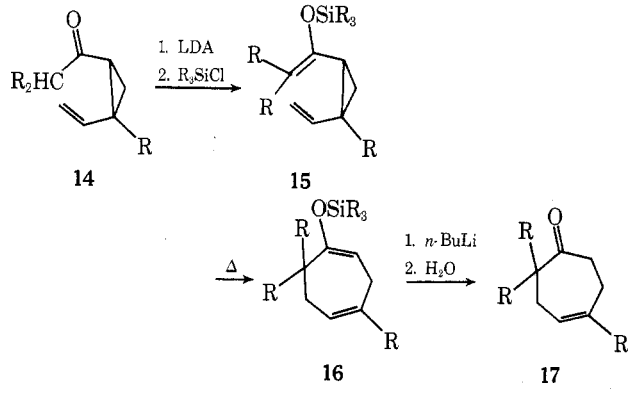
A typical procedure for the above sequence is described below for the conversion of alkoxyenone **1** to ketone **4**. To a −78 °C ether (80 ml) solution of 1-bromo-2-vinylcyclopropane (40 mmol, 7:3 mixture of cis and trans) was added *t*-BuLi (48 mmol, 1.5 M in pentane) over 5 min. The resulting solution was stirred for 1.5 h at −78 °C and subsequently warmed to 0 °C. An ether (10 ml) solution of alkoxyenone **1** (20 mmol) was then added over a period of 2 min. The reaction mixture was stirred for 15 min at 0 °C and 15 min at ambient temperature and then carefully poured into a separatory funnel containing 2 N HCl (100 ml). Intermittent agitation of the above mixture (15 min) followed by standard workup provided in 91% yield (90% purity) the divinylcyclopropanes **3a** and **3b** (7:3 mixture of cis and trans), which were purified by silica gel chromatography (ether–hexane, 3:7).[7] Compounds **3a** and **3b** (2 M benzene solution) upon thermolysis (170–180 °C, 2 h) in a sealed Pyrex tube provided after purification ketone **4** (bp 54–59 °C, 0.15 mm) in 87% yield. Alternatively ketone **4** can be prepared by heating (250 °C, 5 min) the crude mixture of compounds **3a** and **3b** in a distillation apparatus followed directly by distillation of ketone **4**. In either case the method offers an exceptionally straightforward route to the annelated product with an overall yield of 72%.

The above strategy could be readily extended to other cycloheptane systems by varying the starting substrate (latent double bond equivalent). For example, aldehydes could be readily converted to acylvinylcyclopropanes **14** which could be used in the preparation of cyclohept-4-enones as outlined in Scheme II.

Scheme II



In order to test the efficacy of this route to cycloheptenones and examine variations in the lithio reagents, we have investigated this strategy in an approach to karahanaenone (**17**, R = Me).[10] Thus, a mixture of *cis*- and *trans*-1-lithio-2-methyl-2-vinylcyclopropane,[11] obtained from the metallation of the corresponding bromides, upon reaction with isobutyraldehyde and oxidation (pyridinium chlorochromate)[12] of the resulting alcohols provided a mixture of ketones **14** (R = Me, cis and trans). Treatment of this mixture with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) followed by quenching with trimethylsilyl chloride afforded the siloxydivinylcyclopropanes **15** (R = Me, cis and trans). Thermolysis (165–175 °C, 1.5 M benzene solution) of this mixture followed by desilylation (*n*-BuLi, THF, 25 °C, 5 h) of the resulting diene **16** (R = Me) provided karahanaenone (**17**, R = Me) in an overall yield of 54% based on isobutyraldehyde.

Studies on the preparation of more highly functionalized reagents and the application of these reagents in synthesis are in progress.

Acknowledgments. The authors gratefully acknowledge the Research Corporation for financial support of this work. Exact mass analyses were performed by the NIH sponsored Biotechnology Research Resource for mass spectrometry at Massachusetts Institute of Technology.

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(3) The pure *cis*- and *trans*-1-bromo-2-vinylcyclopropanes were obtained in preparative quantities by spinning-band distillation of the mixture of bromides prepared from butadiene. For the preparation of the bromides, see L. Skattebøl, *J. Org. Chem.*, **29**, 2951 (1964), and D. Seyferth, H. Yamazaki, and D. L. Alleston, *ibid.*, **28**, 703 (1963). For stereochemical assignments, see J. Landgrebe and L. Becker, *ibid.*, **33**, 1173 (1968).
(4) Compound **3a:** ir (neat) 1695 and 1635 cm^{-1}; NMR (CCl_4) δ 0.80–2.4 (complex m with br s at 1.71, 11 H) and 4.80–5.68 (m, 3 H).
(5) All new compounds reported were homogeneous by TLC or VPC and gave satisfactory ir and NMR spectra and exact mass or combustion analyses.
(6) Compound **3b:** ir (neat) 1695 and 1635 cm^{-1}; NMR (CCl_4) δ 0.80–2.60 (complex m with br s at 1.71, 11 H) and 4.80–5.50 (m, 3 H).
(7) Alternatively the divinylcyclopropanes may be isolated by distillation in which case the distillate is contaminated with varying amounts of the annelated product depending on the temperature used for the distillation. Pure samples of **3b** obtained by silica gel chromatography, upon standing at ambient temperature, slowly rearranged into compound **4**. In the other cases reported in Table I isolation of the intermediate *cis*-divinylcyclopropanes can only be accomplished by low temperature chromatography owing to significant rearrangement at room temperature.
(8) D. E. Applequist and A. H. Peterson, *J. Am. Chem. Soc.*, **83**, 862 (1961); H. M. Walborsky, F. J. Impastato, and A. E. Young, *ibid.*, **86**, 328 (1964); and M. J. S. Dewar and J. M. Harris, *ibid.*, **91**, 3652 (1969).
(9) Compound **4:** bp 54–59 °C (0.15 mm); ir (neat) 1740 cm^{-1}; NMR (CCl_4) δ 1.09 (s, 3 H), 2.05–3.10 (complex m, 8 H), and 5.30–5.77 (m, 3 H).
(10) Y. Naya and M. Kotake, *Tetrahedron Lett.*, 1645 (1968); E. Demole and P. Enggist, *Helv. Chim. Acta*, **54**, 456 (1971).
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(12) E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975).
(13) Dreyfus Foundation Fellow, 1975–1976.

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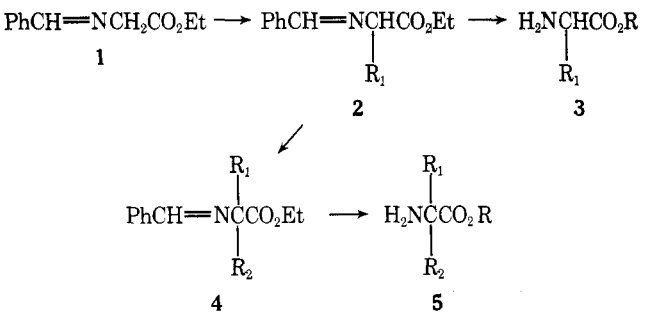
Alkylation and Michael Additions of Glycine Ethyl Ester. Use in α-Amino Acid Synthesis and as Acyl Carbanion Equivalent

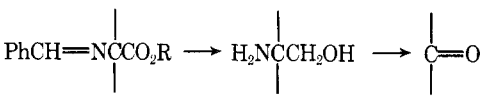
Summary: The benzylidene derivative of glycine ethyl ester can be used in mono- or sequential dialkylations thus leading to very simple syntheses of α-amino esters and acids; michael addition can also be effected readily, especially in protic solvents; the α-amino ester functionality can be transformed into a carbonyl (lithium aluminum hydride; periodate) and glycine ethyl ester is thus an acyl carbanion equivalent.

Sir: We would like to report that the readily available benzylidene derivatives of glycine esters can be alkylated in high yield under a variety of conditions. This obviously provides a particularly simple route to α-amino acids.[1]

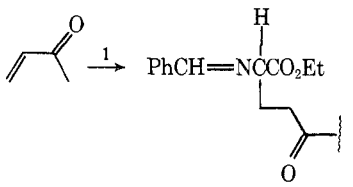
It is especially noteworthy that the relatively high acidity of **1** permits formation of the anion and its alkylation not only with strong bases like lithium diisopropylamide, but with weaker bases such as potassium *tert*-butoxide. Also noteworthy is the fact that these alkylations can be performed not only with the *tert*-butyl ester, but are very satisfactory with the simple ethyl ester, in spite of the "extreme instability" claimed for this substance.[2] Because an α-amino ester is a masked carbonyl group, the anion of a benzylidene glycine ester is also an acyl carbanion equivalent.[3] The latent carbonyl function may be unmasked, inter alia, via the sequence lithium



aluminum hydride reduction–periodate cleavage. Since either monoalkylation or sequential dialkylation of benzylidene glycine esters can be performed, either aldehydes or ketones can be synthesized by this method which is compatible with the presence of acid-sensitive functionality in the molecule.



An especially interesting feature of the anions derived from 1 and related esters, is the ease with which they undergo conjugate addition, e.g., with α,β-unsaturated ketones or esters. This is in contrast to the exclusive 1,2 addition found with the anion from the dialkyl derivatives of glycine esters[4] and is presumably a reflection of the more delocalized (softer)[5] character of the anion of the benzylidene derivative.



Alkylation. A. With Lithium Diisopropylamide (LDA). The lithium salt prepared by dropwise addition of 1.5 mmol of 1 to 1 equiv of LDA in 40 ml of dry tetrahydrofuran (THF) and 2.8 ml of hexamethyl phosphoramide at −78 °C was followed by 1 equiv of 1-iodooctane in THF. Warming to room temperature and stirring for another 4 h gave (workup with ice-cold aqueous ammonium chloride–ether) **2** (R = octyl), bp (k) 155 °C (0.07 mm),[6] in 90% yield. Alkylation with the secondary halide, isopropyl iodide, was effected in the same manner to give a 75% yield of **2** (R = isopropyl), bp (k) 126 °C (0.02 mm).

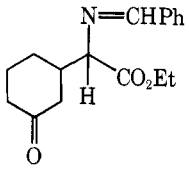
Functionality may also be present in the alkylating agent: ethyl bromoacetate and ethyl 6-bromohexanoate gave the corresponding monoalkylated products **2** (R_1 = $-CH_2CO_2Et$ and R_1 = $-(CH_2)_5CO_2Et$) in 82 and 62% yields, respectively.

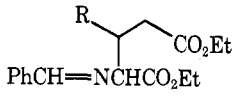
B. With Potassium *tert*-Butoxide. Addition of 4 mmol of 1 in THF to a solution of 1 equiv of sublimed potassium *tert*-butoxide in 12 ml of THF, cooled to −78 °C, was followed by 1-iodooctane in THF. Stirring for 4 h after reaching room temperature and workup gave **2** (R_1 = octyl) in 78% yield.

Alkylation with 2 different alkyl groups could be performed without isolation of the monoalkyl product, e.g., by adding the solution from the first alkylation to another equivalent of LDA, followed by 1 equiv of the second halide. Sequential use of 1-iodobutane and 1-iodooctane thus gave an 81% yield of **4** (R_1 = butyl, R_2 = octyl), bp (k) 155 °C (0.05 mm).

The benzylidene derivatives of readily available α-amino acids can also be used in alkylation reactions. For instance, ethyl α-amino propionate (α-alanine ethyl ester) was alkylated as its benzylidene derivative **2** (R_1 = CH_3) with butyl bromide, by the general procedure A, to give **4** (R_1 = methyl, R_2 = butyl) in 77% yield.

Michael Additions of Benzylidene Glycine Esters. The benzylidene derivative of glycine ethyl ester underwent addition to 2-cyclohexenone in aprotic media, under the conditions described under Alkylation, but without hexamethylphosphoramide, to give the 1,4 adduct **6**, in ~90% yield. It is especially noteworthy that the reaction can also be done easily in protic media, e.g., with 0.1 equiv of sodium ethoxide in dry ethanol at ~0 °C for 2 h to give **6**, also in very high yield. The





corresponding crystalline *tert*-butyl ester, mp 100–101 °C, was similarly obtained. Alkoxide-catalyzed addition was also effected readily with ethyl acrylate, ethyl crotonate, and diethyl fumarate to give **7** (R = H), bp ~143 °C (0.04 mm), **7** (R = CH_3), bp 220 °C (0.2 mm), and **7** (R = CO_2Et), bp (k) 170 °C (0.04 mm), respectively, in 80–90% yields.

Hydrolysis to Amino Acids and Esters. Complete hydrolysis was effected by refluxing for 6 h with concentrated hydrochloric acid, followed by evaporation and addition of ethanol to the aqueous solution adjusted to pH 6. In this way, the (±) α-amino acids **3** (R = H, R_1 = octyl), mp 264–265 °C (reported[7] mp 264 °C), and **3** (R = H, R_1 = isopropyl) (valine), *N*-benzoyl derivative mp 129.5–130.5 °C (reported[8] mp 132.5 °C), were obtained in 90–100% yields. Partial hydrolysis to the α-amino esters could be effected with 5% hydrochloric acid for 2 h at room temperature. In this way, **3** (R = Et, R_1 = octyl), mp 69–71 °C from hexane (77% yield), **3** (R = Et; R_1 = $(CH_2)_2CO_2Et$), and **3** (R = Et; R_1 = $EtO_2CCHCH_2CO_2Et$) were similarly obtained in 70–90% yields and characterized by conversion to the known cyclic lactams.[9,10] In some cases, better results were obtained by passing the benzylidene ester through ~10 times its weight of acid-washed silica gel, followed by elution with ether after removal of benzaldehyde with pentane. The α-amino ester **5** (R = Et, R_1 = butyl, R_2 = octyl) was thus obtained in 82% yield.

Benzylidene Glycine Esters as Acyl Carbanion Equivalents. The aldehyde synthesis is illustrated by the synthesis of nonanal from octyl iodide. Reduction of **3** (R = ethyl, R_1 = octyl) with lithium aluminum hydride gave the related amino alcohol, 2-amino-1-decanol, mp 47.5–48 °C.[11] This was cleaved with a slight excess of periodic acid (room temperature overnight) to give, in essentially quantitative yield for the two steps, nonanal identical with an authentic sample.

The synthesis of ketones is shown by the conversion of **5** (R = ethyl, R_1 = butyl, R_2 = octyl) by the same procedure, in ~82% overall yield, into 5-tridecanone identical with an unambiguously synthesized sample.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health for their support of this work.

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(2) Prepared by treating 10.1 g of glycine ethyl ester hydrochloride in 150 ml of methylene chloride with 1 equiv of benzaldehyde in the presence of 20 ml of triethylamine and 6 g of anhydrous magnesium sulfate at room temperature, filtration, solvent removal (room temperature), water–ether partition washing (brine), drying, and removal of solvent. The substance thus obtained in 95% yield could be kept in the freezer for several months. See also O. Gerngross and A. Olcay, *Ber.*, **96**, 2550 (1963).
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(6) All new compounds gave integrated NMR spectra in complete agreement with their structures which were also confirmed by their further transformations. Kugelrohr distillations are indicated as bp (k).
(7) N. F. Albertson, *J. Am. Chem. Soc.*, **68**, 450 (1946).
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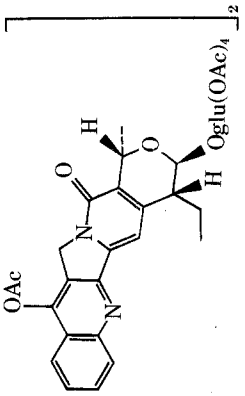
A Biomimetic Synthesis of the Camptothecin Chromophore

Summary: Novel heterocyclic alkaloids (4 and 6), potential synthetic precursors of 20(*S*)-camptothecin (2), are synthesized by 2,3-dichloro-5,6-dicyanobenzoquinone oxidation of tetraacetyl-18,19-dihydrovincoside (18,19-H_2-**1a**) and -isovincoside (18,19-H_2-**1c**) lactams and their corresponding pentaacetyl-18,19-dihydroquinolols (18,19-H_2-**3**).

Sir: We have been studying the chemistry[1] of the penultimate biosynthetic precursor of camptothecin (**2**), isovincoside lactam (**1c**), as a model system for the putative biochemical transformations that occur between **1c** and **2** in vivo.[2] Since D ring oxidation of **1c** to a pyridone may be one requisite of the biosynthetic pathway to **2**, we have examined the oxidation of 18,19-H_2-**1a** and -**1c** using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). Alternatively, D ring oxidation of isovincoside quinolol (**3c**) may be a key oxidative step preceding **2** in vivo, since presently we do not know the exact biochemical sequence of events between **1c** and **2**.[3] With both **1** and **3** oxidation with DDQ has been accomplished efficiently, which should enable a convenient synthesis of **2** and novel indole analogues of it, and which may be relevant to in vivo biosynthetic events.[4]

Oxidation of either 18,19-H_2-**1b** or -**1d** $(OAc)_4$ with DDQ (1 equiv or excess) in methanol (reflux, 5 min, N_2) or in a toluene–methanol mixture (25 °C, 5–10 min, N_2) gave a chromatographically resolvable mixture of **4a** {pale yellow solid: mp 145–150 °C dec; 41%; ir ν_{KBr} 3356 (NH), 1761 (OAc), 1667 (pyridone), and 1230 (C–O) cm^{-1}; uv λ_{max}^{MeOH} 386, 367, 296 (sh), 286 (sh), 273, 260, 252, and 213 nm; MS *m/e* 666.2437 ($M^{\cdot+}$ – CH_2O, calcd for $C_{34}H_{38}N_2O_{12}$ 666.2424), 331.1026 [Glu$(OAc)_4^+$, calcd for $C_{14}H_{19}O_9$ 331.1024]; ^1H NMR (90 MHz) δ^{CDCl_3} 0.93 [t, 3 H, J = 7 Hz, C(18)], 1.89 [m, 2 H, C(19)], 2.00–2.07 (4 s, 12 H, 4 OAc), 2.58 [m, 1 H, C(20)], 2.95 [t, 2 H, J = 7 Hz, C(6)], 3.56 (s, 3 H, OCH_3), 4.35 [t, 2 H, J = 7 Hz, C(5)], 5.41 (d, 1 H, J = 3 Hz, C(21)], 5.70 [s, 1 H, C(17)], 6.32 (s, 1 H, C(14)], 7.08–7.54 (4 aromatic H), and 9.51 (br s, NH), glucosyl protons omitted} and **4b** {yellow needles (MeOH); mp 154–156.5°C; 26.5%; ir ν_{KBr} 3333 (NH), 1754 (OAc), 1658 (pyridone), and 1230 (C–O) cm^{-1}; uv λ_{max}^{EtOH} 418, 395 (sh), 324, 277, 257, 248 (sh), and 218 nm; MS *m/e*, 664.1897 ($M^{\cdot+}$ – CH_2O, calcd for $C_{34}H_{36}N_2O_{12}$ 664.2258), 316.1153 [$M^{\cdot+}$ + 1 – CH_3O – (HO-(Glu$(OAc)_4$, calcd for $C_{20}H_{16}N_2O_2$ 316.1027], and 290.1419 (calcd for $C_{19}H_{18}N_2O$); ^1H NMR (90 MHz) δ^{CDCl_3} 1.02 [t, 3 H, J = 7 Hz, C(18)], 1.90 [m, 2 H, C(19)], 1.96–2.07 (4 s, 12 H, 4 OAc), 2.90 [m, 1 H, C(20)],



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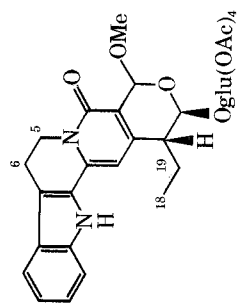
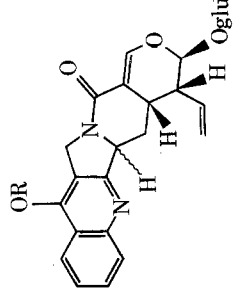


4a

b, $\Delta^{5,6}$



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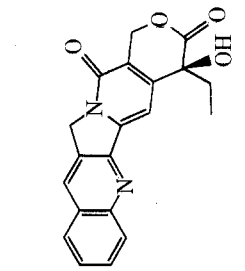
b, C-3 (*R*), R = Ac
c, C-3 (*S*), R = H
d, C-3 (*S*), R = Ac



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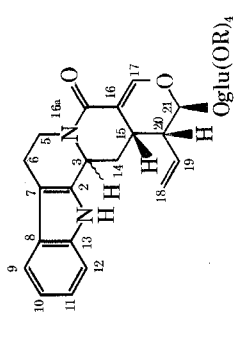

1a, C-3 (*R*), R = H
b, C-3 (*R*), R = Ac
c, C-3 (*S*), R = H
d, C-3 (*S*), R = Ac

Table I. ^{13}C NMR Assignments[a]

	Carbon resonances at 22.6 MHz[b]																	
Compd	18	19	6	5	20	OMe	21	14	17	12	16	10	9	11	8	13	2	3	15	16a
4a	10.4	19.5	22.7	40.6	42.6	56.2	96.0	96.5	100.1	114.6	119.6	120.2	124.6	125.7	127.2	138.7	138.0	146.7	148.3	160.4
4b	11.1	21.1	111.9	108.8	43.8	56.3	96.1	96.1	98.1	110.6	118.6	120.5[c]	126.7	120.7[c]	129.9	132.9	139.8	144.3	146.5	156.6
6	9.4	20.8	123.9	48.8	42.0		98.5	99.4	89.7	130.8	120.1	122.3	127.9[d]	129.6[d]	121.3	150.8	154.0	145.1	149.4	158.5

[a] Determined in $CDCl_3$ relative to TMS as internal standard by consideration of the ^{13}C NMR assignments of 1b and 1d and 2,[7] SFOR proton decoupling, and low power proton decoupling.[8] [b] Glucosyl tetraacetate resonances omitted. [c] These two assignments may be reversed. [d] These two assignments could be interchanged.