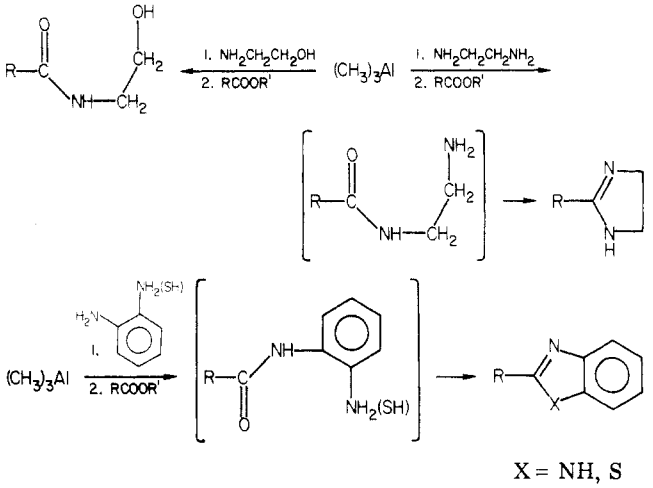
Scheme I



X = NH, S

Table I shows that a wide range of esters is easily transformed according to Scheme I. Some limitations, however, must be mentioned; reaction of dimethylaluminum 2-hydroxyethylamide fails to produce the expected oxazolines, instead quantitative formation of 2-hydroxyethylamides is observed. In the cases of vicinal diamines and amino thiols, ring closure is favored although sometimes prolonged reaction times and excess aluminum organic reagent may be necessary to avoid mixtures of open-chain amides and ring-closed heterocycles. Neighboring group interference is observed in the cases of β-carboline-3-carboxylates and 2-picolinates; their conversion generally stops at the amide stage, so that formation of the corresponding heterocycles requires a separate dehydration step using conventional methodology.[7]

As a control experiment the esters listed in Table I were refluxed in toluene in the presence of 10 mol equiv of ethylenediamine. After 10 h at reflux temperature they were recovered almost unchanged, thin-layer chromatography showing only traces of reaction products.

Experimental Section

Typical Example. Ethylenediamine (3.91 mL, 0.058 mol) is added dropwise to a stirred solution of trimethylaluminum (0.058 mol) in 50 mL of toluene, so that the temperature does not exceed 10 °C. At the end of methane evolution ethyl thiophene-2-carboxylate (5.7 g, 0.036 mol) is gradually added at room temperature. The reaction mixture is refluxed for 3 h (argon atmosphere). After cooling, the solution is treated dropwise with 15 mL of water, diluted with 50 mL of methanol and 50 mL of methylene chloride, and refluxed on a steam bath for 15 min. After filtration over Na_2SO_4 and solvent evaporation the residue is suspended in 200 mL of ethyl acetate and refluxed for another 15 min in order to remove traces of aluminum hydroxides from the crude product. Filtration of the hot solution over Na_2SO_4 and removal of the solvent in vacuo followed by recrystallization of the crude product from ethyl acetate results in pure 2-(2-thienyl)-2-imidazoline: 5.1 g (92% yield); mp 178–180 °C; ^1H NMR (Bruker HX 90, Me_2SO-d_6) δ 3.60 (s, 4 H), 7.12 (dd, J = 5.0, 3.8 Hz, 1 H), 7.52 (dd, J = 3.8, 1.2 Hz, 1 H), 7.64 (dd, J = 5.0, 1.2 Hz, 1 H); IR (KBr) 3140 (NH), 2930 and 2850 (CH), 1600 (C=N) cm^{-1}.

Acknowledgment. We are much indebted to Dr. K. H. Müller of Schering AG Bergkamen for a generous gift of trimethylaluminum.

Registry No. Ethyl thiophene-2-carboxylate, 2810-04-0; ethyl benzoate, 93-89-0; ethyl phenylacetate, 101-97-3; methyl cyclohexanecarboxylate, 4630-82-4; ethyl picolinate, 2524-52-9; ethyl nicotinate, 614-18-6; ethyl isonicotinate, 1570-45-2; ethyl β-carboline-3-carboxylate, 74214-62-3; methyl 6-methyl-8β-ergolinecarboxylate, 35470-53-2; 2-(2-thienyl)-2-imidazoline, 45753-18-2; 2-phenyl-2-imidazoline, 936-49-2; 2-benzyl-2-imidazoline, 59-98-3; 2-cyclohexyl-2-imidazoline, 67277-65-0; *N*-(2-hydroxyethyl)picolinamide, 16347-06-1; 2-(3-pyridinyl)-2-imidazoline, 6302-53-0; 2-(4-pyridinyl)-2-imidazoline, 21381-61-3; 2-[(β-carbolin-3-yl)carbonylamino]ethanol, 77415-47-5; *N*-[(β-carbolin-3-yl)carbonyl]ethylenediamine, 77415-48-6; 8β-(2-benzimidazolin-2-yl)-6-methylergoline, 77429-52-8; 8β-(2-benzothiazolin-2-yl)-6-methylergoline, 77429-53-9; *N*-[(6-methylergolin-8β-yl)carbonyl]-*o*-phenylenediamine, 77415-49-7; *o*-[(6-methylergolin-8β-yl)carbonylamino]benzenethiol, 77415-50-0; ethylenediamine, 107-15-3; 1,2-diaminobenzene, 95-54-5; 2-mercaptoaniline, 137-07-5; 2-aminoethanol, 141-43-5; trimethylaluminum, 75-24-1.

Communications

Total Synthesis of (±)-4′-Demethyl-4-epipodophyllotoxin by Insertion–Cyclization

Summary: The total synthesis of (±)-4′-*O*-demethyl-4-epipodophyllotoxin (**3**) is accomplished in 13 steps and 2.4% overall yield from piperonal through the use of an "insertion–cyclization" reaction to form the aryltetralin ring system.

Sir: The development of the glycosidic lignan lactones etoposide (1)[1] and teniposide (2)[1] into major clinical agents against lung and bladder cancer[2] has spurred recent interest in the efficient total synthesis of their common aglycon, 4′-*O*-demethyl-4-epipodophyllotoxin (3).[3] Despite the pioneering synthesis of podophyllotoxin (4) by Gensler and his school,[4] and the very recent studies by Murphy[5] and Rodrigo,[6] no practical laboratory synthesis of these lignan lactones exists. We now report successful implementation of a new strategy for this purpose.

Our strategy exploits the principle of insertion–cyclization, whereby a slow cyclization between nucleophilic (N) and electrophilic (E) termini of a molecular array can be intercepted by insertion of a reactive moiety U which

(1) Keller-Juslén, C.; Kuhn, M.; von Wartburg, A.; Stähelin, H. *J. Med. Chem.* **1971**, *14*, 936.

(2) For a recent review of clinical data on these two compounds see: Radice, P. A.; Bunn, P. A., Jr.; Ihde, D. C. *Cancer Treat. Rep.* **1979**, *63*, 1231.

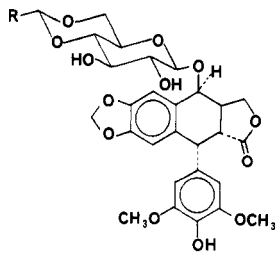
(3) Kuhn, M.; Keller-Juslén, C.; von Wartburg, A. *Helv. Chim. Acta* **1969**, *52*, 944.

(4) (a) Gensler, W. J.; Samour, C. M.; Wang, S. Y.; Johnson, F. *J. Am. Chem. Soc.* **1960**, *82*, 1714. (b) Gensler, W. J.; Gatsonis, C. D. *J. Org. Chem.* **1966**, *31*, 4004. Other innovative approaches to podophyllin lactones are those by: Ziegler, F. E.; Schwartz, J. A. *J. Org. Chem.* **1978**, *43*, 985; Brown, E.; Robin, J.-P.; Dhal, R. *J. Chem. Soc., Chem. Commun.* **1976**, 556; Klemm, L. H.; Olson, D. R.; White, D. V. *J. Org. Chem.* **1971**, *36*, 3740.

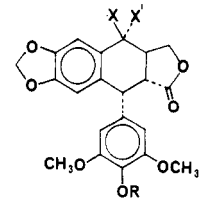
(5) Murphy, W. S.; Wattanasin, S. J. *J. Chem. Soc., Chem. Commun.* **1980**, 262.

(6) Rodrigo, R. *J. Org. Chem.* **1980**, *45*, 4538.

0022-3263/81/1946-2826$01.25/0

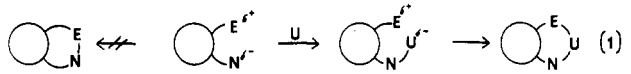


1 R=CH_3
2 R=



3 X=OH X'=H R=H
4 X=H X'=OH R=CH_3

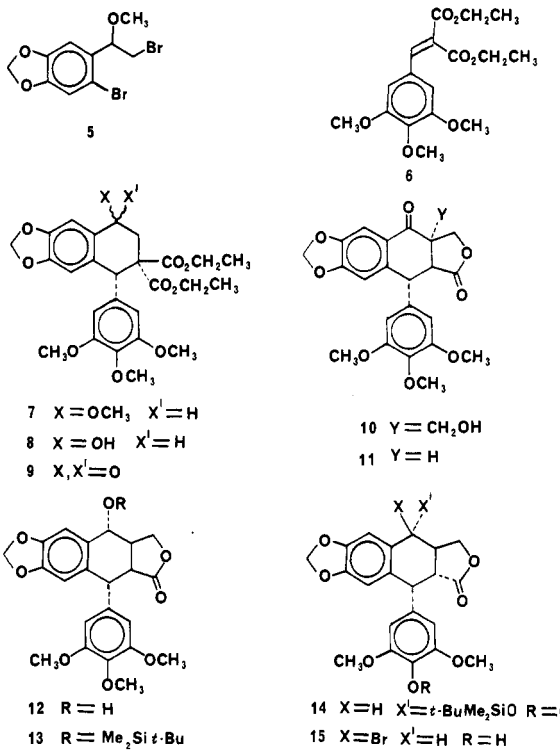
can accept charge and subsequently participate in the desired cyclization step (eq 1).[7]



(1)

Our aim was to design a variant of the insertion–cyclization that would directly yield the 4-oxygenated aryltetralin framework of these lignan lactones, since it appears that late introduction of the C-4 hydroxyl (at the aryltetralin or 4-deoxy lactone stage) is inefficient.[8] Therefore, the methoxy dibromide **5** (mp 87–88.5 °C) was prepared in 70% overall yield by Wittig methylenation of piperonal (1.2 equiv of $Ph_3P^+CH_3Br^-$, K_2CO_3, catalytic 18-crown-6, THF, reflux, 36 h)[9] followed by methoxybromination (3 equiv of Br_2, MeOH, room temperature, 36 h).[10] Lithiation of **5** (1.05 equiv of *n*-BuLi, THF, −100 °C, addition of arylidenemalonate **6**[11] (1.05 equiv in Et_2O), warming to room temperature, and then removal of solvent followed by reflux in dry DME for 1 h gave the diastereomeric mixture of aryltetralin diesters **7** in 88% yield.[12] By this insertion–cyclization all but one carbon atom and much of the functionality of the target aglycon were incorporated in a single synthetic operation.

Solvolysis of **7** (CF_3CO_2H, −10 °C, 5 min, then saturated $NaHCO_3$)[13] gave the corresponding alcohols **8**,[14] which on oxidation (1.5 equiv of $C_5H_5N{\cdot}HCl{\cdot}CrO_3$, CH_2Cl_2, room temperature, 1 h)[15] gave the keto diester **9** in 86% yield after silica gel chromatography (Et_2O/acetone/hexanes, 1:1:2).[16] In an improvement over our earlier procedure,[17] keto diester **9** could be converted to the key intermediate (±)-picropodophyllone (**11**), mp 198–199.5 °C, in 35% overall yield from **9** by hydrolysis (0.31 M KOH in absolute EtOH, reflux, 2.5 h) and decarboxylation to the trans keto acid, hydroxymethylation of the crude keto acid to **10**, and then retroaldol thermolysis.



5
6
7 X=OCH_3 X'=H
8 X=OH X'=H
9 X,X'=O
10 Y=CH_2OH
11 Y=H
12 R=H
13 R=Me_2Si-t-Bu
14 X=H X'=t-$BuMe_2SiO$ R=CH_3
15 X=Br X'=H R=H

Stereospecific reduction of the C-4 carbonyl in picropodophyllone (**11**)[18] was best achieved by using $LiAlH(t\text{-}BuO)_3$ (4 equiv, THF, room temperature, 3 h) to give picropodophyllin (**12**) in 62% yield.[19] In a significant improvement of the Gensler lactone epimerization,[4b] picropodophyllin (**12**) was converted to the silyl ether **13** (2.3 equiv of t-$BuMe_2SiCl$, 4.6 equiv of imidazole, DMF, 75 °C, 3 h)[20] in 94% yield (mp 169–170 °C).[21] A THF solution of ether **13** was treated with 1.25 equiv of LDA at −78 °C, and the resulting enolate was quenched irreversibly with freshly prepared pyridine hydrochloride.[22] Careful

(7) For other reactions of this type see, for example: (a) Parham, W. E.; Jones, L. D.; Sayed, Y. *J. Org. Chem.* **1976**, *41*, 1184; (b) Hergreuter, C. A.; Brewer, P. D.; Tagat, J.; Helquist, P. *Tetrahedron Lett.* **1977**, 4145; (c) Parham, W. E.; Bradsher, C. K.; Hunt, D. A. *J. Org. Chem.* **1978**, *43*, 1606; (d) Kraus, G. A.; Pezzanite, J. O. *Ibid.* **1979**, *44*, 2480. It should be noted that the inserted unit U can in principle accept positive (rather than negative) charge.

(8) On scales of greater than 50 mg, the benzylic oxidation procedure described in ref 17 resulted in low yields and byproduct formation (unpublished observations from these laboratories). For other problems involving C-4 oxygen, see ref 6.

(9) Boden, R. *Synthesis* **1975**, 784.

(10) **5**: mp 87–88.5 °C (MeOH); NMR ($CDCl_3$) δ 6.92 (1 H, s), 6.88 (1 H, s), 5.94 (2 H, s), 4.68 (1 H, dd), 3.44 (2 H, m), 3.29 (3 H, s); mass spectrum, *m/e* 340, 338, 336 (M^+). Anal. Calcd for $C_{10}H_{10}Br_2O_3$: C, 35.50; H, 2.98. Found: C, 35.54; H, 2.86.

(11) Benzylidenemalonate **6** was prepared in 85% yield by Knoevenagel condensation of 3,4,5-trimethoxybenzaldehyde with diethyl malonate (catalytic piperidine, catalytic HOAc, benzene, reflux, 28 h) in a procedure similar to that used by Papadakis and Mathiesen (*J. Org. Chem.* **1956**, *21*, 1976): mp 69–70 °C (95% EtOH); NMR ($CDCl_3$) δ 7.84 (1 H, s), 6.74 (2 H, s), 4.20 (4 H, 2 overlapping q), 3.76 (3 H, s), 3.72 (6 H, s), 1.16 (6 H, 2 overlapping t); mass spectrum *m/e* 338 (M^+).

(12) The product of this reaction could be used without purification. However, the two diastereomers could be separated by careful chromatography (Et_2O/cyclohexane, 1:1), to give the pure compounds in a 2:3 ratio in 88% yield with the more polar diastereomer predominating. Less polar: NMR ($CDCl_3$) δ 6.87 (1 H, s), 6.37 (1 H, s), 6.25 (2 H, s), 5.84 (2 H, s), 4.74 (1 H, s), 4.16 (5 H, m), 3.78 (3 H, s), 3.73 (6 H, s), 3.58 (3 H, s), 2.3–2.7 (2 H, m), 1.20 (6 H, 2 overlapping t); mass spectrum, *m/e* 516 (M^+). More polar: NMR ($CDCl_3$) δ 6.77 (1 H, s), 6.46 (1 H, s), 6.17 (2 H, s), 5.90 (2 H, d), 4.87 (1 H, s), 4.2 (5 H, m), 3.84 (3 H, s), 3.81 (6 H, s), 3.54 (3 H, s), 2.90 (1 H, br d), 2.52 (1 H, dd), 1.20 (6 H, 2 overlapping t); mass spectrum, *m/e* 516 (M^+).

(13) Marsh, J. P.; Goodman, L. *J. Org. Chem.* **1965**, *30*, 249.

(14) Attempted solvolysis of the methyl ether using mineral acids resulted in byproduct formation and capricious yields.

(15) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

(16) **9**: mp 152–153 °C (MeOH); IR ($CHCl_3$) 1730, 1690 cm^{-1}; NMR ($CDCl_3$) δ 7.51 (1 H, s), 6.65 (1 H, s), 6.25 (2 H, s), 6.06 (2 H, s), 5.08 (1 H, s), 4.14 (4 H, 2 overlapping q), 3.82 (3 H, s), 3.75 (6 H, s), 3.25 (2 H, s), 1.16 (6 H, 2 overlapping t); mass spectrum, *m/e* 500 (M^+). Anal. Calcd for $C_{28}H_{28}O_{10}$: C, 62.37; H, 5.64. Found: C, 62.42; H, 5.66.

(17) Kende, A. S.; Liebeskind, L. S.; Mills, J. E.; Rutledge, P. S.; Curran, D. P. *J. Am. Chem. Soc.* **1977**, *99*, 7082.

(18) This step and all subsequent steps were performed with optically active relay material. Picropodophyllone (**11**) was prepared in 68% yield from natural podophyllotoxin (**4**) by epimerization at C-2 (10% aqueous NaOAc, EtOH, reflux, 16 h) as in Borsche and Niemann (*Justus Liebigs Ann. Chem.* **1932**, *494*, 126) and then oxidation at C-4 (1.5 equiv of PCC, CH_2Cl_2, room temperature, 3.5 h).

(19) Interestingly, reduction with diborane–tetrahydrofuran complex (3.7 equiv of BH_3·THF, THF, −78 to 0 °C, 3.5 h at 0 °C) gave a mixture of the α and β alcohol, with the β predominating in a ratio of 4–5:1. The β alcohol, epipicropodophyllin, could be isolated in 57% yield.

(20) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(21) **13**: mp 169–170 °C (MeOH); IR ($CHCl_3$) 1778 cm^{-1}; NMR ($CDCl_3$) δ 6.91 (1 H, s), 6.49 (2 H, s), 6.25 (1 H, s), 5.92 (2 H, s), 4.22–4.64 (3 H, m), 3.95 (1 H, partially obscured d), 3.91 (3 H, s), 3.88 (6 H, s), 3.16–3.34 (1 H, dd), 2.48–2.82 (1 H, m), 1.04 (9 H, s), 0.22 (3 H, s), 0.18 (3 H, s); mass spectrum, *m/e* 528 (M^+). Anal. Calcd for $C_{28}H_{36}O_8Si$: C, 63.61; H, 6.86; Si, 5.31. Found: C, 63.52; H, 6.75; Si, 5.19.

preparative TLC (EtOAc/hexanes, 3:7, three passes) gave 34% of recovered **13** and 36% of the podophyllotoxin derivative **14**;[23] one recycle raised the yield of **13** to 48%.

Desilylation of ether **14** (excess $Et_3N{\cdot}HF$, THF, room temperature, 3 da[24] gave podophyllotoxin (**4**) in 89% yield.[25] Alternatively, ether **14** was reacted with anhydrous HBr[26] (CH_2Cl_2–Et_2O, 0 °C, 8 h). Hydrolysis of the crude 4-epibromo-4′-*O*-demethyl-podophyllotoxin **15** ($CaCO_3$, aqueous Me_2CO, 45 °C, 1 h) gave 47% of white crystalline 4′-*O*-dimethyl-4-epipodophyllotoxin (**3**), mp 244–246 °C (MeOH),[27] identical in all respects with an authentic sample prepared from natural podophyllotoxin.

Our insertion–cyclization strategy and subsequent tactical modifications now make available (±)-podophyllotoxin (**4**) in 12 synthetic steps and 4.5% overall yield from piperonal; aglycon **3** is similarly available in 13 steps and 2.4% overall yield. More convergent variants of our insertion–cyclization scheme in which both the aryltetralin and the γ-lactone are generated in a single operation can be envisioned and are under exploration.

Acknowledgment. Partial support of this work by Grant CA-18846 from the National Cancer Institute (USPHS) and by Sherman Clarke and Elon Huntington Hooker Fellowships to D.P.C. and M.L.K. is gratefully acknowledged.

Registry No. (±)-**3**, 77519-36-9; (±)-**4**, 77519-37-0; (±)-**5**, 77461-23-5; **6**, 51444-50-9; (±)-*cis*-**7**, 77461-24-6; (±)-*trans*-**7**, 77461-25-7; (±)-*cis*-**8**, 77461-26-8; (±)-*trans*-**8**, 77461-27-9; (±)-**9**, 64897-37-6; (±)-**10**, 64897-39-8; (±)-**11**, 64937-82-2; (±)-**12**, 77519-38-1; (±)-**13**, 77461-28-0; (±)-**14**, 77519-39-2; (±)-**15**, 77519-40-5; piperonal, 120-57-0; 3,4,5-trimethoxybenzaldehyde, 86-81-7; diethyl malonate, 105-53-3.

(22) Pyridine hydrochloride was found to give a higher proportion of the trans lactone than was obtained with acetic acid. Use of even more sterically encumbered proton sources, such as collidine hyrochloride, did not result in further improvement of the trans to cis ratio; cf.: Zimmerman, H. E.; Mariano, P. S. *J. Am. Chem. Soc.* **1968**, *90*, 6091 and references therein.

(23) **14**: IR ($CHCl_3$) 1780 cm^{-1}; NMR ($CDCl_3$) δ 6.95 (1 H, s), 6.48 (1 H, s), 6.39 (2 H, s), 5.96 (2 H, s), 4.79 (1 H, d), 4.42–4.66 (2 H, m), 3.8–4.25 (1 H, partially obscured m), 3.82 (3 H, s), 3.72 (6 H, s), 2.70–2.96 (2 H, m), 0.95 (9 H, s), 0.29 (3 H, s), 0.11 (3 H, s); mass spectrum, *m/e* 528 (M^+). Anal. Calcd for $C_{28}H_{36}O_8Si$: C, 63.61; H, 6.86; Si, 5.31. Found: C, 63.55; H, 6.81; Si, 5.26.

(24) Hünig, S.; Wehner, G. *Synthesis* **1975**, 1980.

(25) This material was identical with natural podophyllotoxin.

(26) An analogous procedure was used in ref 3 for preparation of **3** from **4**.

(27) **3**: mp 244–246 °C (MeOH); IR ($CHCl_3$) 3540, 1780 cm^{-1}; NMR ($CDCl_3/Me_2SO$-d_6) δ 6.92 (1 H, d), 6.49 (1 H, s), 6.29 (2 H, s), 6.00 (1 H, s), 5.90 (2 H, s), 4.80 (1 H, d), 4.55 (1 H, d), 4.24–4.46 (2 H, m), 4.24–4.84 (1 H, br s), 3.76 (6 H, s), 3.20–3.48 (1 H, dd), 2.64–2.98 (1 H, m); mass spectrum, *m/e* 400 (M^+). Anal. Calcd for $C_{21}H_{20}O_8$: C, 62.99; H, 5.04. Found: C, 62.83; H, 5.02.

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2,5-Bis(methoxycarbonyl)-4-hydroxycyclopent-2-en-1-one as an Intermediate in Weiss' Glyoxal Reaction. Analogous Chemistry of Malondialdehyde

Summary: Glyoxal and dimethyl 3-oxoglutarate condense at pH <6 to form a reactive intermediate, 2,5-bis(methoxycarbonyl)-4-hydroxycyclopent-2-en-1-one, part of which dimerizes to yield **3** after hydrolysis–decarboxylation. Its structure was proved by single-crystal X-ray crystallography performed on the dimethyl ester. Support for this mechanism comes from studying the analogous reaction of malondialdehyde, which gives 2,6-bis(methoxycarbonyl)phenol at pH 5 but not at pH 8 where phenol formation is usually more rapid. The product at pH 8 is tetramethyl 3,7-dioxobicyclo[3.3.1]nonane-2,4,6,8-tetracarboxylate.

Sir: 4-Hydroxycyclopentenones constitute an exceptionally interesting and important class of organic compounds, considering their role as a structural feature of the naturally occurring pyrethrin insecticides and their synthetic analogues,[1] the pentenomycin antibiotics,[2] and the key intermediates in some syntheses of prostaglandins.[3] We have collected convincing chemical evidence that a simple member of this class, 2,5-bis(methoxycarbonyl)-4-hydroxycyclopent-2-en-1-one (**1**), is the important reactive intermediate formed when dimethyl 3-oxoglutarate and glyoxal are mixed at pH 5. In contrast, at pH 6 the predominant reactive intermediate is 3,5-bis(methoxycarbonyl)-4-oxopent-2-enal (**2**), as proposed by Cook and Weiss.[4] The important new findings are the isolation of the major tetracyclic product **3** at low pH and the demonstration that dimethyl 3-oxoglutarate (**4**) reacts with malondialdehyde by way of intermediates analogous to those it begets with glyoxal. This research clarifies one of the principle mechanistic questions of Weiss' reaction between **4** and glyoxal, viz., which of the proposed possible intermediates[4] is responsible for each of the products.

In 1968 Weiss and Edwards reported[5] that bicyclo[3.3.0]octane-3,7-dione (**5**) was formed in ~15% yield after hydrolysis and decarboxylation of the tetraester **5b** (Scheme I) that collected when **4** and glyoxal were stirred in dilute aqueous solution at pH 5. The endo and exo tetracyclic triketones **6** were later found to accompany **5** in yields of 3.2% and 1.6%, respectively.[6,7] The total yield is substantially increased by buffering the reaction mixture at pH 6 where **7b** can be isolated in 61% yield;[8,9] **7b** gives a 43% yield of **7** upon hydrolysis–decarboxylation.[8] A 12% yield of **5b** is also present at pH 6,[10] as are the usual small amounts of **6**.

A priori, two fundamentally different 1:1 intermediates, **1** and **2**, could be postulated to arise from the interaction of **4** and glyoxal (Scheme I). Either of these might be expected to react further with **4** to give **5b**, which itself could react with **1** or **2** to yield the hexakis(methoxycarbonyl) precursors of **6**.

The isolation of **7b** as the major product at pH 6 im-

(1) Elliott, M.; Jones, N. F. *Chem. Soc. Rev.* **1978**, *7*, 473–505.

(2) Date, T.; Aoe, K.; Kotera, K.; Umino, K. *Chem. Pharm. Bull.* **1974**, *22*, 1963–7.

(3) Bartmann, W. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 337–44.

(4) Yang-Lan, S.; Mueller-Johnson, M.; Oehldrich, J.; Wichman, D.; Cook, J. M.; Weiss, U. *J. Org. Chem.* **1976**, *41*, 4053–8.

(5) Weiss, U.; Edwards, J. M. *Tetrahedron Lett.* **1968**, 4885–7.

(6) Edwards, J. M.; Qureshi, I. H.; Weiss, U.; Akiyama, T.; Silverton, J. V. *J. Org. Chem.* **1973**, *38*, 2919–20.

(7) Rice, K. C.; Sharpless, N. E.; Weiss, U.; Highet, R. J. *Tetrahedron Lett.* **1975**, 3763–6.

(8) Rice, K. C.; Weiss, U.; Akiyama, T.; Highet, R. J.; Lee, T.; Silverton, J. V. *Tetrahedron Lett.* **1975**, 3767–70.

(9) The yield can be improved from the 45% of ref 8 to 61% by adding methanol as a cosolvent, which allows more concentrated solutions of the reactants to be used. In this study we mixed 87.0 g of **4**, 72.5 g of 40% glyoxal, and 250 mL of 50% aqueous methanol containing 3.45 g of monobasic sodium phosphate monohydrate and adjusted the pH to 6 with 17 mL of 10 M NaOH added by drops with vigorous swirling and ice-bath cooling. The product was filtered off after the mixture was stirred for a week at 25 °C.

(10) This yield was measured by quantitative ^{13}C NMR, calibrated with an internal standard (cyclohexane). Gated proton decoupling was used.

0022-3263/81/1946-2828$01.25/0