yields. [c] A 26% yield of the cyclization product, 2,3,5,5-tetraphenyl-2,5-dihydrofuran, was also obtained. [d] *E,E*-isomer isolated.

larly lithium aluminum hydride. A mixture of $TiCl_3$ and $LiAlH_4$ (4:1) is known as the McMurry reagent. However, Geise[11] has found that the $TiCl_3$:$LiAlH_4$ ratio of 2:1 is the most effective, at least in the coupling of ketones, and therefore this reagent was used in this study.[12]

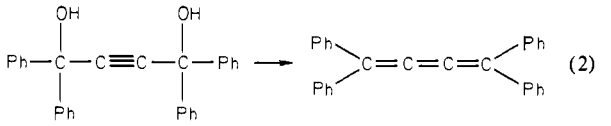
As can be seen from Table I, the yields of diene are very good. This plus the fact that the starting 2-ene-1,4-diols are easy to obtain—condensation of an aldehyde and/or ketone with acetylene followed by reduction—holds promise that this reaction might lead to a general method for the syntheses of 1,3-dienes.

The diol is not essential for the reaction to occur. The monomethyl as well as the dimethyl[13] ether of (*Z*)-2,5-dimethyl-2,5-dihydroxy-3-hexene also gives rise to the corrsponding 2,5-dimethyl-2,4-hexadiene in 82% and 64% yields, respectively. Moreover, both 9,10-dimethyl-9,10-dihydroxyanthracene and the dimethyl ether gave quantitative yields of 9,10-dimethylanthracene by reaction with low-valent titanium (eq 1).



(1)

Furthermore, in an analogous reaction, 1,1,4,4-tetraphenyl-1,4-dihydroxy-2-butyne was reduced to the stable 1,1,4,4-tetraphenyl-1,2,3-butatriene in 83% yield (eq 2).



(2)

The general scope, limitations, and mechanism of this reaction[14,15] are under active investigation, especially concerning the use of other low-valent metals to effect these transformations.

(11) Dams, R.; Malinowski, M.; Westdorp, I.; Geise, N. Y. *J. Org. Chem.* **1982**, *47*, 248.

(12) It is generally believed[4-6,11] that the low-valent species generated in these reductions is Ti(0).

(13) This experiment was performed by C. J. Franson.

(14) To our knowledge the only other example of converting a 2-ene-1,4-diol to a 1,3-diene directly, but in inferior yields, is that reported by Kuhn and Wallenfels (Kuhn, R.; Wallenfels, K. *Ber. Dtsch. Chem. Ges.* **1938**, *71*, 1889) by using P_2I_4 or VCl_2 as reducing reagents. A 2-yne-1,4-diol has been reported to yield a 1,3-diene in 35% yield upon treatment with lithium aluminum hydride: Nayler, P.; Whiting, M. C. *J. Chem. Soc.* **1954**, 4006. For a list of reagents used to convert 2-yne-1,4-diols to cumulenes see: Murray, M. in "Methoden der Organischen Chemie" (Houben-Weyl-Müller), 4th ed.; Verlag: Stuttgart, 1977; Vol. 5, 2a.

(15) **General Procedure. Preparation of Reducing Agent.** A suspension of 3.12 g (20 mmol) of $TiCl_3$ in 60 mL of dry THF was cooled to 0 °C, and 380 mg (10 mmol) of $LiAlH_4$ was added via a Schlenk tube in small portions. The resulting black mixture was stirred at 0 °C for 30 min and then refluxed for an additional hour.

Reduction of 2-Ene-1,4-diol. To the black suspension, cooled to 0 °C, was added 5.0 mmol of diol. After the hydrogen evolution subsided, the reaction mixture was refluxed for 3 h. The reaction mixture was cooled, 40 mL of 2 N hydrochloric acid was added, and the mixture was extracted with chloroform. The chloroform extract was washed with water and dried over anhydrous magnesium sulfate. The chloroform was stripped to yield either a solid, which was then recrystallized, or an oil, which was purified by distillation.

Mechanism and Regioisomeric Control in Palladium(II)-Mediated Cycloalkenylations. A Novel Total Synthesis of (±)-Quadrone

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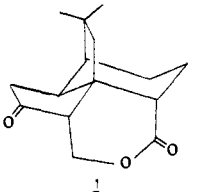
Received June 11, 1982

The direct, intramolecular cycloalkenylation of an enol derivative is a powerful strategy for construction of bridged polycyclic systems, but one that has been hitherto unavailable to the synthetic chemist. We have recently discovered a Pd(II)-mediated cycloalkenylation of silyl enol ethers that offers the first solution to this gap in synthetic methodology.[1] We now report observations bearing on the mechanism and scope of this cyclization and exploit these findings in a remarkably short total synthesis of the tetracyclic antitumor agent (±)-quadrone (**1**).[2]



1

To elucidate the mechanism of our cycloalkenylation reaction, we have compared the behavior of the enol ethers **2a-c** with 1.0 equiv of $Pd(OAc)_2$ in dry MeCN for 4 h at room temperature

(1) Kende, A. S.; Roth, B.; Sanfilippo, P. J. *J. Am. Chem. Soc.* **1982**, *104*, 1784.

(2) Rainieri, R. L.; Calton, G. J. *Tetrahedron Lett.* **1978**, 499. Calton, G. J.; Rainieri, R. L.; Espenshade, M. A. *J. Antibiot.* **1978**, *31*, 38.

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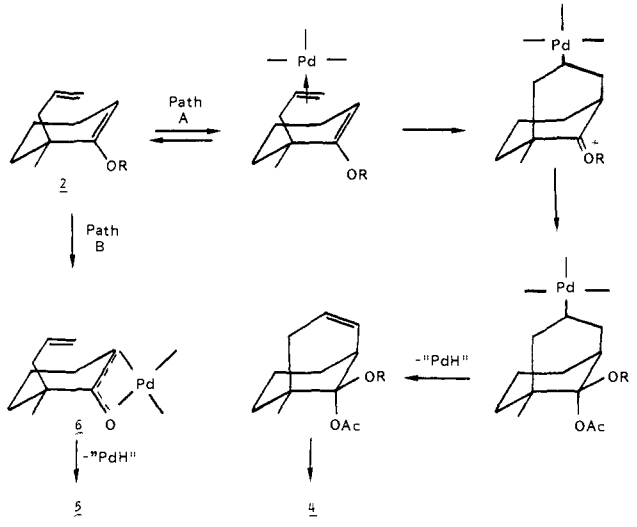
Table I[a]

	4a	4b	5	starting material recovered
2a, X = $SiMe_3$; R = $CH_2CH{=}CH_2$	58	14	15	
2b, X = $SitBuMe_2$; R = $CH_2CH{=}CH_2$	45	22		30
2c, X = CH_3; R = $CH_2CH{=}CH_2$	40	20		30
2d, X = Li; R = $CH_2CH{=}CH_2$			94	
3c, X = CH_3; R = CH_3			2	87

[a] All values in percent.

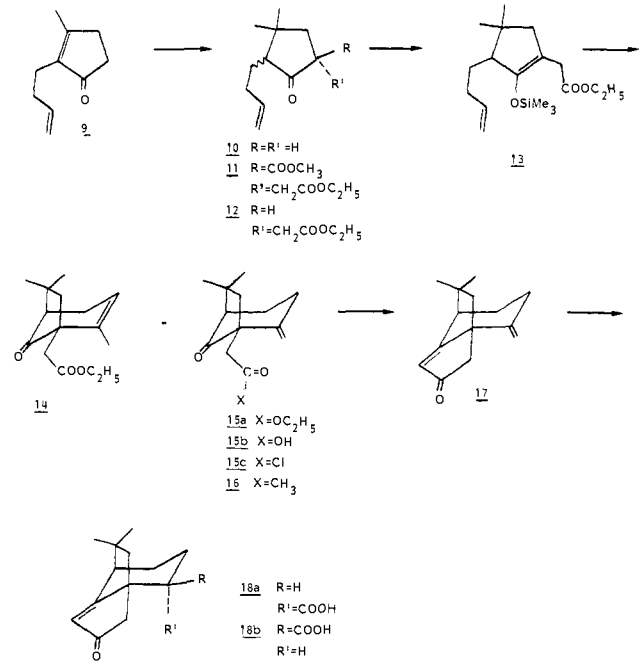
Scheme I



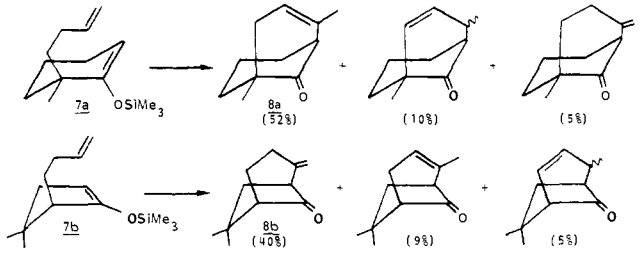
(Table I).[3] In contrast to the smooth formation of bicyclic products **4a** and **4b** from these three reactants, the methyl enol ether **3c** was essentially inert during the above reaction time, whereas the Li enolate **2d** was converted exclusively to enone **5**. These observations seem to be incompatible with the suggestion by the Kyoto group that *both cyclization and enone formation proceed through a common, desilylated oxo-π-allyl species* (cf. **6**).[4] That hypothesis would not explain the differences in product ratios **4**/**5** from **2a** vs. **2b** or **2a** vs. **2d**, nor the fact that **2c** cyclizes rapidly under conditions whereby **3c** is nearly unaffected. Our data are, however, well accommodated by an alternative cyclization mechanism (path A) of Scheme I, wherein the rate-determining step in the cycloalkenylation is *nucleophilic attack of the enol ether double bond upon the Pd-coordinated exocyclic olefin.*[5]

The formation of olefin regioisomers in our cyclizations implies an as yet undefined isomerization mechanism associated with the reaction.[6] However, a regiochemical effect that may be related

Scheme II



to ring strain has already become apparent. Thus, the cyclization of the cyclohexenol silyl ether **7a** leads predominantly to the endocyclic olefin **8a**,[7] whereas the cyclopentenol silyl ether **7b** gives mainly the exocyclic olefin isomer **8b**.



We have exploited these regiochemical results in a novel strategy (Scheme II) for the formation of the C-1 quaternary center of (±)-quadrone (**1**).[9] Our point of departure is the known cyclopentenone **9**,[10] which reacted smoothly with $MeCu{\cdot}BF_3$ (3 equiv, Et_2O, −78 → 0 °C, 4 h) to yield 77% of the cyclopentanone **10**.[11] This was carbomethoxylated (3 equiv of $(MeO)_2CO$, NaH, THF, reflux, 12 h) and directly alkylated (1.2 equiv of $BrCH_2COOC_2H_5$, NaH, DMF, room temperature, 16 h) to give 73% of the expected keto diester **11**. Nucleophilic decarbalkoxylation of **11** with

(3) Reactions were carried out on a 1.0-mmol scale in 10 mL of dry MeCN. After 4 h the reaction was gently concentrated to an oil at room temperature, taken up in pentane, and passed through Celite. The product sets were separated by flash chromatography (silica gel, 40:1 hexane–EtOAc) and characterized by 400-MHz NMR. Compounds **4a**, **4b**, and **5** have been described in our preceding communication.[1]

(4) Ito, Y.; Aoyama, H.; Hirao, T.; Mochizuki, A.; Saegusa, T. *J. Am. Chem. Soc.* **1979**, *101*, 494. Ito, Y.; Aoyama, H.; Saegusa, T. *Ibid.* **1980**, *102*, 4519.

(5) For related mechanisms see: Hegedus, L. S.; Williams, R. E.; McGuire, M. A.; Hayashi, T. *J. Am. Chem. Soc.* **1980**, *102*, 4973. Overman, L. E.; Knoll, F. M. *Ibid.* **1980**, *102*, 865. The possibility of simultaneous coordination by Pd to both double bonds during the cyclization step cannot be excluded.

(6) It is possible that a short-lived "PdH" species formed in the cycloalkenylation process is responsible for some of the olefin isomerization observed. We do not imply in our discussion that full thermodynamic equilibration of olefin regioisomers is achieved in these cycloalkenylations.

(7) **8a**: ^1H NMR ($CDCl_3$) δ 5.65 (br s, 1 H), 2.71 (br s, 1 H), 2.45 (br d, J = 18 Hz, 1 H), 2.30 (br d, J = 18 Hz, 1 H), 1.96 (m, 2 H), 1.80 (m, 2 H), 1.67 (br s, 3 H), 1.55 (m, 2 H), 1.03 (s, 3 H).

(8) **8b**: ^1H HMR ($CDCl_3$) δ 4.75 (br s, 1 H), 4.65 (br s, 1 H), 2.98 (d, J = 6 Hz, 1 H), 2.56 (m, 1 H), 2.20 (dd, J = 6, 14 Hz, 1 H), 2.04 (m, 1 H), 1.92 (br s, 1 H), 1.84 (m, 3 H), 1.22 (s, 3 H), 1.01 (s, 3 H).

(9) Three total syntheses of (±)-quadrone have been reported in recent months: (a) Danishefsky, S.; Vaughan, K.; Gadwood, R.; Tsuzuki, K. *J. Am. Chem. Soc.* **1981**, *103*, 4136; **1980**, *102*, 4262. (b) Bornack, W. K.; Bhagwat, S. S.; Pontan, J.; Helquist, P. *Ibid.* **1980**, *102*, 4262. (c) Burke, S. D.; Murtiashaw, C. W.; Saunders, J. O.; Dike, M. S. *Ibid.* **1982**, *104*, 872.

(10) Sturiale, E. R. *J. Org. Chem.* **1980**, *45*, 3664. A more convenient synthesis of **9** employs the method of Stetter and Kuhlmann (Stetter, H.; Kuhlmann, H. *Synthesis* **1975**, 379), using 5-hexenal and methyl vinyl ketone.

(11) The $MeCu{\cdot}BF_3$ procedure was found superior to alternative methods; see: Yamamoto, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1978**, *100*, 3240. All new compounds employed in our synthetic sequence gave satisfactory analytical and spectroscopic data.

LiI·2H_2O (1.2 equiv, 2,6-lutidine, reflux, 36 h) gave 81% of the γ-keto ester **12**.

Regioselective generation of the requisite silyl enol ether **13** was uniquely achieved in 80% yield by reaction of **12** with 0.95 equiv of LDA (THF, −78 → 0 °C, 30 min), trapping with Me_3SiCl, dilution with hexane, and filtration through Celite and then Florisil. Reaction of the silyl enol ether **13** under our standard cycloalkenylation conditions (1.0 equiv of $Pd(OAc)_2$, CH_3CN, room temperature, 8 h) gave after flash chromatography an 8:1 mixture of the bicyclic olefins **15a** and **14**, which was directly saponified (1 N KOH, aqueous MeOH, reflux, 2 h) to give 55% of the methylene acid **15b**, mp 121–122 °C.[12] Formation of the third ring proceeded through the acid chloride **15c** (from **15b**, 2 equiv of ClCOCOCl, Et_2O, room temperature, 4 h), which was reacted with Me_4Sn (2 equiv) and a catalytic amount of $PhCH_2Pd(Ph_3P)_2Cl$ in HMPA (65 °C, 3 days)[13] to give 82% of the desired diketone **16**, accompanied by traces of the pseudo-acid chloride (mp 75–76 °C, IR: ν_{CO} 1812 cm^{-1}), which was inert to further reagent. When diketone **16** was stirred with NaH (4 equiv., toluene, reflux, 2 h), the tricyclic dienone **17**,[14] mp 56–57 °C, was obtained as the sole product in 83% yield. *We had thus attained the complete carbocyclic framework of the target molecule in 16% yield over nine steps.*

Conversion of the exocyclic methylene group of **17** to an axial COOH group was necessary to complete the synthesis, since Danishefsky had transformed keto acid **18a** to (±)-quadrone in three steps.[8] Initial forays to this end by using 1 equiv of MCPBA (CH_2Cl_2, 25 °C, 8 h) showed no stereoselection at the methylene group, leading to both diastereomeric epoxy enones in a 1:1 ratio.[15] After much exploration it was found that reaction of dienone **17** with 2.0 eq of thexylborane (THF, 0 → 25 °C, 4 h), followed by dichromate oxidation (10 equiv, 25 °C, 12 h), gave 50% of the axial acid **18a** (mp 143–146 °C) and 16% of the equatorial acid **18b** (mp 168–71 °C).[16] Acid **18a** from our sequence was identical in all respects with a sample kindly provided by Professor Danishefsky.

Our formal total synthesis of quadrone, which corresponds to a 14-step sequence in 2.4% overall yield, provides a compelling illustration of the power of a Pd(II)-mediated cycloalkenylation strategy in natural products synthesis. Further development of this reaction is in progress.

Acknowledgment. Partial support of this research by the National Cancer Institute (USPHS) through Grant CA-18846 (to A.S.K.) and postdoctoral fellowships CA-07185 (to B.R.) and CA-06530 (to T.J.B.) is gratefully acknowledged. Valuable discussions with Professor W. D. Jones and P. Fludzinski of this department contributed significantly to the success of this work.

Registry No. (±)-**1**, 74807-65-1; **2a**, 82951-15-3; **2b**, 82951-16-4; **2c**, 82951-17-5; **2d**, 82951-18-6; **3c**, 73741-66-9; **4a**, 82951-19-7; **4b**, 82951-20-0; **5** (R = $CH_2CH{=}CH_2$), 82951-21-1; **5** (R = CH_3), 6553-64-6; **7a**, 82951-22-2; **7b**, 82951-23-3; **7b**, 82951-23-3; **8a**, 82951-24-4; **8b**, 82951-26-6; **9**, 60924-91-6; **10** (R = R′ = H), 82951-29-9; **10** (R = $COOCH_3$, R′ = H), 82951-30-2; **11**, 82951-31-3; **12**, 82951-32-4; **13**, 82951-33-5; **14**, 82951-34-6; **15a**, 82951-35-7; **15b**, 82951-36-8; **15c**, 82951-37-9; **15c** pseudo-acid chloride, 82951-40-4; **16**, 82951-38-0; **17**, 82951-39-1; **18a**, 82978-37-8; $Pd(OAc)_2$, 3375-31-3; 1,4-dimethylbicyclo[3.3.1]non-2-en-9-one, 80954-09-2; 1-methyl-4-methylenebicyclo[3.3.1]nonan-9-one, 82951-25-5; 2,6,6-trimethylbicyclo[3.2.1]-oct-2-en-8-one, 82951-27-7; 2,6,6-trimethylbicyclo[3.2.1]oct-3-en-8-one, 82951-28-8.

(12) **15b**: ^1H NMR ($CDCl_3$) δ 4.80 (d, J = 2 Hz, 1 H), 4.66 (d, J = 2 Hz, 1 H), 2.88 (d, J = 16 Hz, 1 H), 2.72 (d, J = 16 Hz, 1 H), 2.66 (m, 1 H), 2.25 (dd, J = 7, 14 Hz, 1 H), 2.10 (d, J = 14 Hz, 1 H), 2.06 (m, 2 H), 1.89 (d, J = 14 Hz, 1H), 1.82 (m, 1 H), 1.22 (s, 3 H), 1.01 (s, 3 H). No conjugated enone was found in this cyclization.

(13) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636.

(14) **17**: ^1H NMR ($CDCl_3$) δ 5.68 (s, 1 H), 4.74 (d, J = 2 Hz, 1 H), 4.60 (d, J = 2 Hz, 1 H), 2.99 (d, J = 18 Hz, 1 H), 2.55 (m, 1 H), 2.28 (dd, J = 7, 15 Hz, 1 H), 2.19 (d, J = 18 Hz, 1 H), 2.05 (m, 1 H), 1.90 (d, J = 14 Hz, 1 H), 1.75 (m, 1 H), 1.46 (d, J = 14 Hz, 1 H), 1.26 (s, 3 H), 0.99 (s, 1 H).

(15) Lewis acid catalyzed rearrangement of these epoxy enones gave mixtures of aldehydes in which skeletal rearrangement predominated.

(16) The acids **18a** and **18b** were readily separated by preparative TLC on silica gel with 60:1:1 CH_2Cl_2–CH_3OH–HOAc. We are grateful to Professor M. Goldstein (Cornell) for suggesting the dichromate procedure of Brown et al. (Brown, H. C.; Rothberg, I.; Van der Jagt, D. L. *J. Org. Chem.* **1972**, *37*, 4098), which was superior to the use of H_2O_2–OH^- and Jones reagent in this system.

^1H NMR Studies of ^{15}N-Labeled *Escherichia coli* $tRNA_f^{Met}$. Use of $^1J_{^1H-^{15}N}$ Couplings to Identify Imino Resonances of Uridine-Related Bases

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Received June 1, 1982

Since the pioneering experiments of Kearns and Shulman,[1,2] high-resolution proton nuclear magnetic resonance spectroscopy (^1H NMR) has become the preferred technique for studying the structure of tRNA in solution. The richest source of information is the region between 11 and 15 ppm,[3] where the imino protons of bases involved in stable secondary and tertiary interactions resonate. When properly assigned, these signals give important information about tertiary structure and conformational dynamics. Several techniques,[4-7] including analysis of tRNA fragments, empirical calculations of chemical shifts based on shielding interactions, chemical modification, comparative studies of different tRNAs, and most recently, nuclear Overhauser effects (NOEs),[7-11] have been used to assign chemical shifts. However, a typical class I tRNA contains 23–27 individual, often overlapping, peaks between 11 and 15 ppm, and assignment of resonances has proved to be a difficult and controversial task. The problems associated with making assignments would be simplified if peaks could be unambiguously assigned to imino resonances in uridine or guanosine. An approach that offers this possibility is the regiospecific introduction of ^{15}N into N(3) of uridine and structurally related bases. Replacement of ^{14}N by this isotope introduces a ^1H–^{15}N coupling interaction which should be clearly visible in the ^1H spectra of labeled tRNAs. In this and the following communication we report the first experiments with tRNA regiospecifically labeled with ^{15}N.

E. coli $tRNA_f^{Met}$ labeled with ^{15}N at N(3) in uridine and all bases derived biosynthetically from uridine (D, rT, Ψ, and s^4U) was isolated from the SΦ-187 auxotroph of the bacterium grown on medium containing [3-^{15}N]uracil.[12-15] Substantial enrichments

(1) Kearns, D. R.; Patel, D. J.; Shulman, R. G. *Nature (London)* **1971**, *229*, 338–339.

(2) Kearns, D. R.; Patel, D. J.; Shulman, R. G.; Yamane, T. *J. Mol. Biol.* **1971**, *61*, 265–270.

(3) Abbreviations used: NOE, nuclear Overhauser effect; EDTA, ethylenediaminetetraacetic acid; ppm, parts per million; D, dihydrouridine; Ψ, pseudouridine; rT, ribothymidine; s^4U, 4-thiouridine; m^7G, 7-methylguanosine; A, adenosine; U, uridine; G, guanosine; C, cytosine; P, phosphate.

(4) Reid, B. R.; Hurd, R. E. *Acc. Chem. Res.* **1977**, *10*, 396–402.

(5) Reid, B. R. *Methods Enzymol.* **1979**, *59*, 21–57.

(6) Robillard, G. T.; Reid, B. R. "Biological Applications of Magnetic Resonance"; Shulman, R. G., Ed.; Academic Press: New York, 1979; pp 45–112.

(7) Schimmel, P. R.; Redfield, A. G. *Ann. Rev. Biophys. Bioeng.* **1980**, *9*, 181–221.

(8) Johnston, P. D.; Redfield, A. G. *Nucleic Acid Res.* **1978**, *5*, 3913–3927.

(9) Roy, S.; Redfield, A. G. *Nucleic Acids Res.* **1981**, *9*, 7073–7083.

(10) Tropp, J.; Redfield, A. G. *Biochemistry* **1981**, *20*, 2133–2140.

(11) Sanchez, V.; Redfield, A. G.; Johnston, P. D.; Tropp, J. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 5659–5662.

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