implicated by the formation of the aforementioned ether, 9,9dimethylfluorene (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.



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 peroxides¹⁵ 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 9methylfluorene 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.

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 theoretical¹⁷ 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 $(1.8 \times 10^{10} \text{ s}^{-1})$ 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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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–Claisen⁶ rearrangements have been shown

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Table I.	Reaction of a	δ -Dioxygenated	(E) - α,β -Enoates	with	Organocopper	Reagents ^a
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	substrate ^b	reagent	pro	diastereoselection		
entry			reduction	γ -alkylated	α -alkylated	of α -alkyl product ^c
1	3c	Me ₂ CuLi·BF ₃	6 (26)		7 (66)	>99:1
2	4b	Me ₂ CuLi•BF ₃	9 (34)		10 (40)	>99:1
3	4c	Me ₂ CuLi·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 ₂ CuLi		13 (23)	14b (70)	98:2
6	5b	n-Bu ₂ CuLi·2BF ₃		13 (19)	14b (71)	98:2
7	5b	Me ₂ CuLi·2BF ₃			14a (93)	95:5
8	5b	Me ₂ CuLi·2AlCl ₃			14a (89)	95:5
9	3b	Me ₂ Cu(CN)Li ₂ ·BF ₃			7 (98)	97:3
10	3c	Me ₂ Cu(CN)Li ₂ ·BF ₃			7 (97)	>99:1
11	4b	Me ₂ Cu(CN)Li ₂ ·BF ₃			10 (96)	>99:1
12	4c	Me ₂ Cu(CN)Li ₂ ·BF ₃			10 (96)	>99:1
13	5b	Me ₂ Cu(CN)Li ₂ ·BF ₃			14a (98)	96:4
14	5b	n-Bu ₂ Cu(CN)Li ₂ ·BF ₃			14b (94)	>99:1

^aAll reactions were carried out at least in duplicate at -78 °C for 30 min in a mixture of THF-Et₂O (ca. 10:2) except entries 5, 6, and 14 [THF-hexane (ca. 10:2)] using 3 mol equiv of reagents. ^bSubstrates **4a**-c were racemates. ^cDiastereoselections 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 5a¹³)

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

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

(4S,5R,6R)-methyl-5,7-bis(benzyloxy)-4,6-dihydroxy-2-heptenoate, which was (a), β_{1} (b), β_{2} (b), β_{2} (b), β_{2} (b), β_{2} (b), β_{2} (c), β_{2} (c),

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 (13) The substrates 5a-b were prepared in similar ways to the 3 series from

reactions, we did not detect any α - or γ -methylated product by TLC, GLC, and ¹H 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 ·BF₃ (entries 1 and 2). Comparable results were obtained by reaction of the mesylate 4c with Me₂CuLi·BF₃ or the higher order heterocuprate Me₂Cu(CN)Li₂ (entries 3 and 4). In these reactions, the diastereoselection of the α -alkylation products 7 and 10 is over 99% judging from GLC and ¹H and ¹³C 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 (2R,5R)-trans-2-methyl-5-hexanolide 8^{17} and its $(2S^*,5R^*)$ -cis isomer 11, 2b,18 a sex pheromone of the carpenter bee Xylocopa hirufissima,19 respectively, by a sequence of reactions [(i) $H_2/10\%\ \mbox{Pd-C}$ in MeOH; (ii) MeCN-BF₃·Et₂O-HF (98:1:1), 20 °C, 2.5 h].

Treatment of the mesylate 5b with n-Bu₂CuLi or n-Bu₂CuLi-2BF₃ 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 ¹H 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-BF₃ 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-BF3 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-Et₂O (10:2) or THF-hexane (10:2) is the solvent of choice for the chirality transfers since reaction in Et₂O 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, ¹H NMR, ¹³C NMR) for 7, 8, 10, 11, 13, 14, 15, and 16 (3 pages). Ordering information is given on any current masthead page.

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-CH₂FH₄), forms a potent $(K_i = 10^{-11} \text{ M}^{-1})$ ternary inhibitor complex,¹ with distinctive near-UV absorption bands at 322 and 375 nm (with ϵ 59800, 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 characterization⁶⁻⁹ of a proteolyzed fragment to which FdUMP and CH₂FH₄ 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 ($\lambda_{max} = 272$ nm). Suggested assignments to the benzenoid ring modes¹⁰ are indicated. Similar spectra are seen

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