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A Method for Effecting the Equivalent of a de Mayo Reaction with Formyl Acetic Ester[1a]

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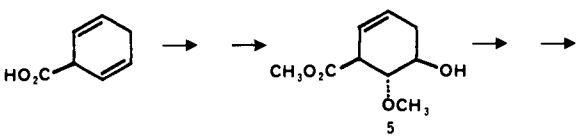
Contribution from the Department of Chemistry, Columbia University, New York, New York 10027. *Received February 24, 1978*

Abstract: Both Woodward reserpine precursor **1** and Corey prostaglandin precursor **3** are monocyclic compounds with vicinal carboxaldehyde and acetic ester appendages. Disconnection of these appendages (along with disconnection of the two oxygen substituents of **1**) generates hypothetical precursors (1,4-dihydrobenzoic acid and *cis*-cyclopentene-3,5-diol) both of which are readily available. Therefore, both reserpine and the prostaglandins might become available by short synthetic sequences if a method existed for the placement of vicinal carboxaldehyde and acetic ester appendages onto double bonds. This paper reports a five-step sequence that accomplishes this transformation for the case of 4-hydroxycyclohexene.

Introduction

Reserpine (**2**) and the prostaglandins (for example, $PGF_{2\alpha}$ [**4**]) are natural products whose physiological effects make them of great value in medicine, reserpine as an antihypertensive[2] and the prostaglandins as agents for the regulation of fertility.[3] Since their structures are relatively complex, total synthesis would seem to be an unlikely means of procurement but, due to the elegant and classic work of Woodward[4] and Corey,[5] some pharmaceutical companies have seriously considered the use of total synthesis to obtain their supplies.[2,5c,6] Not only are these two syntheses commercially feasible, but they also were considered by I. Fleming to be so artistically "beautiful" [7] that he arranged his book "Selected Organic Syntheses" so as to present them as the final two chapters.

However, these two syntheses have one striking feature in common: namely, that cyclic compounds with vicinal carboxaldehyde and acetic ester appendages (**1** and **3**) are key intermediates. Moreover, disconnection of these appendages (along with disconnection of the two oxygen substituents of **1**) generates olefins that are readily available (1,4-dihydrobenzoic acid[8] and *cis*-cyclopentene-3,5-diol,[9] respectively). *Thus, both reserpine and the prostaglandins might become available by even simpler synthetic routes if a sufficiently simple method existed for the placement of vicinal carboxaldehyde and acetic ester appendages onto double bonds.*



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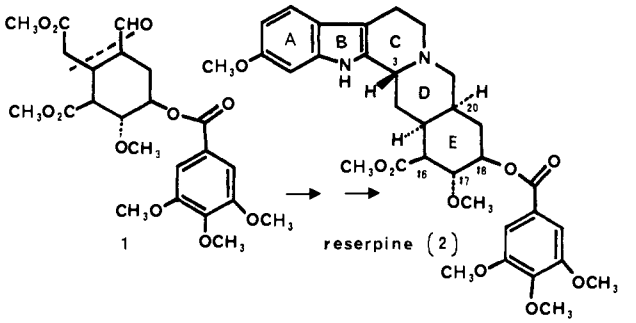

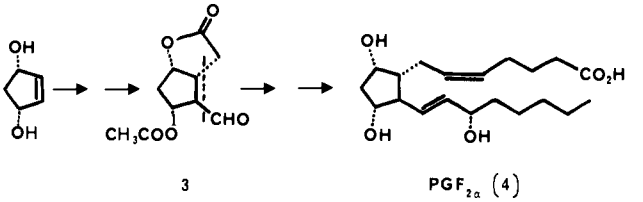

Actually, sequences which effect attachment of vicinal two-carbon and one-carbon appendages onto a ring are known.[10-15] However, none of this methodology was deemed appropriate for the two intended applications. Therefore, research directed toward filling this gap in synthetic methodology was undertaken.

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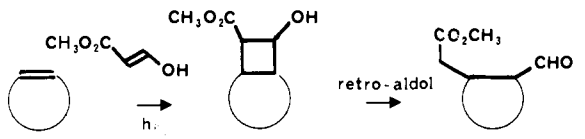
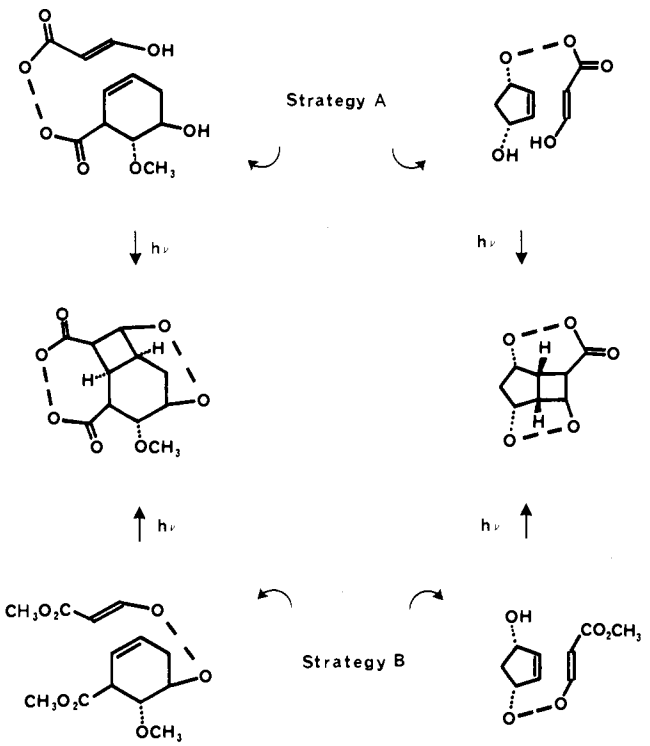
The general strategy for the attachment of vicinal carboxaldehyde and acetic ester appendages to a double bond that was investigated is that of photochemical [2 + 2] cycloaddition of formyl acetic ester (or some equivalent) to the olefin, as sketched below:



This plan is attractive because the three requisite carbon atoms would be delivered to the double bond in the correct oxidation state in one step. Of course, some means of coping with nonregiospecificity and nonstereospecificity in the cycloaddition step is essential, since both olefinic substrates are unsymmetrical. However, both olefins possess "extra" functional groups in proximity to their double bonds which, if connected covalently to the formyl acetic ester, might deliver it to the double bond with the correct orientation.



Also, loss of the correct stereochemistry at the aldehyde-bearing carbon during the retro-aldol step should not be a matter for concern, since both **1**[16] and **3**[17] should prevail over their aldehyde epimers at equilibrium. Thus, the regiochemical and stereochemical problems inherent in the [2 + 2] cycloaddition step are solvable in theory.

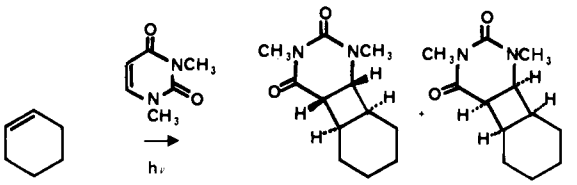
Indeed, there is some justification for the proposition that formyl acetic ester itself might be capable of photoadding to unactivated olefins to form hydroxycyclobutane carboxylic esters: specifically, that β-diketones,[18] β-dialdehydes,[19] and β-ketoaldehydes[20] are known to undergo this reaction (the "de Mayo reaction"). However, enols of β-keto esters have been reported to undergo other reactions upon irradiation (specifically, deconjugation to the keto tautomer[21] and oxetane formation[18b,22]), and formyl acetic ester is a type of β-keto ester. Thus, a reasonable presumption is that formyl acetic ester should be incapable of photoadding to unactivated olefins. However, even if it were to have this capability, its synthetic utility would still be limited because it dimerizes and/or trimerizes even in neutral media below room temperature,[23] so that synthesis of compounds with the formyl acetic ester and the olefinic substrate linked together would be troublesome.

Thus, the research described below was directed toward finding, first, a stable equivalent of formyl acetic ester[24] and, second, a means of delivering it to the two aforementioned olefins with the correct stereochemical and regiochemical orientation.

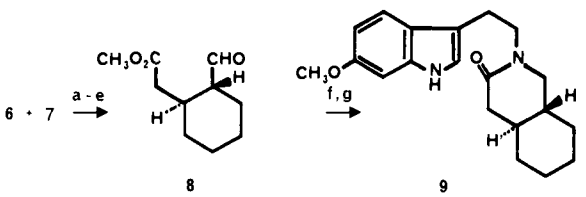
Results and Discussion

One candidate for a formyl acetic ester equivalent felt to be particularly promising was uracil. Not only is it highly stable and not only does it happen to have the same oxidation pattern as formyl acetic ester, but also it is well-known that it is capable of photoadding both to itself[25] and to nucleophilic olefins such as vinyl acetate and ketene-diethyl ketal.[26]

Indeed, we found that 1,3-dimethyluracil photoadds to cyclohexene, under the published conditions,[26] to give a 56:44 mixture of 1:1 adducts in 87% combined yield.

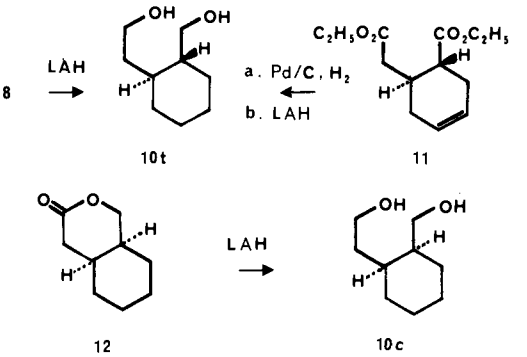


Moreover, the major isomer **6**[27] can be converted into the corresponding vicinal aldehydo ester **8** by a simple sequence of operations (indicated below) in 29% overall yield. The structure of the material thus obtained was established as **8** by spectral information (NMR, IR, MS) as well as by conversion of the material into 11-methoxy-2,3-seco-3-oxoyohimbane (**9**), mp (vac) = 217.5–219 °C, by the steps indicated below.



(a) NaOH, 45 °C, 2 days; (b) NaONO, H_2SO_4, 0 °C; (c) KOH, H_2O, ether, room temp. (d) HCl, CH_3OH, Δ, 4 h; (e) HCl, H_2O; (f) 6-methoxytryptamine, C_6H_6/CH_3OH, room temp; (g) $NaBH_4$, CH_3OH

There was one apparent complication: namely, that epimerization occurred at the aldehyde-bearing carbon during the acid-catalyzed retro-Mannich cyclobutane opening. This is implied by the fact that the diol derived from $LiAlH_4$ reduction of **8** was predominantly (>95%) the trans isomer **10t** (determined by spectral and GC[28] correspondence with an authentic sample of **10t**[29] and noncorrespondence of spectra and GC with an authentic sample of **10c**[30]).

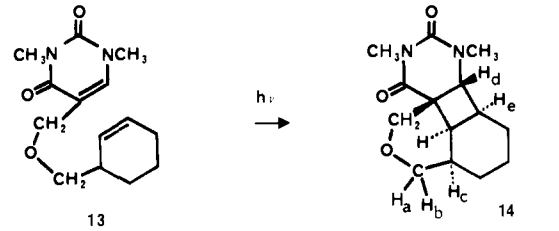


However, aldehyde epimerization should not be a problem in the two natural product syntheses in which the method is to be applied (vide supra). Thus, the study of methods for correcting

the stereochemistry at the aldehyde-bearing carbon was not warranted. The next appropriate objective was to find a connecting chain capable of delivering the uracil to the double bond with the correct orientation, so studies directed toward this end were undertaken and will be discussed below.

As pointed out above, two alternative strategies were available, one being to connect the uracil to the C-16 carbomethoxy substituent of ring E (strategy A) and the other being to connect it to the C-18 hydroxyl (strategy B). We decided arbitrarily to investigate strategy A.

The first compound chosen for study, the ether **13,** upon photolysis, underwent intramolecular [2 + 2] cycloaddition to give a cyclobutane-containing adduct in excellent yield and in completely isomerically pure form (by ^{13}C NMR, 220-MHz NMR, and GC [5% SE-30, 250 °C, R_t = 9.4 min]). Of course,

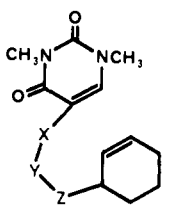


13 14

$J_{ac} = J_{bc} = 0$ Hz

$J_{de} = 8$ Hz

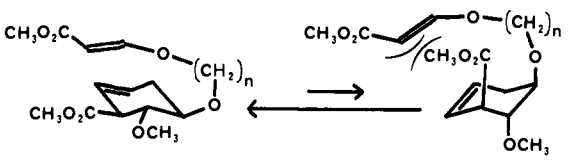
the possibility exists that the adduct may not be the desired isomer **14.** However, none of the determinable NMR coupling constants at the relevant stereocenters (indicated in the figure) are inconsistent with the desired structure (**14**). Of course, in any case, the ether connecting chain is impractical, because conversion of the ether bridge into something of the oxidation state of the corresponding anhydride would require a lengthy sequence of reactions. Thus, we next elected to study the



	X	Y	Z
15	CO	NCH_3	CO
16	CO	O	CH_2
17	CO	NH	CH_2
18	CH_2	O	CO

photochemistry of compounds with the correct level of oxidation built into their connecting chains (**15–18**). Unfortunately, photolyses of these compounds resulted in the formation of various undesired products.[31] Thus, strategy A had to be abandoned. Our efforts to implement strategy B will now be described.

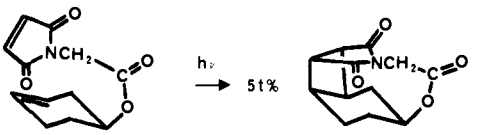
Actually, with strategy B, there is legitimate reason to doubt whether any connecting chain of fewer than three members (**19,** $n < 3$) would be capable of delivering the formyl acetic



19 19

ester equivalent to the double bond intramolecularly, in that to do so would require the formyl acetic ester equivalent to be in a diaxial relationship with the carbomethoxy substituent in the transition state. Therefore, the first compound chosen for study was one (**20**) whose connecting chain was long enough that the formyl acetic ester equivalent containing chain could reach the double bond of the cyclohexene while being equatorial. Normally, of course, closure of a nine-membered ring is a highly unfavorable transformation,[32] but in this case the cyclization should be facile because, of the eight bonds in the substrate that would make up the nine-membered ring in the product, free rotation is possible around only four. Indeed, several bis-maleimides analogous to **20** had been observed to cyclize to even larger membered ring-containing adducts.[33]

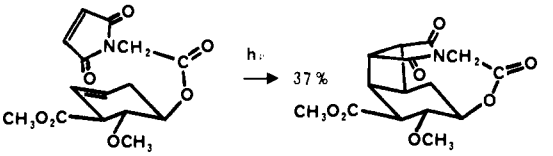
Thus, maleoyl glycinate ester **20** was synthesized and then photolyzed. As hoped, the glycine connecting chain did deliver the maleimide ring to the double bond intramolecularly, in the



20 21

cases of both the model substrate **20** and the potential reserpine precursor **22.**

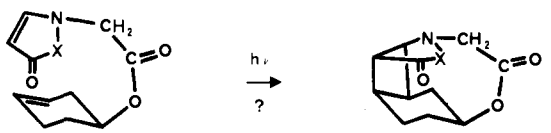
Now, completion of a synthesis of Woodward reserpine precursor **1** requires only that one of the two carboxyl groups of the succinimide ring of **23** be selectively decarboxylated.



22 23

Unfortunately, however, the succinimide rings of both **21** and **23** were impervious to hydrolysis, methanolysis, and hydrazinolysis, at least under conditions in which the cyclobutane ring was stable. Presumably, this inertness of the maleimide ring is due to steric hindrance by the cyclohexane ring.[34]

To avoid having to deal with these hydrolysis difficulties, as well as to avoid the anticipated problem of differentiation of the two carboxyl groups, we next adopted the strategy of using a heterocycle of the general type **24.** Not only would the adducts **25** be relatively easy to degrade, but the aldehydoester



24 25

X = O, OCO, NH, CONH, etc.

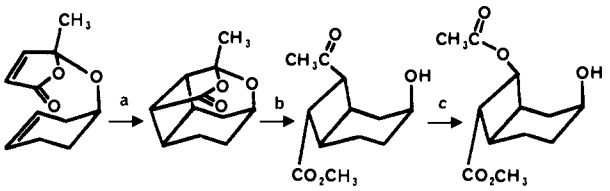
ultimately obtained could only be the desired regioisomer. Our single reservation about this strategy was that the glycine connecting chain might be poorly suited for the delivery of these heterocycles, since it was designed specifically for the delivery of the maleimide ring. Indeed, unfortunately, the model compound **24** (X = NCH_3CO)[35] failed to cyclize intramolecularly to any detectable extent.

With this result, investigations into the "short" delivery chain variant of strategy B were undertaken: although putatively dubious, this strategy proved workable.

Compound **26** was our initial choice for study. The reason a butenolide ring was chosen to be the chromophore was that simple butenolides had been reported to cycloadd to olefins[36] and the latent aldehydo ester functionality of the adduct **27** should be relatively simple to unmask, assuming that the lactone ring is not extraordinarily hindered. Of course, this formyl acetic ester equivalent does have an asymmetric center, which is an unattractive feature inasmuch as linkage of it to **5** would give not only the desired ketal but also an approximately equal

amount of the diastereomer, which would be incapable of cyclizing. However, at least in theory (and, as it turned out, in practice in the case of reserpine[37]), the "wrong" diastereomer could be separated and hydrolyzed back to **5**, so that none of **5** need be lost.

The required model compound **26** was prepared in 74% yield from 4-hydroxycyclohexene as a 1:1 mixture of diastereomers (inseparable by silica gel column chromatography) by treatment with the readily available[38] pseudo acid bromide of cis-β-acetylacrylic acid in the presence of Ag_2O/crushed $CaSO_4$. On photolysis, **26** does undergo the desired cycloaddition in somewhat less than 45% yield (at 0.006 M, based on the diastereomer capable of cyclizing; at 0.066 M, 28%).



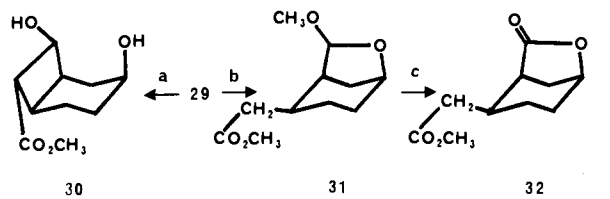
26 27 28 29

(a) *hv*; (b) H_2SO_4, CH_3OH, Δ, 19 h; (c) F_3CCO_3H, CH_2Cl_2, room temp, 3 h

The adduct **27** was then transformed into the acetoxycyclobutane **29** by refluxing in acidic methanol followed by treatment with trifluoroperacetic acid.

Thus, a method for effecting the [2 + 2] cycloaddition of the enol acetate of formyl acetic ester to the double bond of 4-hydroxycyclohexene with the correct stereochemical and regiochemical orientation relative to the hydroxyl group had been found. Now, what remained to be shown was only that **29** could be induced to undergo retroaldolization. Since even relatively unstrained β-hydroxy carboxylic esters such as dihydrogibberellic acid are known to undergo retroaldolization in aqueous base at room temperature,[40] **29** might be expected to undergo retroaldolization with great facility, perhaps spontaneously,[18] upon deacetylation.

Actually, on submission of **29** to acidic methanol at room temperature for 1.5 h, the unopened β-hydroxy ester **30** is formed in 85% yield. However, retroaldolization occurs smoothly upon refluxing in acidic methanol for 14 h.



30 31 32

(a) H_2SO_4, CH_3OH, room temp, 1.5 h; (b) H_2SO_4, CH_3OH, Δ, 14 h; (c) Jones'

The fact that the lactol methyl ether obtained (**31**) has the all-cis structure claimed is implied by the fact that it derives from the cage compound **27**. Nonetheless, to prove this assignment, independent proof is desirable. Thus, this material was oxidized with Jones' reagent to the corresponding lactone **32**, which was found to be identical with a sample of **32** prepared by an unambiguous literature[41] route by NMR, IR, TLC (2:1 $CHCl_3$/EtOAc, SiO_2), and melting point comparison, and also by undepression of the melting points upon admixture.

Thus, a method has been found for the execution of the equivalent of a stereospecific and regiospecific de Mayo reaction with formyl acetic ester on 4-hydroxycyclohexene, which was the object of this study.

Experimental Section

All photolyses were done with an Ace-Hanovia 550-W, high-pressure, mercury-vapor lamp housed in a quartz cooling jacket.

Routine nuclear magnetic resonance (NMR) spectra were taken on a Varian Model T-60 spectrometer in $CDCl_3$ solution. High resolution spectra were taken on either a Varian HA-100 or Varian HR-220 spectrometer. Chemical shift values (δ) are reported in parts per million (ppm) downfield from Me_4Si.

Carbon-13 magnetic resonance (^{13}C NMR) spectra were recorded on a JEOL PS 100 instrument in $CDCl_3$ solution with Me_4Si as internal standard. Values are reported in parts per million downfield from Me_4Si.

Electron-impact (EI) mass spectra were recorded on either a Jeolco Model JMS-07 or a Finnigan 3300 mass spectrometer. Chemical ionization (CI) mass spectra were recorded on the latter instrument.

Infrared (IR) spectra were recorded on either a Perkin-Elmer 137, a Perkin-Elmer 007, or a JASCO IRA-1 spectrometer, with polystyrene as standard. Values are reported in reciprocal centimeters.

Melting points were determined on a Buchi capillary melting point apparatus and are uncorrected.

Combustion analyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. 60076.

***cis-anti-cis*-1,3-Dimethyluracil–Cyclohexene Adduct (6).** A solution of 1,3-dimethyluracil[42] (25.0 g, 0.179 mol), cyclohexene (49.2 g, 0.601 mol), and acetone (12.2 g, 0.210 mol) in 347 mL of acetonitrile ("Chromatoquality," MCB) was degassed with nitrogen, then photolyzed internally through a Corex filter for 102 h. The crude reaction mixture was then concentrated to a viscous oil, which was distilled (135–144 °C/0.12–0.17 mm) through a short path to give another viscous oil, a 56:44 mixture of two isomers (by NMR integration). Yield: 35.56 g (0.156 mol, 87%). Fractional crystallization from ether/hexane gave the major isomer as colorless prisms, mp 81–82 °C: NMR (100 MHz) 1.0–2.0 (8 H, mults), 2.71 (2 H, br mults), 2.95 (3 H, s), 3.26 (3 H, s), 3.38 (1 H, dd, J = 9.5, 3 Hz), 3.94 (1 H, dd, J = 9.5, 7 Hz); IR (KBr) 1650, 1690; MS (CI) 223 (M^+ + 1, 100%). Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 65.22; H, 8.30; N, 12.60.

***trans*-2-Carbomethoxymethylcyclohexane-1-carboxaldehyde (8).** A suspension of the distilled dimethyluracil–cyclohexene adduct (2.231 g, 10.05 mol) in 20 mL of 2.83 M NaOH was stirred at 45 °C for 2 days, then cooled to 0 °C and treated successively with sodium nitrite (2.044 g, 29.6 mmol) and concentrated H_2SO_4 (6.106 g, 62.3 mmol). The reaction mixture was then allowed to warm up to room temperature, diluted with 100 mL of water, extracted with 100 mL of methylene chloride, and the extract dried ($MgSO_4$) and concentrated to a dark red oil. This oil was then taken up in 15 mL ether and stirred over 15 mL of 1.6 M KOH for 45 min at ambient temperature. The aqueous layer was neutralized with H_2SO_4 and concentrated to a reddish solid, which was taken up in 50 mL of 8% HCl/CH_3OH and refluxed for 4 h, the bulk of the methanol removed in vacuo, and the residue partitioned between 100 mL of water and 100 mL of methylene chloride. After shaking, the organic layer was dried ($MgSO_4$), concentrated, and carefully chromatographed on 50 g of SiO_2 ($CHCl_3$ eluent) to give a colorless oil that decomposed on standing: yield, 0.298 g (1.62 mmol, 29% based on anti isomer **6**); NMR (60 MHz) 1.2–2.0 (9 H, envelope), 2.0–2.5 (3 H, envelope), 3.63 (3 H, s), 9.51 (0.6 H, br s); IR (film) 1725 (shoulder), 1735, 2720; MS (CI) 185 (M^+ + 1, 27%), 153 (100).

***cis-syn-cis*-1,3-Dimethyluracil–Cyclohexene Adduct (7).** Continued elution of the column from the above experiment gave the title compound as a colorless oil. Recovery: 0.228 g (1.03 mmol, 23%). Crystallization from ether/hexane gave rectangular prisms, mp 97.5–98.5 °C; NMR (100 MHz) 1.3–2.0 (8 H, envelope), 2.3–2.8 (2 H, mults), 3.00 (3 H, s), ca. 3.1 (1 H, pattern obscured), 3.20 (3 H, s), 3.66 (1 H, dd, J = 8, 5 Hz); IR (KBr) 1660, 1700; MS (CI): 223 (M^+ + 1, 100%); UV (CH_3CN) end absorption only. Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16. Found: C, 64.68; H, 8.23.

11-Methoxy-2,3-*seco*-3-oxoyohimbane (9). A solution of aldehydo ester **8** (77 mg, 0.42 mmol) in 3 mL of benzene was treated with a solution of 6-methoxytryptamine[4] (92 mg, 0.49 mmol) in 9 mL of 5% methanol/benzene (the methanol being added for solubility) and allowed to stir at room temperature for 6 min; then the solvents were removed in vacuo at 50 °C. The oily residue was immediately taken up in 9 mL of methanol, treated with $NaBH_4$ (0.636 g, 16.7 mmol),

stirred at room temperature until the last of the $NaBH_4$ had been spent (10 min), then refluxed for 5 min, poured into 80 mL of 5% HCl, extracted with methylene chloride (2 × 50 mL), dried ($MgSO_4$), and concentrated to give a light green solid. Yield: 57 mg. Chromatography on 10 g of silica gel (20% ethyl acetate/chloroform as eluent) gave a white solid. Yield: 25 mg (0.077 mmol, 18%). Two recrystallizations from ethyl acetate gave white crystals, mp (vac) 217.5–219 °C; NMR (100 MHz) 1.0–2.6 (12 H, various mults), 3.01 (4 H, overlapping mults), 3.59 (1 H, d, J = 8 Hz), 3.66 (1 H, d, J = 9 Hz), 3.82 (3 H, s), 6.71 (1 H, d, J = 2 Hz), 6.82 (1 H, s), 6.87 (1 H, d, J = 2 Hz), 7.50 (1 H, d, J = 8 Hz), 8.40 (1 H, br s); IR (KBr) 1620, 3250; MS (CI) 327 (M^+ + 1, 100%). Anal. Calcd for $C_{20}H_{26}N_2O_2$: *m/e* 326.1994. Found: *m/e* 326.1995.

11,13-Diaza-11,13-dimethyl-12,14-dioxo-3-oxa-5α,9α,10β,15α-tetracyclo[7.5.1.0^{1,10}0^{5,15}]pentadecane (14). A solution of 3-hydroxymethylcyclohexene[43] (2.13 g, 19.0 mmol) in 25 mL of dry THF was treated with 100% NaH (0.637 g, 26.5 mmol) and stirred at room temperature until gas evolution ceased (1 h), then treated with 5-chloromethyl-1,3-dimethyluracil[44] (2.824 g, 15.0 mmol) and allowed to stir at room temperature for 3 h. The solution was then filtered through celite and concentrated to give a yellowish liquid. Examination by TLC (ethyl acetate, SiO_2) revealed a single product contaminated by a minor amount of starting alcohol. Since the product is only slightly more polar than the starting alcohol, chromatographic separation would be difficult at this stage, so the crude product mixture was acetylated by stirring with acetic anhydride (2.05 g, 20.1 mmol) and pyridine (3.17 g, 40.2 mmol) in 10 mL of methylene chloride at room temperature for 24 h. The reaction mixture was then worked up as usual to give 2.675 g of a yellow oil, which was chromatographed on 150 g of silica gel to afford a colorless oil: yield, 1.480 g (5.61 mmol, 37%); NMR (60 MHz) 1.5–1.8 (4 H, mults), 1.93 (3 H, mult), 3.35 (3 H, s), 3.42 (3H, s), 3.42 (2 H, d, J = 5 Hz), 4.27 (2 H, d, J = 1 Hz), 5.67 (2 H, br s), 7.22 (1 H, t, J = 1 Hz); IR (film) 1640–1660, 1705; MS (EI) 264 (M^+, 3%), 153 (100); UV (CH_3CN) λ_{max} 267 nm. A solution of the above oil (1.150 g, 4.36 mmol) and acetone (12.2 g, 0.211 mol) in 408 mL of CH_3CN was degassed with nitrogen, then photolyzed internally through a Pyrex filter until all the starting material had been consumed (11 h). The solvents were then removed in vacuo to leave 1.10 g of a yellow oil, completely pure by TLC (ethyl acetate, silica gel) and NMR. Chromatography on 70 g of silica gel (2:1 chloroform/ethyl acetate eluent) gave a white solid, mp 89–94 °C, homogeneous on GC (5% SE-30, 250 °C, R_t = 9.4 min) and TLC. Yield: 0.750 g (2.84 mmol, 65%). Two recrystallizations from ethyl acetate/hexane gave colorless prisms, mp 111.5–113.5 °C; NMR (220 MHz) 1.23 (1 H, br mult), 1.40–1.65 (3 H, mult), 1.75–1.95 (3 H, mult), 2.60 (1 H, dq, J = 2, 10 Hz), 2.77 (1 H, t, J = 10 Hz), 3.08 (3 H, s), 3.21 (3 H, s), 3.54 (1 H, d, J = 12 Hz), 3.58 (1 H, d, J = 12 Hz), 3.63 (1 H, d, J = 8 Hz), 3.74 (1 H, d, J = 12 Hz), 3.83 (1 H, d, J = 12 Hz); ^{13}C NMR ($CDCl_3$) 21.12, 24.74, 27.62, 28.08, 29.46, 32.16, 35.25, 36.90, 43.97, 60.51, 69.63, 70.27, 208.6, 210.9; IR (KBr) 1660, 1705; MS (EI) 264 (M^+, 3%), 153 (100); UV (CH_3CN) end absorption only. Anal. Calcd for $C_{14}H_{20}O_3N_2$: C, 63.62; H, 7.63. Found: C, 63.38; H, 7.62.

4-Hydroxycyclohexene. A solution of 2,5-dihydroanisole[45] (33.16 g, 0.301 mol) in 300 mL of ether was added to a solution of 20.0 g of acetic acid in 300 mL of water. The two-phase mixture was stirred vigorously until the hydrolysis was complete (33 h) by TLC (chloroform, SiO_2). The acetic acid was then neutralized with solid $NaHCO_3$ (45.0 g, 0.536 mol), the ether layer separated, and the aqueous layer extracted with ether (2 × 100 mL). The combined extracts were then dried ($MgSO_4$) and concentrated carefully by Rotovap to leave a colorless liquid: NMR (60 MHz) 2.50 (4 H, br s), 2.90 (2 H, br s), 5.90 (2 H, br s); IR (film) 1730. A solution of the above liquid in 200 mL of ether was added dropwise to a mechanically stirred, ice-cooled suspension of LAH (20.0 g, 0.527 mol) in 300 mL of ether. After the addition was complete (30 min), the reaction mixture was allowed to stir at room temperature for 9 h, then recooled to 0 °C and quenched successively with 20 mL of water, 20 mL of 15% NaOH, and 60 mL of water. The reaction mixture was then stirred until the gray precipitate had turned white, then filtered. The ether was then removed by Rotovap and the residual colorless liquid distilled (94–96 °C/58 mm) to give another colorless liquid: yield, 23.53 g (0.240 mol, 80%); NMR (60 MHz) 1.5–2.0 (2 H, mult), 2.0–2.4 (4 H, envelope), 3.60 (1 H, s; disappears on addition of D_2O), 3.93 (1 H, mult), 5.72 (2 H, br s); IR (film) 1660 (weak), 3300; MS (EI) 98 (M^+, 3%), 80 (100).

7-Aza-12-oxa-6,8,13-trioxo-1α,4α,5α,9α,10α-tetracyclo[5.4.3.0^{4,10}.0^{5,9}]tetradecane (21). A solution of ester **20**[46] (4.542 g, 19.34 mmol) in 420 mL of acetone was degassed with nitrogen, then photolyzed internally through a Pyrex filter until TLC (15% ethyl acetate/chloroform, SiO_2) analysis indicated the absence of starting material (1.5 h). The solvent was then removed in vacuo to leave a glass, which consisted of one component plus polar garbage by TLC. Chromatography on 110 g of silica gel (1:1 ethyl acetate/chloroform eluent) furnished a white solid. Yield: 1.632 g (6.95 mmol, 36%). Recrystallization from ethyl acetate/cyclohexane gave a white crystalline powder, mp 162–164 °C (dec to a colorless oil, immobile on TLC); NMR (60 MHz) 1.2–2.1 (6 H, envelope), 3.0–3.6 (4 H, br s), 4.07 (1 H, d, J = 15 Hz), 4.50 (1 H, d, J = 15 Hz), 4.90 (1 H, br s); IR (KBr) 1705, 1758; MS (CI) 236 (M^+ + 1, 100%); UV (CH_3CN) end absorption only. Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57. Found: C, 61.07; H, 5.61.

7-Aza-3β-carbomethoxy-2α-methoxy-12-oxa-6,8,13-trioxo-1α,4α,5α,9α,10α-tetracyclo[5.4.3.0^{4,10}.0^{5,0}]tetradecane (23). A solution of ester **22**[47] (0.351 g, 1.087 mmol) and acetone (12.2 g, 0.211 mol) in 408 mL of methylene chloride was degassed with nitrogen and then photolyzed internally through a Pyrex filter for 2 h, at which time a TLC (30% ethyl acetate/chloroform, SiO_2) indicated the absence of starting material and formation of one major product with both more polar and less polar contaminants. The solvents were then removed in vacuo to leave 0.637 g of a colorless oil, which was chromatographed on 20 g of silica gel (25% ethyl acetate/chloroform eluent) to furnish a colorless oil which crystallized on standing. Yield: 0.131 g (0.406 mmol, 37%). Recrystallization from chloroform/ethyl acetate gave prisms, mp 185–188 °C; NMR (100 MHz) 1.8–1.9 (2 H, mult), 3.00 (1 H, dd, J = 11, 1 Hz), 3.34 (3 H, s), 3.2–4.1 (4 H, several partially obscured symmetrical mults), 3.86 (3 H, s), 4.17 (1 H, dd, J = 4, 1 Hz), 4.22 (1 H, d, J = 15 Hz), 4.54 (1 H, d, J = 15 Hz), 5.08 (1 H, dt, J = 4, 3 Hz; simplifies to t, J = 3 Hz on irr at 4.17; simplifies to d, J = 4 Hz on irr at 1.8–1.9); IR (KBr) 1700, 1730, 1740, 1765; MS (EI) 323 (M^+, 3%), 109 (100). Anal. Calcd for $C_{15}H_{17}NO_7$: C, 55.73; H, 5.30. Found: C, 55.56; H, 5.30.

5-Cyclohexen-4'-yloxy-2,5-dihydro-5-methyl-2-oxofuran (26). A solution of *cis*-β-acetylacrylic acid, pseudo-acid bromide[38] (2.244 g, 12.69 mmol) and 4-hydroxycyclohexene (1.116 g, 11.39 mmol) in 21 mL of methylene chloride was stirred over crushed $CaSO_4$ (6.04 g, 44.4 mmol) for 10 min, then treated with silver oxide (2.859 g, 12.32 mmol) and stirred at room temperature for 12.5 h, at which time both starting materials had been consumed by TLC (CH_2Cl_2, SiO_2). The crude reaction mixture was then filtered through celite and concentrated to give 2.428 g of a yellow oil. Chromatography on 46 g of SiO_2 ($CHCl_3$ eluent) gave a slightly yellow oil: yield, 1.628 g (8.39 mmol, 74%); NMR (60MHz) 1.6–1.9 (2 H, mults), 1.67 (3 H, s), 1.9–2.3 (4 H, envelope), 3.68 (1 H, mult), 5.60 (2 H, br s), 6.18 (1 H, d, J = 6 Hz), 7.12 (0.5 H, d, J = 6 Hz), 7.14 (0.5 H, d, J = 6); IR (film) 1765; MS (EI) 194 (M^+, 5%), 97 (100).

7,12-Dioxa-8α-methyl-6-oxo-1α,4α,5α,9α,10α-tetracyclo[6.3.1.0^{4,10}.0^{5,9}]dodecane (27). A solution of pseudoester **26** (0.984 g, 5.08 mmol) in 420 mL of acetone was degassed with nitrogen, then photolyzed internally through a Pyrex filter until a TLC (CH_2Cl_2, SiO_2) indicated that the reaction was complete (5 h). The photolysate was then concentrated to a yellow oil weighing 1.288 g. Column chromatography on 26 g of SiO_2 (2% ethyl acetate/chloroform eluent) afforded a white solid, homogeneous by TLC but not quite homogeneous by NMR. Yield: 0.221 g. Three recrystallizations from ethyl acetate/hexane gave white prisms, mp 121–124 °C, still slightly impure by NMR: NMR (100 MHz) 1.59 (3 H, s), 1.5–2.5 (6 H, envelope), 2.90 (3 H, mults), 3.36 (1 H, mult), 4.35 (1 H, mult); IR (KBr) 1755; MS (EI) 194 (M^+, 7%), 43 (100). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.87; H, 7.33.

8α-Acetyl-7β-carbomethoxy-3βhydroxy-1α,6α-bicyclo[4.2.0]octane (28). A solution of cyclobutane **27** (0.982 g, ≤ 5.06 mmol) in 15 mL of methanol was treated with 15 drops of concentrated H_2SO_4 and the solution refluxed for 19 h, then quenched with solid $NaHCO_3$ (1.666 g, 19.84 mmol). The methanol was then removed in vacuo and the off-white solid residue extracted with 50 mL of methylene chloride; evaporation of the methylene chloride afforded 1.116 g of a yellow oil, consisting of one major and several minor, less polar, components by TLC (ethyl acetate, SiO_2). The major component was isolated in pure form as a yellow oil by column chromatography (20 g of SiO_2, 10% ethyl acetate/chloroform eluent): yield, 0.700 g (3.10 mmol, ≥61%); NMR (100 MHz) 1.4–1.9 (6 H, envelope), 2.14 (3 H, s),

2.2–2.6 (2 H, obscured mults), 2.40 (1 H, br s), 3.21 (1 H, dd, J = 9.5, 7.5 Hz), 3.66 (3 H, s), 3.87 (1 H, t, J = 9.5 Hz), 4.06 (1 H, quint, J = 3.5 Hz); IR (film) 1705, 1735, 3470; MS (EI) 226 (M^+, 8%), 43 (100); Anal. Calcd for $C_{12}H_{18}O_4$: *m/e* 226.1205. Found: *m/e* 226.1210.

8α-Acetoxy-7β-carbomethoxy-3β-hydroxy-1α,6α-bicyclo[4.2.0]-octane (29). A solution of methyl ketone **28** (0.354 g, 1.57 mmol) in 5 mL of methylene chloride, stirred over solid Na_2HPO_4 (1.43 g, 10.1 mmol), was cooled to 0 °C and treated with a solution of trifluoroperacetic acid[48] in methylene chloride, prepared by stirring 90% H_2O_2 (0.141 g, 3.73 mmol) and trifluoroacetic anhydride (0.785 g, 3.74 mmol) together in 4 mL of methylene chloride at room temperature for 30 min. The reaction mixture was stirred at room temperature for 3 h, then poured into a solution of 5 g of Na_2CO_3 and 5 g of Na_2SO_3 in 70 mL of water and extracted with methylene chloride (2 × 25 mL). The extracts were dried ($MgSO_4$), then concentrated to a yellow oil weighing 0.400 g, essentially pure by NMR and TLC (1:1 ethyl acetate/chloroform, SiO_2). Column chromatography on 10 g of SiO_2 (10% ethyl acetate/chloroform eluent) afforded a pale yellow oil: yield, 0.332 g (1.370 mmol, 87%); NMR (100 MHz) 1.1–2.7 (8 H, mults), 2.03 (3 H, s), 2.22 (1 H, br s), 3.06 (1 H, t, J = 8.5 Hz), 3.67 (3 H, s), 4.09 (1 H, quint, J = 3.5 Hz), 5.56 (1 H, t, J = 8.5 Hz); IR (film) 1735, 3470; MS (CI) 243 (M^+ + 1, 100%). Anal. Calcd for $C_{12}H_{18}O_5$: *m/e* 242.1154. Found: *m/e* 242.1160.

7β-Carbomethoxy-3β,8α-dihydroxy-1α,6α-bicyclo[4.2.0]octane (30). A solution of acetoxycyclobutane **29** (0.296 g, 1.22 mmol) in 15 mL of methanol was treated with 15 drops of concentrated H_2SO_4 and stirred at room temperature for 1.5 h, at which time a TLC (ethyl acetate, SiO_2) indicated the absence of starting material. The acid was then quenched with 2.0 g of solid $NaHCO_3$, the methanol evaporated, and the white solid residue thoroughly extracted with 50 mL of methylene chloride; evaporation of the methylene chloride then afforded a viscous, pale yellow oil: yield, 0.208 g (1.04 mmol, 85%); NMR (60 MHz, $CDCl_3$ + D_2O) 1.4–1.9 (6 H, envelope), 2.0–2.6 (2 H, mults), 2.83 (1 H, t, J = 7 Hz), 3.67 (3 H, s), 4.07 (1 H, br s), 4.71 (1 H, t, J = 8 Hz); IR (film) 1730, 3200–3550; MS (CI) 201 (M^+ + 1, 43%), 183 (100). A solution of cyclobutanol **30** (28 mg) and 3 mL of triethylamine in 5 mL of benzene was refluxed for 22 h, then concentrated to a yellow oil, identical with the starting material by NMR.

2β-Carbomethoxymethyl-7α-methoxy-6-oxa-1α,5α-bicyclo[3.2.1]-octane (31). A solution of acetoxycyclobutane **29** (from 0.787 mmol of **28**) in 7 mL of methanol was treated with 7 drops of concentrated H_2SO_4 and refluxed until a TLC (1:1 ethyl acetate/chloroform, SiO_2) indicated that disappearance of **30** was complete (14 h). The sulfuric acid was then quenched with solid $NaHCO_3$ (0.91 g), the methanol evaporated, and the solid residue chromatographed on 10 g of silica gel (chloroform eluent) to afford a pale yellow oil: yield, 0.107 g (0.499 mmol, 63% from **28**); NMR (60 MHz) 1.2–2.4 (10 H, envelope), 3.32 (3 H, s), 3.66 (3 H, s), 4.47 (1 H, t, J = 5 Hz), 4.77 (1 H, s); IR (film) 1735; MS (CI) 215 (M^+ + 1, 11%), 185 (100), 184 (100).

2β-Carbomethoxymethyl-6-oxa-7-oxo-1α,5α-bicyclo[3.2.1]octane (32). A solution of lactol methyl ether **31** (18 mg, 0.082 mmol) in 5 mL of acetone was treated with 0.5 mL of Jones' reagent and stirred at room temperature for 15 h. The reaction mixture was then quenched with 1.5 mL of isopropyl alcohol, poured into 50 mL of 5% $NaHCO_3$, and extracted with methylene chloride (2 × 25 mL). The extracts were dried ($MgSO_4$) and concentrated to a yellow oil weighing 18 mg. Chromatography of 38 mg of crude lactone (from two experiments) on 9 g of SiO_2 (chloroform eluent) afforded a yellow oil. Yield: 25 mg (0.127 mmol, 74%). Crystallization from ethyl acetate/hexane gave fine white needles, mp 83–85 °C; NMR (60 MHz) 1.3–2.7 (10 H, mults), 3.68 (3 H, s), 4.83 (1 H, mult); IR (KBr) 1730, 1765; MS (EI) 198 (M^+, 38%), 80 (100). The NMR, IR, MS, melting point, and TLC mobility (2:1 chloroform/ethyl acetate, SiO_2) of this product were absolutely identical with those of a sample prepared by the route of Bellau.[41] On melting together and resolidification at −78 °C, the melting point was undepressed: 84–86 °C.

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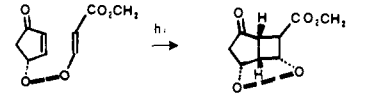
(22) M. Tada, T. Kokubo, and T. Sato, *Bull. Chem. Soc. Jpn.*, **43**, 2162 (1970).
(23) H. von Pechmann, *Ann.*, **264**, 261 (1891).
(24) One alternative to the search for a photochemical equivalent of formyl acetic ester (applicable for the synthesis of **3** but not **1**) is to use some derivative of formyl acetic ester as the unactivated double bond partner in the [2 + 2] cycloaddition, as sketched below.



Indeed, recently two groups (T. Ogino, K. Yamada, and K. I. Sogai, *Tetrahedron Lett.*, 2445 (1977); M. Van Audenhove, D. Termont, D. De Keukeleire, M. Vandewalle, and M. Claeys, *ibid.*, 2057 (1978)) have reported that cyclopentenone does photoadd intermolecularly to various enol derivatives of formyl acetic ester to afford cyclobutane-containing adducts which are transformable into C-11 deoxy analogues of **3**. Nonetheless, the finding of a suitable photochemical equivalent of formyl acetic ester might still be useful because, with such a reagent, *cis*-cyclopentene-3,5-diol could be exploited as the starting material.
(25) (a) A. Wacker, D. Weinblum, L. Trager, and Z. H. Moustafa, *J. Mol. Biol.*, **3**, 790 (1961); (b) D. Elad, C. Kruger, and G. M. J. Schmidt, *Photochem. Photobiol.*, **6**, 495 (1967); (c) G. Fuerst, E. Fahr, and H. Wieser, *Z. Naturforsch. B*, **22**, 354 (1967).
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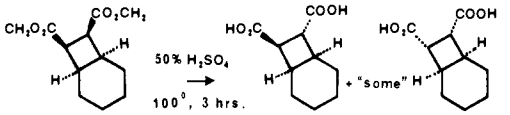
(27) We tentatively assign the cis-anti-cis structure to the major isomer **6** and the cis-syn-cis structure to the minor isomer **7** by analogy with the reports (G. O. Schenck, J. Kuhls, and C. H. Krauch, *Ann.*, **693**, 20 (1966); R. Robson, P. W. Grubb, and J. A. Barltrop, *J. Chem. Soc.*, 2153 (1964)) that the major (49%) and minor (34%) maleic anhydride/cyclohexene photoadducts are respectively the cis-anti-cis and the cis-syn-cis isomers. Further support for these assignments is provided by the fact that the major isomer **6**

undergoes hydrolysis to a urea-acid in mild base (2.8 N NaOH, 45 °C, 2 days), whereas the minor isomer resists both hydrolysis and epimerization even under much more forcing conditions (10 N NaOH, 70 °C, 2 days), assuming an analogy with the report (T. Kunieda and B. Witkop, *J. Am. Chem. Soc.*, **93**, 3478, 3493 (1971)) that head-to-tail *exo*-thymine dimer hydrolyzes in aqueous base much more readily than does head-to-head *endo*-thymine dimer.
(28) 5% SE-30, 170 °C; R_t(**10t**) = 9.7 min; R_t (**10c**) = 10.9 min.
(29) Prepared from 11 (F. V. Brutcher and D. D. Rosenfeld, *J. Org. Chem.*, **29**, 3154 (1964)) by catalytic hydrogenation followed by LAH reduction.
(30) Prepared from **12** (G. Stork and R. K. Hill, *J. Am. Chem. Soc.*, **79**, 495 (1957)) by LAH reduction.
(31) These results will be the subject of a forthcoming paper.
(32) See C. Galli, G. Illuminati, and L. Mandolini, *J. Am. Chem. Soc.*, **95**, 8374 (1973), and references cited therein.
(33) J. Put and F. C. De Schryver, *J. Am. Chem. Soc.*, **95**, 137 (1973).
(34) The rate of hydrolysis of esters decreases with increasing steric hindrance in base (see E. A. S. Cavell, N.B. Chapman, and M. D. Johnson, *J. Chem. Soc.*, 1413 (1960); E. L. Eliel, H. Haubenstock, and R. V. Acharya, *J. Am. Chem. Soc.*, **83**, 2351 (1961); also, footnote 27) and in dilute acid (N. B. Chapman, J. Shorter, and K. J. Toyne, *J. Chem. Soc.*, 2543 (1961)), although the rate increases with increasing steric hindrance in 95% H_2SO_4 (H. Van Bekkum, H. M. A. Buurmans, B. M. Wepster, and A. M. Van Wijk, *Recl. Trav. Chim. Pays-Bas*, **88**, 301 (1969)).
(35) Prepared from cyclohexen-4-yl bromoacetate and 2,4-bis(trimethylsiloxy)pyrimidine by the procedure of E. Wittenburg, *Chem. Ber.*, **101**, 2132 (1968).
(36) (a) H. Yoshioka, T. J. Mabry, and A. Higo, *J. Am. Chem. Soc.*, **92**, 923 (1970); (b) K. Ohga and T. Matsuo, *Bull. Chem. Soc. Jpn.*, **43**, 3505 (1970).
(37) Bruce A. Pearlman, *J. Am. Chem. Soc.*, following paper in this issue.
(38) G. Fuchs and N. Hellstrom, *Lantbrukshoegsk. Ann.*, **30**, 615 (1964); *Chem. Abstr.*, **63**, 6850g (1965).
(39) The acetyl substituent of **28** is presumed to have the exo configuration because it is expected to enolize under the reaction conditions (H. Schechter, M. J. Collis, R. Dessy, Y. Okuzumi, and A. Chen, *J. Am. Chem. Soc.*, **84**, 2905 (1962)), and the exo isomer is expected to be more stable than the endo isomer by analogy with the result indicated below (R. Robson, P. W. Grubb, and J. A. Barltrop, *J. Chem. Soc.*, 2153 (1964)).



(40) B. E. Cross, J. F. Grove, and A. Morrison, *J. Chem. Soc.*, 2498 (1961).
(41) B. Bellau and D. Dvornik, *Can. J. Chem.*, **43**, 2545 (1965).
(42) D. Davidson and O. Baudisch, *J. Am. Chem. Soc.*, **48**, 2379 (1926).
(43) Prepared by LAH reduction (ether, Δ, 19 h, 90%) of cyclohexene-3-carboxylic acid, which was prepared by a double-Birch reduction of benzoic acid by using the procedure developed by F. Camps, J. Coll, and J. Pascual (*J. Org. Chem.*, **32**, 2563 (1967)) for double-Birch reductions of substituted benzoic acids.
(44) Prepared from 5-hydroxymethyluracil (R. E. Cline, R. M. Fink, and K. Fink, *J. Am. Chem. Soc.*, **81**, 2521 (1959)) by treatment with excess ethereal CH_2N_2 in methanol at room temperature followed by stirring in neat $SOCl_2$ at room temperature for 3 h.
(45) (a) A. J. Birch, *J. Chem. Soc.*, 593 (1946); (b) A. J. Birch and G. Subba Rao, *Adv. Org. Chem.*, **8**, 1 (1972).
(46) Prepared in 77% yield by treatment of a cold (−78 °C) solution of 4-hydroxycyclohexene and 1.2 equiv of maleoylglycyl chloride (L. Paul, A. Dittmar, and C. Rusch, *Chem. Ber.*, **100**, 2757 (1967)) in methylene chloride with 1.4 equiv of triethylamine followed by warming to room temperature.
(47) Prepared in 61% yield by treatment of an ice-cooled solution of **5**[37] and 1.4 equiv of maleoylglycyl chloride in methylene chloride with 2.0 equiv of triethylamine.
(48) W. D. Emmons and G. B. Lucas, *J. Am. Chem. Soc.*, **77**, 2287 (1955).

A Total Synthesis of Reserpine[1a]

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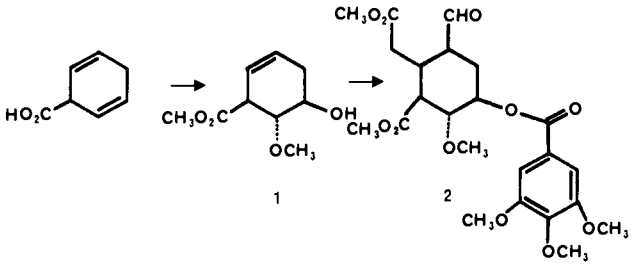
Abstract: Woodward reserpine precursor **2** has been synthesized from 1,4-dihydrobenzoic acid, using the novel methodology described in the preceding paper.

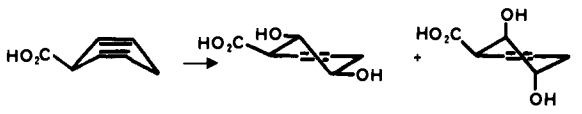
Introduction

The preceding paper[2] describes a method for effecting the equivalent of a de Mayo reaction with formyl acetic ester. In this paper, we report that application of this method to olefin **1** affords Woodward reserpine precursor **2**, and that olefin **1** is available by a short (four step) sequence from 1,4-dihydrobenzoic acid.



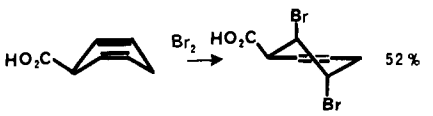
1 2

Synthesis of 1. The strategy of using 1,4-dihydrobenzoic acid[3] (see Experimental Section for an improved method of preparation) as the starting material for preparation of **1** is superficially attractive because the only difference between **1** and 1,4-dihydrobenzoic acid is that the former has two oxygen functionalities instead of a double bond. Moreover, this strategy is advantageous in practice: treatment of 1,4-dihydrobenzoic acid with 1 equiv of performic acid at room temperature for 30 h, then at reflux for 1 h, followed by boiling in water for 4.5 h (to hydrolyze the formates) affords the desired "diequatorial" diol **3** in multi-gram quantities.



3 4

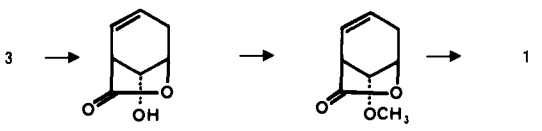
Presumably, the undesired "diaxial" isomer **4** is the major product of this reaction,[4] by analogy with the report that the major product of bromination of 1,4-dihydrobenzoic acid is the diaxial isomer **5**.[5] However, **3** is formed in sufficiently high



5

yield that this method of preparation is attractive.

Of course, diol **3** is of no value unless its C-4 hydroxyl can be selectively methylated. However, in fact, this can be accomplished straightforwardly by the sequence of thermolysis (180 °C, 1.5 h), methyl etherification (Ag_2O, CH_3I, crushed $CaSO_4$),[6] and methanolysis (H_2SO_4, CH_3OH, Δ, 2 h).



6 7

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