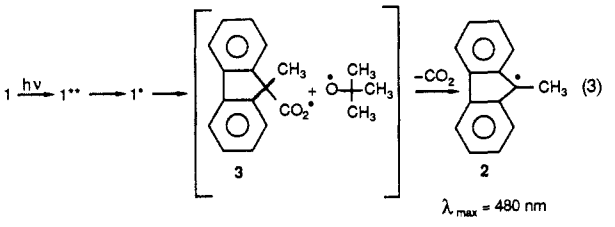
implicated by the formation of the aforementioned ether, 9,9-dimethylfluorene (6%); the symmetrical coupling product 9,9'-dimethyl-9,9'-bifluorene (67%); and 9-(cyanomethyl)-9-methylfluorene (12% from reactions in acetonitrile). The relative yields of these products depend on the extent of reaction since the ether and the dimer are both photolabile.

The 9-methylfluorenyl radical was also detected spectroscopically. Direct or triplet-sensitized irradiation of perester **1** with a laser pulse of ca. 15-ns duration (direct, 266 nm; triplet sensitized with *p*-methoxyacetophenone at 337 nm) generates a transient intermediate with absorption maxima at 445 and 480 nm. On the timescale of these experiments, the intermediate is formed instantaneously and then decays over a period of several microseconds in a kinetically complex way. The structure of the intermediate was assigned to radical **2** by comparison of its spectrum with that of an authentic sample prepared independently by laser irradiation of di-*tert*-butyl peroxide containing a small amount of dissolved 9-methylfluorene.[14] This spectrum is shown in Figure 1.

Irradiation of perester **1** with the quadrupled output of a mode-locked Nd:YAG laser (266 nm, 18 ps, 4 mJ) similarly leads to the formation of fluorenyl radical **2**. However, on this time scale the radical does not appear instantaneously, Figure 2. Its absorption grows according to a first-order rate law from a precursor that has a 55 ± 15 ps lifetime. There are several chemical and physical processes that must occur between the absorption of a photon at 266 nm by peroxide **1** and the appearance of the methylfluorenyl radical. The kinetic result reports the rate of the slowest of these steps. The proposed reaction sequence is outlined in eq 3.



(3)

The UV absorption spectrum of perester **1** is nearly superimposable on that of model compound 9-carbomethoxy-9-methylfluorene (**4**) except for a broad, weak band characteristic of peroxides[15] which extends the absorption out past 400 nm. When perester **1** absorbs a 266-nm photon, the initially formed excited state (**1****) is heavily localized in the π-system of the fluorenyl chromophore. It is conceivable that the slow step in the formation of radical **2** is the "transfer" of energy to the lowest excited singlet state (**1***) localized on the peroxide group. This possibility was excluded by comparison of the behavior of **1** with ester **4** and other model compounds. The fluorescence efficiency of the perester is 0.8% that of the ester, but the lifetime of this weak emission is approximately the same (6.9 ns) as the ester. Since it is unlikely that the purity of the perester is greater than 99.2%, the residual emission is logically assigned to a trace of ester (or acid) in the perester sample. Irradiation of either ester **4**, fluorene, or 9-methylfluorene with the picosecond laser forms similarly absorbing transient species assigned by correlation of lifetime to the excited singlet state of the common fluorene-like chromophore. Irradiation of perester **1** under identical conditions gives no trace of this absorption. Thus, as expected from studies of analogous examples of intramolecular energy transfer,[16] the lifetime of **1**** is too short to allow detectable fluorescence or excited-state absorption. And, concomitantly, the formation of **1*** is too fast to be the slow step in the formation of radical **2**.

(14) Paul, H.; Small, Jr., R. D.; Scaiano, J. C. *J. Am. Chem. Soc.* **1978**, *100*, 4520.
(15) (a) Holt, R. B.; McLane, C. K.; Oldenberg, O. *J. Chem. Phys.* **1948**, *16*, 225. (b) Silbert, L. S. In *Organic Peroxides*; Swern, D., Ed.; Wiley-Interscience: New York, 1970; Vol. II, pp 678-683.
(16) (a) Schnepp, O.; Levy, M. *J. Am. Chem. Soc.* **1962**, *84*, 172. (b) Anderson, R. W.; Hochstrasser, R. M.; Lutz, H.; Scott, G. W. *Chem. Phys. Lett.* **1975**, *32*, 204.

The second step in the sequence is cleavage of the O-O bond of the excited perester to form acyloxy radical **3** and the *tert*-butoxy radical. All theoretical[17] and experimental[15,18] analyses of the lowest excited states of peroxides have identified them as dissociative. This appears to be the case for perester **1** from consideration of the distinctive shape of its absorption spectrum. Thus it seem likely that cleavage of this bond is instantaneous and thus cannot be the slow step in the sequence that gives radical **2**.

These considerations identify decarboxylation of radical **3** as the rate-determining step in the reaction sequence shown in eq 3. Molecular symmetry analyses for simpler examples of this decarboxylation reveal a barrier caused by an intended state crossing.[19] The height of this barrier is predicted to decrease as the stability of the radical formed increases. Our results reveal that the rate constant for this reaction is about 20 times greater for the formation of the methylfluorenyl radical (1.8×10^{10} s^{-1}) than that estimated for methyl radical formation but still far from instantaneous.[20] It is difficult to imagine a carbon-centered radical that is more highly stabilized than the methylfluorenyl radical. Thus it appears that all such acyloxy radicals will have a definable, if brief, lifetime.

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(17) (a) Evleth, E. M. *J. Am. Chem. Soc.* **1976**, *98*, 1637. (b) Rauk, A.; Barriel, J. M. *Chem. Phys.* **1977**, *25*, 409. (c) Chevaldonnet, C.; Cardy, H.; Dargelos, A. *Chem. Phys.* **1976**, *102*, 55.
(18) (a) Encinas, M. V.; Lissi, E. A. *J. Photochem.* **1982**, *20*, 153. (b) Scaiano, J. C.; Wubbels, G. G. *J. Am. Chem. Soc.* **1981**, *103*, 640.
(19) Pacansky, J.; Brown, D. W. *J. Phys. Chem.* **1983**, *87*, 1553.
(20) The lifetime of the acyloxy radical could conceivably be longer if 266-nm photolysis generates a vibrationally excited species.

Organocopper-Lewis Acid Mediated 1,3-Chirality Transfer of Acyclic γ,δ-Dioxygenated (*E*)-α,β-Enoates. Regio-, (*E*)-Stereo-, and Diastereoselective α-Alkylation Approaching 100% Selectivity

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The enantio- or diastereoselective α-alkylation of esters and lactones is a crucial problem in the synthesis of biologically active natural products. During the last few years, stereoselective alkylations of chiral metal enolates,[1] intra- and extraannular chirality transfer reactions,[2] asymmetric syntheses via chiral oxazolines,[3] asymmetric hydrogenations,[4] and sigmatropic rearrangements such as Claisen-[5] and Ireland-Claisen[6] rearrangements have been shown

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(1) (a) For an excellent review, see: Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed; Academic Press: New York, 1984; Vol. 3, p 1. (b) Fleming, I.; Hill, J. H. M.; Parker, D.; Waterson, D. *J. Chem. Soc., Chem. Commun.* **1985**, 318.
(2) (a) For a report on the 1,3-chirality transfer of 5-alkenyl-γ-lactones and their congeners with alkyl cyanocuprates, see: Trost, B. M.; Klun, T. P. *J. Org. Chem.* **1980**, *45*, 4256. (b) Narasaka, K.; Ukaji, Y. *Chem. Lett.* **1986**, 81 and references cited.
(3) (a) Evans, D. A.; Dow, R. L. *Tetrahedron Lett.* **1986**, *27*, 1007. (b) Evans, D. A.; Dimare, M. *J. Am. Chem. Soc.* **1986**, *108*, 2476 and references cited.
(4) (a) For a review, see: Koenig, K. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed; Academic Press: New York, 1985; Vol. 5, p 71. (b) Evans, D. A.; Morrissey, M. M.; Dow, R. L. *Tetrahedron Lett.* **1985**, *26*, 6005.

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Table I. Reaction of γ,δ-Dioxygenated (*E*)-α,β-Enoates with Organocopper Reagents[a]

entry	substrate[b]	reagent	product (isolated yield, %) reduction	γ-alkylated	α-alkylated	diastereoselection of α-alkyl product[c]
1	**3c**	$Me_2CuLi{\cdot}BF_3$	**6** (26)		**7** (66)	>99:1
2	**4b**	$Me_2CuLi{\cdot}BF_3$	9 (34)		**10** (40)	>99:1
3	**4c**	$Me_2CuLi{\cdot}BF_3$	**9** (25)		**10** (61)	>99:1
4	**4c**	$Me_2Cu(CN)Li_2$	**9** (11)		**10** (78)	>99:1
5	**5b**	*n*-Bu_2CuLi		**13** (23)	**14b** (70)	98:2
6	**5b**	*n*-$Bu_2CuLi{\cdot}2BF_3$		**13** (19)	**14b** (71)	98:2
7	**5b**	$Me_2CuLi{\cdot}2BF_3$			**14a** (93)	95:5
8	**5b**	$Me_2CuLi{\cdot}2AlCl_3$			**14a** (89)	95:5
9	**3b**	$Me_2Cu(CN)Li_2{\cdot}BF_3$			**7** (98)	97:3
10	**3c**	$Me_2Cu(CN)Li_2{\cdot}BF_3$			**7** (97)	>99:1
11	**4b**	$Me_2Cu(CN)Li_2{\cdot}BF_3$			**10** (96)	>99:1
12	**4c**	$Me_2Cu(CN)Li_2{\cdot}BF_3$			**10** (96)	>99:1
13	**5b**	$Me_2Cu(CN)Li_2{\cdot}BF_3$			**14a** (98)	96:4
14	**5b**	*n*-$Bu_2Cu(CN)Li_2{\cdot}BF_3$			**14b** (94)	>99:1

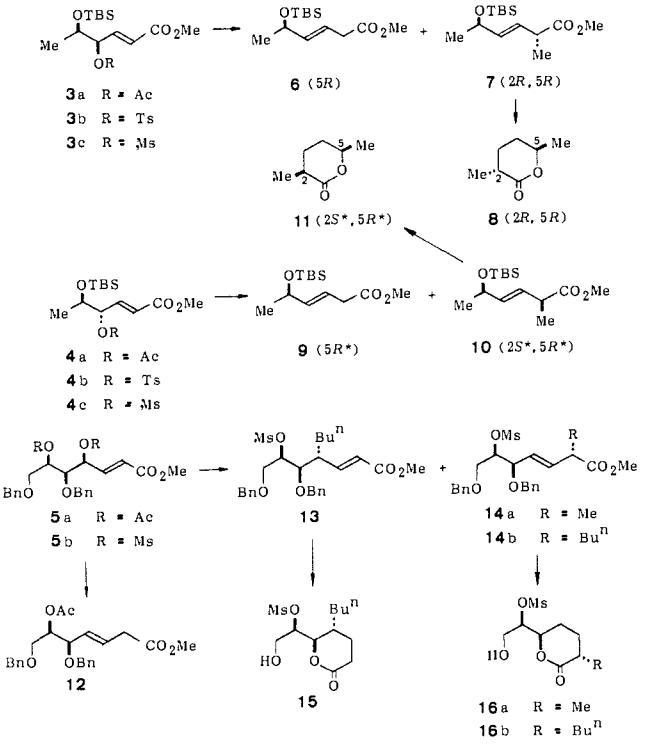
[a] All reactions were carried out at least in duplicate at −78 °C for 30 min in a mixture of THF–Et_2O (ca. 10:2) except entries 5, 6, and 14 [THF–hexane (ca. 10:2)] using 3 mol equiv of reagents. [b] Substrates **4a–c** were racemates. [c] Diastereoselections were determined by ^1H NMR (200 and/or 400 MHz).

to be useful methods for enantio- and diastereoselective α-alkylations. Unfortunately, however, some of the previous methods[7,8] for the syntheses of natural products gave unsatisfactory results. In connection with our work on a biologically active natural product synthesis, we required an efficient diastereoselective chirality transfer method typified by the conversion of **1** into **2**.

Scanning the literature revealed that no general method for the efficient regio-, (*E*)-stereo-, and diastereoselective α-alkylation procedure by the chirality transfer reactions to such acyclic γ,δ-dioxygenated (*E*)-α,β-enoates was available.[9] We report for the first time the 1,3-chirality transfer approaching 100% diastereomer excess (de) via organocopper–Lewis acid reagents.[10]

Reaction of the γ-acetoxy (*E*)-α,β-enoates (**3a**,[11] **4a**,[12] and **5a**[13])

Scheme I[a]



[a] Abbreviations: TBS = *tert*-butyldimethylsilyl; Ac = acetyl; Ms = methylsulfonyl; Ts = 4-methylbenzenesulfonyl.

with Me_2CuLi or $Me_2CuLi{\cdot}BF_3$ yielded the corresponding reduction products (**6**, **9**, and **12**)[14] in ca. 75% yields.[15] In these

(5) (a) For a review, see: Hill, R. K. In *Asymmetric Synthesis*; Morrison, J. D., Ed; Academic Press: New York, 1984; Vol. 3, p 503. (b) Ziegler, F. E.; Kneisley, A.; Wester, R. T. *Tetrahedron Lett.* **1986**, *27*, 1221. (c) Bartlett, P. A.; Holm, K. H.; Morimoto, A. *J. Org. Chem.* **1985**, *50*, 5179.

(6) (a) Ireland, R. E.; Wutz, P. G. M.; Ernst, B. *J. Am. Chem. Soc.* **1981**, *103*, 3205. (b) Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1981**, *46*, 479.

(7) (a) Zibuk, R.; Liverton, N. J.; Smith, A. B., III. *J. Am. Chem. Soc.* **1986**, *108*, 2451. (b) Rocca, J. R.; Tumlinson, J. H.; Glancey, B. M.; Lofgren, C. S. *Tetrahedron Lett.* **1983**, *24*, 1893. (c) Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1979**, *44*, 2169.

(8) Fujimoto, Y.; Iwadate, H.; Ikekawa, N. *J. Chem. Soc., Perkin Trans 1* **1985**, 2701.

(9) For regioselective alkylations of simple allylic derivatives, see: (a) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 2318. (b) Kallmerten, J. *Tetrahedron Lett.* **1984**, *24*, 2843. (c) Kang, J.; Cho, W.; Lee, W. K. *J. Org. Chem.* **1984**, *49*, 1838. (d) Rickards, R. W.; Rönneberg, H. *J. Org. Chem.* **1984**, *49*, 572. (e) Hayashi, T.; Yamamoto, A.; Hagihara, T. *J. Org. Chem.* **1986**, *51*, 723. (f) Gallina, C. *Tetrahedron Lett.* **1985**, *26*, 519.

(10) (a) For a review on organocopper–Lewis acid reagents, see: Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.*, in press. (b) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishihara, Y.; Maruyama, K. *J. Org. Chem.* **1982**, *47*, 119. (c) Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Org. Chem.* **1979**, *44*, 1744. (d) Ibuka, T.; Aoyagi, T.; Kitada, K.; Yoneda, F.; Yamamoto, Y. *J. Organomet. Chem.* **1985**, *287*, C 18. (e) Ibuka, T.; Tabushi, E. *J. Chem. Soc., Chem. Commun.* **1982**, 703. (f) Oppolzer, W.; Dudfield, P.; Stevenson, T.; Godel, T. *Helv. Chim. Acta* **1985**, *68*, 212. (g) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015, 6019. (h) Eis, M. J.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 1153. (i) Still, W. C.; Galynker, I. *J. Am. Chem. Soc.* **1982**, *104*, 1174. (j) Smith, A. B., III; Jerris, P. J. *J. Am. Chem. Soc.* **1981**, *103*, 194. (k) Schostarez, H.; Paquette, L. A. *J. Am. Chem. Soc.* **1981**, *103*, 722.

(11) The substrates **3a–c** were prepared from (4*R*,5*R*)-methyl-4,5-dihydroxy-2-hexenoate, which was obtained from L-threonine according to the literature (Fronza, G.; Fuganti, C.; Grasseli, P.; Marinoni, G. *Tetrahedron Lett.* **1979**, 3883). Thus, selective *tert*-butyldimethylsilylation (*t*-Bu(Me)$_2$SiCl, imidazole, CH_2Cl_2; 49%) followed by acetylation (Ac_2O/pyridine), tosylation (TsCl/pyridine), and mesylation (MsCl/pyridine) gave **3a** (99%), **3b** (97%), and **3c** (99%), respectively.

(12) The substrates **4a–c** were prepared from (4*S**,5*R**)-methyl-4,5-dihydroxy-2-hexenoate, which was obtained from (*E*,*E*)-sorbic acid according to the literature (Dyong, I.; Knollmann, R.; Hohenbrink, W.; Bendlin, H. *Chem. Ber.* **1977**, *110*, 1175). Selective silylation of (4*S**,5*R**)-methyl-4,5-dihydroxy-2-hexenoate followed by acetylation, tosylation, and mesylation in similar ways to the **3** series yielded the substrates **4a**, **4b**, and **4c**, respectively, in high yields.

(13) The substrates **5a–b** were prepared in similar ways to the **3** series from (4*S*,5*R*,6*R*)-methyl-5,7-bis(benzyloxy)-4,6-dihydroxy-2-heptenoate, which was obtained from D-(+)-xylose according to the literature (Matsuda, F.; Kawanishi, M.; Terashima, S. *Tetrahedron Lett.* **1985**, *26*, 4639).

(14) Organocopper–Lewis acid reagent undergoes conjugate addition to γ-acetoxy α,β-enones (Ibuka, T.; Minakata, H.; Mitsui, Y.; Kinoshita, K.; Kawami, Y. *J. Chem. Soc., Chem. Commun.* **1980**, 1193). In contrast, reaction of γ-acetoxy α,β-enoates with organocopper reagents results in reductive deoxygenation (Ibuka, T.; Minakata, H. *Synth. Commun.* **1980**, *10*, 119). For zinc-mediated reductive deoxygenations of γ-oxygenated α,β-enoates, see: (a) Overman, L. E.; Fukaya, C. *J. Am. Chem. Soc.* **1980**, *102*, 1454. (b) Corey, E. J.; Clark, D. A.; Goto, G.; Marfat, A. Mioskowski, C.; Samuelsson, B.; Hammarström, S. *J. Am. Chem. Soc.* **1980**, *102*, 1436.

reactions, we did not detect any α- or γ-methylated product by TLC, GLC, and ^{1}H NMR analyses. In contrast, as shown in Table I, the mesylate **3c** and the tosylate **4b** gave the regio-, (*E*)-stereo-, and diastereoselective α-alkylation products **7** and **10**, respectively, as the major products by treatment with $Me_2CuLi{\cdot}BF_3$ (entries 1 and 2). Comparable results were obtained by reaction of the mesylate **4c** with $Me_2CuLi{\cdot}BF_3$ or the higher order heterocuprate $Me_2Cu(CN)Li_2$ (entries 3 and 4). In these reactions, the diastereoselection of the α-alkylation products **7** and **10** is over 99% judging from GLC and ^{1}H and ^{13}C NMR analyses. Thus it is shown that the stereochemistry of the α-position of the chirality transfer products **7** and **10** was governed by the stereochemistry at the γ-position of the substrates (anti SN_2' reaction).[16] The stereochemistries of **7** and **10** were determined by converting them into known (2*R*,5*R*)-*trans*-2-methyl-5-hexanolide **8**[17] and its (2*S**,5*R**)-cis isomer **11**,[2b,18] a sex pheromone of the carpenter bee *Xylocopa hirufissima*,[19] respectively, by a sequence of reactions [(i) H_2/10% Pd-C in MeOH; (ii) MeCN-$BF_3{\cdot}Et_2O$-HF (98:1:1), 20 °C, 2.5 h].

Treatment of the mesylate **5b** with *n*-Bu_2CuLi or *n*-$Bu_2CuLi{\cdot}2BF_3$ yielded the α-butylated product **14b** along with the γ-isomer **13** as a minor product. Here also, the α-alkylation proceeded with very high diastereoselectivity (98%). The stereochemistries of **13** and **14b** were determined as depicted in Scheme I by ^{1}H NMR spectral analyses of the lactones **15** and **16b** derived from **13** and **14b**, respectively, by the same sequence of reactions described above.

Although very high diastereoselectivity was realized with the cuprate-BF_3 reagent, the reduction or γ-alkylated product was always accompanied as a byproduct. Fortunately, this difficulty was overcome by use of the higher order heterocuprate-BF_3 reagent,[20] and the desired α-alkylated product was obtained with nearly 100% de in an essentially quantitative yield under a very mild reaction condition (-78 °C, 30 min) (entries 9-14).

It should be noted that the chemical yield of the present chirality transfer varies considerably depending on the solvent used. Although the reason for solvent effects is still not clear, THF-Et_2O (10:2) or THF-hexane (10:2) is the solvent of choice for the chirality transfers since reaction in Et_2O alone is too sluggish to be practicable.[21]

It is apparent from these preliminary data that by judicious selection of organocopper-Lewis acid reagents, the present method offers unusually facile entry to synthetically useful and stereochemically pure α-alkyl-δ-oxygenated (*E*)-β,γ-enoates. Application of this method for a synthesis of natural products is under investigation.

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Supplementary Material Available: Experimental details and data (IR, ^{1}H NMR, ^{13}C NMR) for **7**, **8**, **10**, **11**, **13**, **14**, **15**, and **16** (3 pages). Ordering information is given on any current masthead page.

(15) All new compounds have been fully characterized spectrally and have elemental compositions determined by high-resolution mass spectroscopy and/or combustion analysis. We thank Professor T. Shingu, Kobe Gakuin University, for help with 400-MHz NMR measurements.

(16) Extensive stereochemical and mechanistic studies reported by Goering and his co-workers on the alkylation of allylic compounds with ordinary organocopper reagents have demonstrated that anti stereochemistry is favored for alkylation in both cyclic and acyclic systems. Goering, H. L.; Tseng, C. C. *J. Org. Chem.* **1985**, *50*, 1597. Goering, H. L.; Kantner, S. S.; Seitz, E. P., Jr. *J. Org. Chem.* **1985**, *50*, 5495 and references cited.

(17) For syntheses of racemate, see: (a) Bäckvall, J. E.; Byström, S. E.; Nyström, J. E. *Tetrahedron* **1985**, *41*, 5761. (b) Reference 2b. For synthesis of 2*R*,5*R* and 2*S*,5*S* forms, see ref 7c.

(18) Mori, K.; Senda, S. *Tetrahedron* **1985**, *41*, 541. (b) Hanessian, S.; Damailly, G.; Chapleur, Y.; Leger, S. *J. Chem. Soc., Chem. Commun.* **1981**, 1125. (c) Bacardit, R.; Manas, M. M. *J. Chem. Ecol.* **1983**, *9*, 703. (d) Reference 2b. (e) Reference 7c.

(19) Wheeler, J. W.; Evans, S. E.; Blum, M. S.; Velthius, H. H. V.; de Camargo, J. M. F. *Tetrahedron Lett.* **1976**, 4029.

(20) Lipshutz, B. H.; Parker, D. A.; Kozlowski, J. A.; Nguyen, S. L. *Tetrahedron Lett.* **1984**, *25*, 5959. (b) Mioskowski, C.; Manna, S.; Falck, J. R. *Tetrahedron Lett.* **1983**, *24*, 5521.

(21) For solvent effects on substitution reactions with ordinary organocopper reagents, see: (a) House, H. O.; Wilkins, J. M. *J. Org. Chem.* **1978** *43*, 2443 and references cited. (b) Lipschutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *J. Org. Chem.* **1984**, *49*, 3938. (c) Johnson, C. R.; Herr, R. W.; Wieland, D. M. *J. Org. Chem.* **1973**, *38*, 4263.

Resonance Raman Spectroscopic Evidence for Alternative Structures in the *Native* Ternary Complex Formed with Thymidylate Synthase

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We present evidence from resonance Raman (RR) spectroscopy for coexisting alternative structures in the native ternary inhibitor complex formed with thymidylate synthase (EC 2.1.1.45, TSase) isolated from the bacterium *Lactobacillus casei*. Inhibition of TSase is well established to be an important aspect of the mechanism of action of the widely used cancer chemotherapeutic agent, 5-fluorouracil (5-FU). A metabolite of 5-FU, 5-fluoro-2′-deoxyuridylate (FdUMP), together with the cofactor (+)-5,10-methylenetetrahydrofolate (5,10-CH_2FH_4), forms a potent (K_i = 10^{-11} M^{-1}) ternary inhibitor complex,[1] with distinctive near-UV absorption bands at 322 and 375 nm (with ϵ 59 800, and 7000 M^{-1} cm^{-1}),[2,3] which undergoes slow ($t_{1/2}$ = 10 h) dissociation.[4] The current structural model for this complex,[5] shown as II in Figure 1, is based on extensive characterization[6-9] of a proteolyzed fragment to which FdUMP and CH_2FH_4 are covalently attached.[3]

Figure 2 shows RR spectra of the native ternary complex, obtained with 337- and 356-nm Kr^+ laser excitation near resonance with the two near-UV absorption bands. Also shown at the top is the spectrum of (*p*-aminobenzoyl)glutamate (PABA-Glu) obtained with 266-nm excitation, in resonance with its strong absorption band (λ_{max} = 272 nm). Suggested assignments to the benzenoid ring modes[10] are indicated. Similar spectra are seen

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(1) Danenberg, P. V. *Biochim. Biophys. Acta* **1977**, *473*, 73.
(2) Aull, J. L.; Lyon, J. A.; Dunlap, R. B. *Arch. Biochem. Biophys.* **1974**, *165*, 805.
(3) Donato, A., Jr.; Aull, J. L.; Lyon, J. A.; Reinsch, J. W.; Dunlap, R. B. *J. Biol. Chem.* **1976**, *251*, 1303.
(4) Santi, D. V.; Pogolotti, A. L., Jr.; Newman, E. M.; Watay, Y. In *Biomedicinal Aspects of Fluorine Chemistry*; Elsevier Biomedical: New York, 1982.
(5) *Biochemistry*, Stryer, L., ed.; W. H. Freeman and Co.: San Francisco, 1981.
(6) James T. L.; Pogolotti, A. L., Jr.; Ivanetich, K. M.; Wataya, Y.; Lam, S. S. M.; Santi, D. V. *Biochem. Biophys. Res. Commun.* **1976**, *72*, 404.
(7) Byrd, R. A.; Dawson, W. H.; Ellis, P. D.; Dunlap, R. B. *J. Am. Chem. Soc.* **1977**, *99*, 6136; **1978**, *100*, 7478.
(8) Sommer, H.; Santi, D. V. *Biochem. Biophys. Res. Commun.* **1974**, *57*, 689.
(9) Danenberg, P. V.; Heidelberger, C. *Biochemistry* **1976**, *15*, 1331.
(10) Dollish, F. R.; Fatdy, W. G.; Bentley, In *Characteristic Raman Frequencies of Organic Compounds*; Wiley: New York, 1974.

0002-7863/86/1508-7422$01.50/0