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**Registry No.** 1, 87174-91-2; 2, 87174-92-3; 3, 87174-93-4; 4, 87174-94-5; 5, 87174-95-6.

**Supplementary Material Available:** Listings of atomic coordinates, anisotropic thermal parameters, bond lengths, and bond angles (12 pages). Ordering information is given on any current masthead page.

# Studies in Cephalotaxus Alkaloids. Stereospecific Total Synthesis of Homoharringtonine

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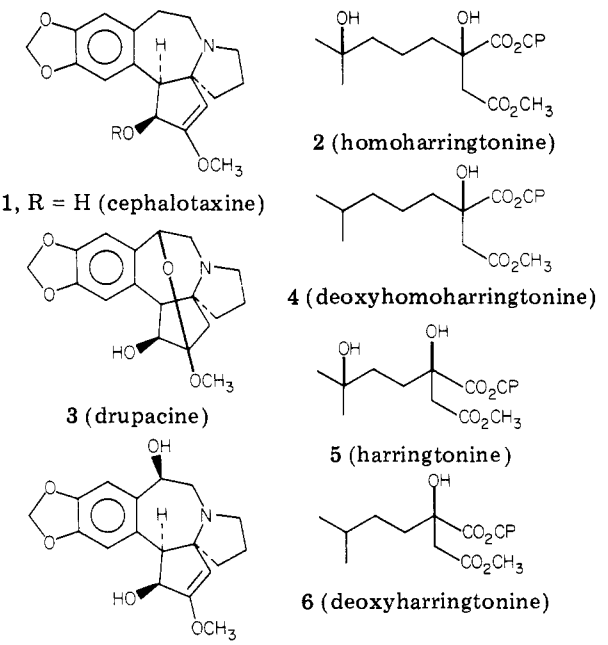
The alkaloid ester homoharringtonine (**2**) was synthesized stereospecifically via the Reformatsky reaction of methyl α-bromoacetate with cephalotaxyl pyruvate (**16**) obtained by esterification of cephalotaxine with acid chloride derived from **15**. The preparations of **2** and its unsaturated derivative **13** are described in detail. Possible explanations of the steric requirements in the esterification of cephalotaxine and of the steric outcome of the Reformatsky reaction leading to **2** and **13** are advanced.

## Introduction

During the last decade the esters of the unusual homoerythrina alkaloid cephalotaxine (**1**, Chart I) have been scrutinized not only by the medical profession searching for antitumor activities but also by the community of synthetic chemists attracted by the unique structures of these alkaloids. Following their isolation from various species of *Cephalotaxus* native to Japan and China, most notably from the evergreen bush *Cephalotaxus harringtonia* and *Cephalotaxus drupacea* and *Cephalotaxus fortunei*,[2] the alkaloids have been subjected to a number of structural,[3] biosynthetic,[4] and synthetic studies.[5,6]

Chart I[a]




[a] CP = cephalotaxyl.

Some of the cephalotaxine esters have been prepared from the parent alkaloid by sequential esterification: the

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(2) *Initial detection*: (a) Wall, M. E. *J. Am. Pharm. Assoc.* **1954**, *43*, 505. *Isolation and partial structure*: (b) Paudler, W. W.; Kerley, G. I.; McKay, J. *J. Org. Chem.* **1963**, *28*, 2194. Isolation of harringtonines: (c) Powell, R. G.; Weisleder, D.; Smith, C. R., Jr., Rohwedder, W. K. *Tetrahedron Lett.* **1970**, 815. (d) Powell, R. G.; Rogovin, S. P.; Smith, C. R., Jr. *Ind. Eng. Chem. Prod. Res. Dev.* **1974**, *13*, 129.

(3) *Cephalotaxine*: (a) Powell, R. G.; Weisleder, D.; Smith, C. R., Jr.; Wolff, I. A. *Tetrahedron Lett.* **1969**, 4081. (b) Abraham, D. J.; Rosenstein, R. D.; McGandy, E. L. *Ibid.* **1969**, 4085 (X-ray). (c) Arora, S. K.; Bates, R. B.; Grady, R. A.; Powell, R. G. *J. Org. Chem.* **1974**, *39*, 1269. (d) Arora, S. K.; Bates, R. B.; Grady, R. A.; Germain, G.; Declercq, J. P.; Powell, R. G. *Ibid.* **1976**, *41*, 551 (X-ray). (e) Paudler, W. W.; McKay, J. *Ibid.* **1973**, *38*, 2110 (minor constituents of cephalotaxus). (f) Weisleder, D.; Powell, R. G.; Smith, C. R., Jr. *Org. Magn. Res.* **1980**, *13*, 114 ($^{13}C$ NMR). *Cephalotaxine esters*: (g) Reference 2c above for harringtonine, isoharringtonine, homoharringtonine; ref 2d for desoxyharringtonine. See also ref 6c for the latest excellent summary of bibliography regarding isolation, structure, and synthesis of cephalotaxine esters. *Relative and absolute configuration of side-chain acids*: (h) Ipaktchi, T.; Weinreb, S. M. *Tetrahedron Lett.* **1973**, 3895 (relative configuration in isoharringtonine). (j) Brandrange, S.; Josephson, S.; Vallen, S. *Acta Chem. Scand. B* **1974**, *28*, 153 (absolute Configuration of side-chain acids for *all* cephalotaxine esters).

(4) *Biosynthetic studies*. See for example: (a) Gitterman, A.; Parry, R. J.; Durfresne, R. F.; Sternbach, D. D.; Cabelli, M. D. *J. Am. Chem. Soc.* **1980**, *102*, 2074. (b) Schwab, J. M.; Chang, M. N. T.; Parry, R. J. *Ibid.* **1977**, *99*, 2368.

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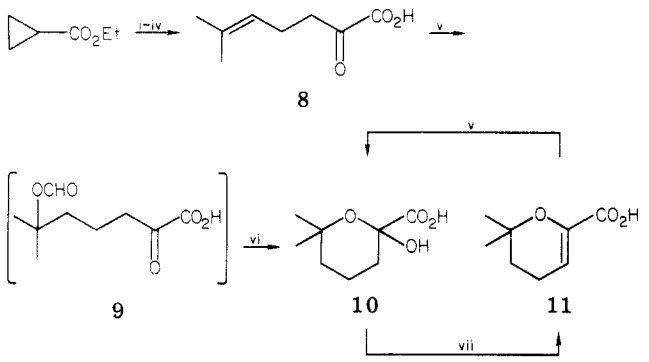
Chart II[a]




[a] Reagents: i, 2MeMgBr/$Et_2O$; ii, HBr (48%); iii, Mg/THF/$(CO_2Et)_2$; iv, KOH/$H_2O$; v, $HCO_2H/HClO_4/\Delta$; vi, $NaOH/H_2O/\Delta$; vii, $HCl/H_2O$.

hindered hydroxyl of cephalotaxine was esterified by a suitable fragment equipped with a functionality that permitted the attachment of the remaining moieties. The esters of 1 (with the exception of 2 and 4) have been attained by the application of the above method. Homoharringtonine (2) was synthesized in 1981 and 1982 by three independent reports,[7-9] while deoxyhomoharringtonine, although unsynthesized to date, becomes available through hydrogenation of 13.

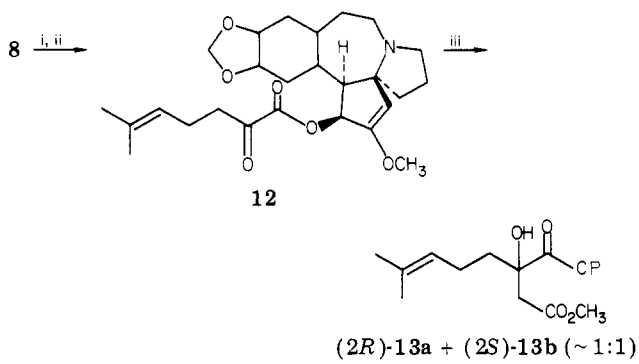
## Results and Discussion

We chose sequential esterification of cephalotaxine as our approach to 2 following the lack of success in other attempts.[10]

On the basis of a report dealing with the synthesis of deoxyharringtonine, we decided to use the Reformatsky reaction as the means of introducing the side-chain methyl acetate fragment.[5n] The olefinic acid 8[11] was selected as a convenient agent for the esterification of 1 since its carboxylic group was relatively unhindered and since its terminal olefin could be manipulated oxidatively either before or after joining with cephalotaxine.[12]

The acid was prepared in good yield from ethyl cyclopropanecarboxylate as outlined in Chart II. Interaction of the cyclopropyl ester with 2 equiv of MeMgI yielded a tertiary carbinol, which was rearranged to 4-methylpent-3-enyl bromide in aqueous HBr.[13] Exposure of the Grignard reagent derived from this halide to diethyl oxalate gave, after hydrolysis, the required acid 8. Some byproducts of the Grignard reaction and some rearrangement products from the attempted purification of the ethyl ester of 8 were identified.[12] We attempted functionalization at the olefinic site of 8 but failed to do so[12] in all instances but the formylation depicted in Chart II. We were able to utilize the dihydropyran 10 and the hydroxy acid 11 in subsequent syntheses of homoharringtonine. The pyran derivatives produced in the formylation of 8 proved to be interconvertible depending on the reaction and workup conditions employed (see Experimental Section).

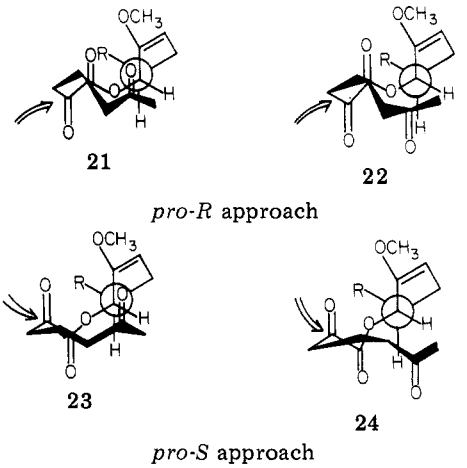
Chart III[a]




(2R)-13a + (2S)-13b (~1:1)

[a] Reagents: i, $(COCl)_2$; ii, cephalotaxine/pyridine/$CH_2Cl_2$/(dimethylamino)pyridine; iii, $ZnCl_2$/K/THF/$BrCH_2CO_2CH_3$. CP = cephalotaxyl.

Scheme I[a]




[a] R = aromatic part of cephalotaxine.

(5) *Synthesis. Cephalotaxine*: (a) Auerbach, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1972**, *94*, 7172; **1975**, *97*, 2503. (b) Semmelhack, M. F.; Chong, B. P.; Jones, L. D. *Ibid.* **1972**, *94*, 8629. (c) Semmelhack, M. F.; Stauffer, R. D.; Rogerson, T. D. *Tetrahedron Lett.* **1973**, 4519. (d) Semmelhack, M. F.; Chong, B. P.; Stauffer, R. D.; Rogerson, T. D.; Chong, A.; Jones, L. D. *J. Am. Chem. Soc.* **1974**, *96*, 2507. Incomplete syntheses or approaches: (e) Dolby, L. J.; Nelson, S. J.; Senkovich, D. *J. Org. Chem.* **1972**, *37*, 3691. (f) Weinstein, B.; Craig, A. R. *J. Org. Chem.* **1976**, *41*, 875. (g) Tse, I.; Snieckus, V. *J. Chem. Soc., Chem. Commun.* **1976**, 505. *Side Chain Acids*: (h) Kelly, T. R.; McKenna, J. C.; Christenson, P. A. *Tetrahedron Lett.* **1973**, 3501. (i) Auerbach, J.; Ipaktchi, T.; Weinreb, S. M. *Ibid.* **1973** 4561; also ref 3h above. (j) Bates, R. B.; Cutler, R. S.; Freeman, R. M. *J. Org. Chem.* **1977**, *42*, 4162. *Harringtonine*: (k) Kelly, T. R.; McNutt, R. W., Jr.; Montury, M.; Tosches, N. P.; Mikolajczak, K. L.; Smith, C. R.; Jr.; Weisleder, D. *Ibid.* **1979**, *44*, 63. (l) Mikolajczak, K. L.; Smith, C. R., Jr. *Ibid* **1978**, *43*, 4762. (m) Huang, W.-K.; et al., *Chem. Abstr.* **1977**, *86*, 171690e. Deoxyharringtonine: (n) Huang, W.-K.; Li, Y.-L.; Pan, X. *Scientia Sinica* **1980**, *23*, 835. (o) Li, S. W.; et al. *Chem. Abstr.* **1976**, *84*, 150812q. (p) Mikolajczak, K. L.; Smith, C. R., Jr.; Weisleder, D.; Kelly, T. R.; McKenna, J. C.; Christenson, P. A. *Tetrahedron Lett.* **1974**, 283. *Other esters of Cephalotaxine*: (q) Mikolajczak, K. L.; Smith, C. R., Jr.; Weisleder, D. *J. Med. Chem.* **1977**, *20*, 328.

(6) An excellent summary of synthetic and medicinal endeavors in the field of cephalotaxine esters is offered in the following references: (a) Weinreb, S. M.; Semmelhack, M. F. *Acc. Chem. Res.* **1975**, *8*, 158. (b) Footnotes in ref 5k above address numerous unpublished but nevertheless important experimental details regarding esterification studies. (c) Smith, C. R., Jr.; Mikolajczak, K. L.; Powell, R. G. In "Antitumor Agents Based on Natural Product Models"; Academic Press: New York, 1980; Chapter 11.

(7) Wang, Y. K.; Li, Y.-L.; Pan, H.-F.; Li, C. P.; Huang, W.-K. *Tongbao* **1980**, *25*, 624. (b) *K'o Hsueh T'Ung Pao* **1980**, *25*, 576; *Chem. Abstr.* **1981**, *94*, 103628f.

(8) Zhao, Z.-Z.; Xi, Y.-G.; Zhao, H.-F.; Hou, J.-Y.; Zhang, J.-Y.; Wang, Z.-H. *Yao Hsueh Hsueh Pao* **1980**, *15*, 46; *Chem. Abstr.* **1981**, *94*, 103627e.

(9) Hiranuma, S.; Hudlicky, T. *Tetrahedron Lett.* **1982**, 3431.

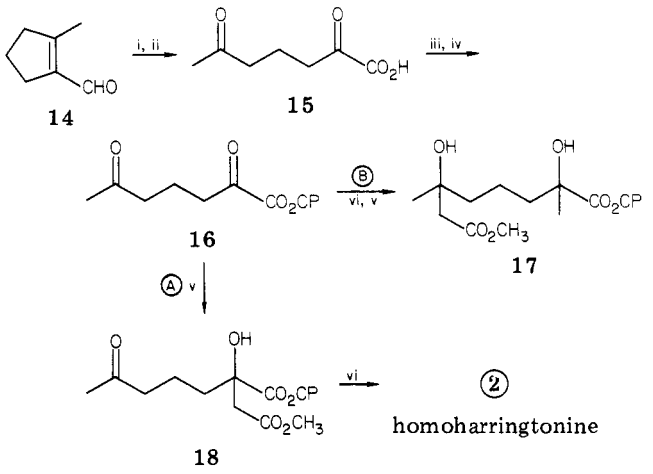
(10) We attempted a synthesis of hydroxycephalotaxine by direct oxidation of cephalotaxine as well as by a modification of the known cephalotaxine synthesis. Our negative results in this area can be found in the Supplementary Material section of this manuscript.

(11) An alternate preparation of this acid from 2-oxo-6,6-dimethylpyranone by acylation with diethyl oxalate has been reported in ref 8.

(12) Our attempts at the functionalization of acid 8 by hydration or epoxidation were unsuccessful as were any attempts to prepare 8 from already hydroxylated precursors. The negative results and the descriptions of any side reactions connected to the preparation and functionalization of 8 are contained in the supplementary material.

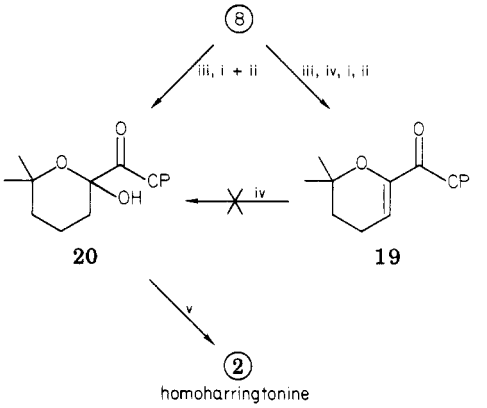
(13) Adapted from W. Oppolzer and G. Bird, private communication.

Scheme II[a]




[a] Reagents: i, $Ag_2O$; ii, $O_3/Me_2S$; iii, $(COCl)_2$; iv, cephalotaxine/pyridine/$CH_2Cl_2$; v, Zn/$BrCH_2CO_2Me$/THF; vi, MeMgI/−20 °C. CP = cephalotaxyl.

Chart IV[a]




[a] Reagents: i, $(COCl)_2$; ii, cephalotaxine/pyridine/$CH_2Cl_2$; iii, $HCO_2H/HClO_4$; iv, $HCl/H_2O$; v, Zn/$BrCH_2CO_2Me$/THF. CP = cephalotaxyl.

**Preparation of Dehydrodeoxyhomoharringtonine (13) (Chart III).** The exposure of acid **8** to oxalyl chloride gave the corresponding acyl halide, which smoothly acylated cephalotaxine in 70% under conditions obtained by a slight modification of a well-tested and documented method.[5k] Careful Reformatsky reaction[5m,n] (activated zinc prepared from anhydrous $ZnCl_2$ and potassium was used) of methyl $\alpha$-bromoacetate with **12** gave a mixture (in approximately 1:1 ratio) of two diastereomers, **13a** and **13b**, which were separable by preparative TLC. We assigned 3*R* configuration to **13a** and 3*S* to **13b** on the basis of the difference in their $^1H$ NMR spectra. Of the two diastereomers, **13a** resembled most closely the pattern observed for homoharringtonine or deoxyharringtonine,[5n] while the patterns of the methoxy groups and of the oxomethine for **13b** closely correspond with those of the deoxyharringtonine epimer.[5n] The configuration for C-3 in homoharringtonine has been established as *R*.[3j]

**Preparation of Homoharringtonine (2).**[14] The title compound was attained by a very *carefully controlled* sequence of reactions, starting with ester **16**. Examination of molecular models informed us that the chain of homoharringtonine (as well the size of **16**) is slightly longer than the effective length of the cephalotaxine nucleus. Allowing for approximately 180° domain of free rotation of this side chain, the terminal carbonyl group can be found quite unhindered when the side chain rotates *away* from the nucleus of the molecule. On the other hand, the pyruvate carbonyl is quite hindered *except* in *two* of the conformations of **16** depicted in Scheme I. It is likely that one of these conformations represents an energetic minimum for **16** although no calculations have been performed to test this supposition. We had hoped that any one of the following premises might hold for the interaction of **16** with incoming nucleophiles: (a) the terminal acetyl carbonyl is more available, (b) the pyruvate carbonyl, although hindered, is the more reactive one, and (c) use of divalent metals (Mg in the Grignard reagent, Zn in the Reformatsky reagent) may result in enhanced reactivity of the pyruvate not only because of coordination of these metals with the neighboring ester oxygen but also beause of the ideal proximity of the enol ether oxygen and the acetyl group for a possible crown ether like metal complexation of the three oxygens involved in the conformations shown in Scheme I. The ester **16** was attained in high yield by the esterification of cephalotaxine with the acyl chloride of acid **15**. This acid was in turn obtained from the oxidation/ozonolysis sequence of methyl cyclopentyl aldehyde **14**, which was abundant in our laboratories in connection with other projects (Scheme II).[15] Although the ester **16** was obtained in high yield, it was unstable to any purification procedures. It decomposed to cephalotaxine during an overnight attempt to record its $^{13}C$ NMR spectrum in $CDCl_3$. It was therefore freshly prepared and immediately used in the next step. The Reformatsky reaction performed on **16** gave an excellent yield of ketone **18**, which existed as a mixture of the carbonyl compound and its cyclic hemiacetal. This compound was previously reported in the literature as having arisen from the acid hydrolysis of its ethylene glycol ketal.[8,14] Treatment of **18** with 2 equiv of MeMgI at −20 °C gave back some cephalotaxine and a *single diastereomer* of homoharringtonine (**2**) in a modest yield. The alkaloid was purified by preparative TLC prior to the determination of its 300-MHz $^1H$ NMR spectrum, which was found to be superimposable on the spectrum of the natural product recorded on the same instrument and donated to us by R. Powell of USDA's Northern Regional Research Center in Peoria, IL. If the sequence of the two reactions above was reversed and the MeMgI reaction performed *first*, a compound was isolated that gave an NMR spectrum *similar* to homoharringtonine save the methoxy group pattern. It was identical with homoharringtonine on TLC and HPLC and was assigned the structure **17** rather than that of the other diastereomer of **2**, since it did not seem reasonable that *the order* of reactions would alter the steric course. Homoharringtonine obtained by path A in Scheme II was not accompanied by **17**; conversely, homoharringtonine was completely absent in the reaction mixtures containing **17** and obtained by path B above. From the fractions of preparative TLC, the material with lower $R_f$ than **2** was cephalotaxine. Any material with higher $R_f$ than **2** did not have convincing NMR patterns in the olefinic region to qualify as a diastereomer of **2**.

This surprising stereoselectivity (see the Conclusions part for a possible explanation) prompted us to consider

(14) We have also attempted to prepare **2** by the repetition of both published procedures (ref 7 and 8) but were unable to do so without the benefit of exact experimental details. In our hands, any conditions of acidic hydrolysis of hydration led to complete disintegration of cephalotaxine within minutes.

(15) Short, R. P.; Naqvi, S.; Srnak, A.; Hudlicky, T. unpublished results.

future improvements in the overall yield of homoharringtonine now obtainable in perhaps ~10% yield from cephalotaxine.

**Alternate Methods of Synthesis of 2.** The chloride of dihydropyranic acid **10** acylated cephalotaxine in nearly quantitative yield (probably because of its compact size) to give the ester **19** (Chart IV). To our surprise it proved also possible to obtain **20** by generating the acid chloride of **11** in the presence of cephalotaxine. Exposure of **20** (which could not be obtained by hydration of **19**, although such hydration has been reported to work quite well on the corresponding five-membered homologue[5l]) to the Reformatsky reagent derived from methyl bromoacetate gave homoharringtonine in a higher yield than that obtained in the sequence **16** → **18** → **2**. Although these reaction mixtures were much easier to handle (there appeared to be less cleavage to cephalotaxine during the Reformatsky reaction as compared to the Grignard reaction), we do not know the steric outcome of this reaction sequence at this time.

## Conclusions

We can now offer a few speculations regarding (a) the feasibility of esterification of cephalotaxine and (b) the remarkable difference in stereoselectivities observed during the additions to the carbonyl groups in **12** and **16**. Of the various conformations that the side chain can assume, the four "best guess" minima are depicted in Scheme I as **21–24**. In all of these, the side chain is almost perpendicular to the horizontal plane of the cephalotaxine nucleus. The extreme of this perpendicularity should represent the most stable conformation in the absence of coordinative forces. One can visualize a crown ether like coordination of the oxygens involved with the zinc complex of the Reformatsky reagent. In a transition state that is inclined toward *products*, the zinc moiety will be interacting with the incipient alkoxide. Such interaction will be possible only from one face of the pyruvate carbonyl (see arrows) since the other is blocked by the side chain, which, in turn, is coordinated through its acetyl moiety to the ester, the carbonyl, or the enol ether oxygens. Therefore the addition of the zinc reagent could possibly produce only one diastereomer, either *R* (through **21** or **22**) or *S* (via **23** or **24**). One will immediately note that *the only operational distinction* between the observed selectivity in the case of **16** and the complete lack thereof in **12** is the *terminal* functionality of their side chains. While the acetyl in **16** may be coordinatively held to the various oxygens, thereby blocking one face of the molecule as shown (incidently, any conformations of the side chain other than **21–24** are blocked by the aromatic nucleus), there is no such coordinative force for the olefin in **12**. Careful study of all of the reported partial esterifications of cephalotaxine revealed either saturated termini of the side chain or the presence of groups too large (ethylene ketal) to effectively coordinate to the oxygens. If the above reasoning with regard to Reformatsky reaction of the pyruvate is correct, then in all such molecules the preferred conformation would have been one with the side chain perpendicular to the cephalotaxine nucleus. This would necessitate diastereomeric compositions due to the equal exposure of either side of the carbonyl group to the attacking species. It may prove sufficient to position a less basic oxygen at the terminus of the side chain to achieve similar coordinative and directing effects, provided that the functionality containing this oxygen not be so large as to prevent effective coordination due to steric crowding with the cyclopentenol ring of cephalotaxine. It remains to be seen whether the formate in **9** or the alkoxide in oxygenated derivatives of acid **8** could satisfy these requirements.

Regarding the steric requirements of the esterification of cephalotaxine, it would appear that the *length* of the terminal functionality is relatively unimportant compared to the *hybridization of carbon 2* of the side chain. If this carbon is already $sp^3$ hybridized (as it was in the precursory acid side chains used in some of the earlier unsuccessful attempts at the esterification), then the transition state in any acylation reaction will resemble the conformation of cephalotaxine esters. It can be seen immediately from models that the radius of rotation of the methyl acetate side chain is large enough for severe steric crowding with either the cyclopentenol or the aromatic moieties. Rotation would be diminished as would be the number of other possible conformations the molecule could assume. Consequently the number of possible approaches of an acyl moiety already containing this acetate unit prior to the esterification would be greatly reduced also.

Without exception, all of the successful esterifications to date had the acetate unit either introduced last or they utilized synthons *containing* this acetate but in a compact, non freely rotating form (lactone, for example).[5k,6b] The large space filled by the freely rotating C1–C2 bond may also explain the resistance of cephalotaxine esters to methanolysis as observed earlier.[5k,6b]

The amount of experimental data gathered in the area of cephalotaxine esters seems tremendous. Appropriately dissected and analyzed, all of the past experiments as well as the work described herein would bear out the aove speculations. The task that now awaits us is the improvement of the yield of homoharringtonine to a preparatively presentable state (our aim would place this yield at 40–45% *from* cephalotaxine) to make it available in quantity for large-scale screening.

## Experimental Section

Melting and boiling points are uncorrected. All small-scale reactions were run in glassware washed successively with chromic acid and ethanolic potassium hydroxide. All nonhydrolytic reactions were performed under an inert atmosphere ($N_2$, argon). Solvents were distilled from appropriate drying agents prior to use (see guidelines in Gordon, A. J.; Ford, R. A. "The Chemist's Companion"; Wiley: New York). Infrared spectra were determined on Perkin-Elmer 257 or Pye-Unicam spectrophotometers. $^1H$ NMR spectra were recorded on Varian T60 or Nicolet-300 instruments at 60 and 300 MHz, respectively, with tetramethylsilane as an internal standard. $^{13}C$ NMR spectra were acquired at 20 MHz on a Varian CFT-20 spectrometer with the same internal standard. All assignments are based on off-resonance, partially decoupled spectra. Mass spectral measurements were obtained on a DuPont 20-491 instrument (low resolution) or on a double-focusing DuPont 21-110C instrument (high resolution/exact mass).

The purity standard of all compounds was ascertained by spectral ($^1H$ and $^{13}C$ NMR) and chromatographic means (analytical TLC, reversed-phase HPLC with a UV detector using a 253-nm filter).

**2-Oxo-6-methylhept-5-enoic Acid (8).** To a three-necked round-bottom flask equipped with a mechanical stirrer and containing 5 g of Mg turnings covered with 70 mL of anhydrous ether was added dropwise 20 g of MeI. After the mixture was stirred at room temperature for 30 min, 8 g (0.07 mol) of ethyl cyclopropanecarboxylate was added dropwise. After completed addition the mixture was refluxed for 1 h, cooled, and poured on crushed ice. Extraction with ether, washing with 3 N HCl and saturated NaCl solution, drying ($Na_2SO_4$), and evaporation yielded 6.5 g (92.7%) of 2-cyclopropylpropan-2-ol suitable for use in the next step. Typically, 7.5 g of the alcohol was cooled in an ice bath and 25 g of 48% HBr solution added dropwise. The two-phase mixture was stirred for 30 min, diluted with 30 mL of $H_2O$, and extracted with ether. The organic layer was washed with $NaHCO_3$ and NaCl solutions, dried, and evaporated to give 10.2 g (83%)

of oil. Distillation yielded pure 4-methylpent-3-enyl bromide:[13] bp 70 °C (20 mm); IR (neat) 1660 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.6 (br s, 3 H), 1.75 (br s, 3 H), 2.5 (m, 2 H), 3.2 (t, 2 H, $J$ = 7 Hz), 5.2 (br t, 1 H).

Magnesium (147 mg, 0.0061 mol) was activated with iodine vapor under nitrogen. To this activated metal were added 5 mL of THF (distilled from benzophenone and potassium) and 1 g (0.0061 mol) of 4-methylpent-3-enyl bromide.[13] The mixture was stirred at room temperature until the initial vigorous reaction subsided, and then it was refluxed until the eventual disappearance of all of the magnesium turnings. The reaction mixture was diluted to 20 mL with dry THF. In a separate reaction vessel, 900 mg (0.0061 mol) of diethyl oxalate was dissolved in 5 mL of THF and cooled to −78 °C under nitrogen. The Grignard reagent of **13** was added dropwise. After the addition was complete (15–20 min), the reaction mixture was stirred at −78 °C for 30 min, and then the temperature was raised to −20 °C during a 1-h period. The mixture was quenched with 30% $NH_4Cl$ solution and extracted with ether. The organic layer was washed with 3 M HCl and saturated NaCl solutions, dried over $Na_2SO_4$, and evaporated to give 1.1 g of an oil (97.3%). This mixture was chromatographed (hexane/ether (95:5), silica) to give identifiable byproducts[12] and 550 mg (49%) of pure ethyl ester of **8**: IR (neat 1730, 1720, 1620 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.25 (t, 3 H, $J$ = 7 Hz), 1.6 (br s, 3 H), 1.7 (br s, 3 H), 2.3 (m, 2 H), 2.9 (m, 2 H), 4.3 (q, 2 H, $J$ = 7 Hz), 5.1 (br t, 1 H); mass spectrum (70 eV), $m/e$ (relative intensity) 184 (50, $M^+$), 155 (48), 138 (50), 111 (20), 83 (18), 69 (B), 55 (30); exact mass calcd for $C_{10}H_{16}O_3$ 184.1099, found 184.1101.

The ethyl ester obtained above (200 mg, 0.0011 mol) was dissolved in 20 mL of 95% ethanol. To this solution was added 200 mg of KOH in 3 mL of $H_2O$, and the mixture was refluxed for 3 h. The mixture was evaporated to dryness and taken up in 10 mL of $H_2O$. The aqueous solution was extracted *once* with ether and then acidified with 10% HCl and extracted several times with ether. The organic layer was washed with NaCl solution, dried, and evaporated to give 150 mg of an oil, which was distilled to afford 135 mg (79.8%) of pure acid **8**: bp 130–135 °C (bath temperature) (1 mm); IR (neat) 3300–2400, 1720, 1710 (br) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.7 (br s, 3 H), 1.8 (br s, 3 H), 2.4 (dt, 2 H), 3.0 (t, 2 H, $J$ = 7 Hz), 5.15 (br t, 1 H), 9.1 (s, 1 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 17.6 (q), 21.8 (q), 25.5 (t), 37.9 (t), 121.4 (d), 132.8 (s), 173.4 (s), 195.6 (s); mass spectrum (70 eV), $m/e$ (relative intensity) 156 (15, $M^+$), 138 (10), 111 (24), 69 (85), 59 (45), 55 (40), 44 (B); exact mass calcd for $C_8H_{12}O_3$ 156.0786, found 156.0783.

**6,6-Dimethyl-2-carboxy-5,6-dihydropyran (11).** Keto acid **8** (300 mg, 0.0019 mol) was refluxed for 15 min in 20 mL of 88% formic acid containing 1 drop of 70% $HClO_4$. The mixture was evaporated to dryness, dissolved in 30 mL of 6 N NaOH, and brought to reflux for an additional 15 min. The alkaline solution was acidified and extracted with $CH_2Cl_2$. The combined organic layer was throughly shaken with 20% KOH. The aqueous layer was reacidified[16] and extracted with methylene chloride, and the extract was dried over $Na_2SO_4$. Evaporation of solvent gave 220 mg (73%) of pure acid **11**: IR (neat) 3400–2700, 1720, 1660, 1600 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.3 (s, 6 H), 1.5–1.9 (m, 2 H), 2.0–2.4 (m, 2 H), 6.05 (t, 1 H, $J$ = 4 Hz), 9.7 (s, 1 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 18.9 (t), 26.0 (q, double intensity), 31.8 (t), 75.3 (s), 110.6 (d), 142.3 (s), 167.1 (s); mass spectrum (70 eV), $m/e$ (relative intensity) 156 (18, $M^+$), 138 (5), 111 (18), 95 (27), 69 (15), 56 (B), 55 (78); exact mass calcd for $C_8H_{12}O_3$ 156.0786, found 156.0790.

**2-Hydroxy-6,6-dimethyltetrahydropyran-2-carboxylic Acid (10).** Acid **8** (150 mg, 0.000 96 mol) was refluxed for 30 min in 88% $HCO_2H$ containing 1 drop of $HClO_4$. The mixture was evaporated to dryness, partitioned between NaCl solution and $CH_2Cl_2$, and extracted with $CH_2Cl_2$. Evaporation of the solvent gave 140 mg (80.4%) of **10**:[16] IR (KBr) 3400–2800, 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.4 (s, 6 H), 1.6–2.2 (m, 6 H), 7.8 (s, 1 H, acid H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 18.8 (t), 25.3 (q, double intensity), 33.1 (t), 33.6 (t), 76.5 (s), 83.4 (s), 178.8 (s).

**Cephalotaxyl 2-Oxo-6-methylhept-5-enoate (12).** Acid **8** (100 mg, 0.00064 mol) was dissolved in 1 mL of 7% $Na_2CO_3$ solution. This solution was evaporated to dryness. Small amounts of residual $H_2O$ were removed by evaporation in vacuo with dry benzene. The sodium salt was suspended in 2 mL of dry benzene containing 1 drop of pyridine and cooled to 0 °C. To this solution was added 1 mL of oxalyl chloride (freshly distilled), and the resulting mixture was stirred at room temperature for 5 h. The solvents were removed in vacuo, and evaporation repeated twice with dry $CH_2Cl_2$ and cooled to 0 °C. Cephalotaxine[17] (120 mg) in 1 mL of pyridine and 3 mL of $CH_2Cl_2$ was added followed by 5 mg of 4-(dimethylamino)pyridine. This reaction mixture was stirred overnight at room temperature, whereupon it was diluted with $CH_2Cl_2$ (20 mL) and extracted with $H_2O$. The aqueous layers were then extracted with $CH_2Cl_2$, and the organic layers were combined and washed with 10% $Na_2CO_3$ and NaCl solutions, dried, and evaporated. Trituration of the resulting semisolid with hexane/ether (1:1) gave 120 mg (69.5%) of **2** as a powder: IR ($CHCl_3$) 1730, 1710, 1640 (strong); $^1H$ NMR ($CDCl_3$) $\delta$ 1.54 (s, 3 H), 1.55 (s, 3 H), 1.6–1.9 (m, 2 H), 2.0 (m, 2 H), 2.3 (m, 2 H), 2.6 (m, 2 H), 2.8 (m, 2 H), 3.05 (m, 2 H), 3.3 (m, 2 H), 3.7 (s, 3 H), 3.81 (d, 1 H, $J$ = 9.7 Hz), 4.9 (t, 1 H, $J$ = 5.6 Hz), 5.08 (s, 1 H), 5.6 (d, 2 H), 5.88 (d, 1 H, $J$ = 9.7 Hz), 6.54 (s, 1 H), 6.55 (s, 1 H); mass spectrum (70 eV), $m/e$ (relative intensity) 453 (12, $M^+$), 422 (7), 314 (4), 298 (12), 282 (5), 266 (7), 150 (12), 95 (12), 84 (65), 83 (B), 69 (25), 55 (72); exact mass calcd for $C_{26}H_{31}NO_6$ 453.2151, found 453.2141.

**Methyl 3-Carbocephalotaxyl-3-hydroxy-7-methyloct-6-enoate (13a) (Dehydrodeoxyhomoharringtonine) and Its Epimer (13b).** Zinc chloride (337 mg) was activated for 4 h at 150 °C under vacuum. It was suspended in 3.16 mL of dry THF, and 185 mg of potassium was added. The reaction mixture was *not* disturbed until the reduction commenced (5–10 min) whereupon it was refluxed with stirring for 2 h and cooled to 0 °C and 0.02 mL of methyl $\alpha$-bromoacetate was added, followed by 100 mg of keto ester **16** and 100 mg of bromoacetate in 0.5 mL of dry THF. The reaction mixture was stirred at room temperature for 1 h and then refluxed for 30 min and cooled. The reaction was quenched with 10 mL of $NH_4OH/NH_4Cl/H_2O$ (1:1.5:3) and excess Zn was removed by filtration. Extraction of the aqueous layer with $CH_2Cl_2$, washing with $NH_4Cl$ and NaCl solutions, drying over $Na_2SO_4$, and solvent removal gave 110 mg of a semisolid, which was separated by using preparative TLC (silica gel, $CH_2Cl_2$/MeOH (85:15)) to give two major products: **13a** ($R_f$ 0.4) and **13b** ($R_f$ 0.55).

**13a**: IR ($CHCl_3$) 3300, 1720, 1715, 1640 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.6 (br s, 6 H), 1.8 (m, 4 H), 2.05 (br AB q, 2 H), 2.4 (dd, 2 H), 2.6 (m, 2 H), 2.9 (m, 2 H), 3.1 (m, 2 H), 3.3 (m, 2 H), 3.65 (s, 3 H), 3.76 (s, 3 H), 3.78 (d, 1 H, $J$ = 9.4 Hz), 5.06 (s, 1 H), 5.53 (t, 1 H, $J$ = 3.5 Hz), 5.81 (s, 1 H), 5.84 (s, 1 H), 5.96 (d, 1 H, $J$ = 9.4 Hz), 6.57 (s, 2 H), mass spectrum (70 eV), m/e (relative intensity) 527 (40, $M^+$), 512 (2), 496 (15), 445 (6), 314 (10), 298 (80), 282 (12), 266 (18), 254 (10), 150 (42), 133 (18), 95 (20), 82 (27), 69 (B), 55 (70); exact mass calcd for $C_{29}H_{27}NO_8$ 527.2519, found 527.2534.

**13b**: The following differences were noted in the $^1H$ NMR below 3.2 ppm ($CDCl_3$): $\delta$ 3.65 (s, 3 H), 3.66 (s, 3 H), 3.79 (d, 1 H, $J$ = 9 Hz), 5.05 (s, 1 H), 5.07 (t, 1 H, $J$ = 3 Hz), 5.78 (s, 1 H), 5.80 (s, 1 H), 6.0 (d, 1 H, $J$ = 9 Hz), 6.53 (s, 1 H), 6.68 (s, 1 H).

**2,6-Dioxoheptanoic Acid (15).** 2-Methylcyclopent-1-enal (**14**; prepared from methylcyclohexene by ozonolysis and subsequent cyclization of the enamine;[15] 2 g, 0.018 mol) was dissovled in 50 mL of absolute EtOH, and 6.66 g of $AgNO_3$ in 8 mL of $H_2O$ was added.[18] The solution was cooled in ice, and 90 mL of 8% KOH solution was added with stirring. After 2 h of stirring at 0 °C, the mixture was filtered and the precipitate was washed with 50 mL of hot $H_2O$. The aqueous layer was washed once with ether, acidified, and extracted with $CH_2Cl_2$. Drying and removal of solvent gave a yellow solid, which was recrystallized from hexane

(16) Omission of this double-washing procedure gave mixtures of **10** and **11**. Pure **11** could be obtained in ~90% if small volumes of NaOH and HCl were used. Pure **10** could be isolated if either **11** or a mixture of **10** and **11** were refluxed in $HCO_2H$ for 30 min.

(17) Initially these experiments were performed with cephalotaxine donated to us by NCI (see Acknowledgement), R. G. Powell of USDA, Peoria, as well as with our own synthetic material. We have prepared several grams of cephalotaxine by the updated experimental procedure of Weinreb and Auerbach's synthesis and obtained the alkaloid in a slightly higher overall yield. We found this method to be extremely reliable.

(18) Adapted from: Campaigne, E.; LeSuer, W. M. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, p 919.

to give 1.8 g (78.6%) of yellowish crystals of 2-methylcyclopent-1-enoic acid: mp 128 °C (lit.[19] mp 129–130 °C); IR ($CHCl_3$) 3400–2800, 1695, 1640 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.75 (t, 2 H, $J$ = 7 Hz), 2.07 (br s, 3 H), 2.2–2.6 (m, 4 H), 10.5 (br s, 1 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 16.5 (q), 21.2 (t), 33.3 (t), 41.4 (t), 126.81 (s), 159.2 (s), 172.03 (s); mass spectrum (70 eV), $m/e$ (relative intensity) 126 (25 $M^+$), 111 (15), 81 (B), 79 (35), 53 (30); exact mass calcd for $C_7H_{10}O_2$ 126.0681, found 126.0684.

The above acid (1.2 g, 0.0095 mol) was dissolved in 50 mL of $CH_2Cl_2$. Ozone was passed through this solution at −78 °C.[20,21] When a deep blue color of the solution persisted, the solution was degassed with $N_2$, and 3 g of $Me_2S$ was added at 0 °C. This mixture was stirred at room temperature for 1 h, whereupon excess solvents were removed in vacuo to give 1.2 g (80%) of reasonably pure acid **15**: IR (neat) 3300–2800, 1700 (br) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.85 (m, 2 H), 2.1 (s, 3 H), 2.5 (t, 2 H, $J$ = 6 Hz), 2.86 (t, 2 H, $J$ = 6 Hz), 9.3 (br s, 1 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 16.9 (t), 18.5 (q), 37.3 (t), 41.9 (t), 161.3 (s), 195.2 (s), 209.1 (s); mass spectrum (70 eV), $m/e$ (relative intensity) $M^+$ not detected, 140 (35), 112 (95), 84 (B), 67 (30), 55 (35); exact mass calcd for $C_6H_{10}O_3$ ($M^+$ − CO) 140.0473, found 140.0477.

**Cephalotaxyl 2,6-Dioxoheptanoate (16).** Carboxylic acid **15** (200 mg, 0.001 27 mol), oxalyl chloride (0.2 mL), pyridine (1 drop), and benzene (2 mL) were mixed at 0 °C and then stirred at room temperature for 6 h. Excess solvents were evaporated, giving pure acid chloride (IR 1775 $cm^{-1}$) suitable for the next step. Cephalotaxine (200 mg, 0.000 63 mol), pyridine (120 mg, 1.2 equiv), 4-(dimethylamino)pyridine (5 mg) were dissolved in 2 mL of $CH_2Cl_2$ and cooled to 0 °C. The solution of the above acid chloride in $CH_2Cl_2$ (2 mL) was added dropwise. The reaction was stirred at room temperature for 6 h, quenched with an *ice cold* solution of $NaHCO_3$, and extracted with $CH_2Cl_2$. Removal of solvents gave 220 mg (78.6%) of a semisolid that was ~85% pure **16** by NMR. Any attempts at purification of this compound led to its decomposition to cephalotaxine. It decomposed readily on standing in $CDCl_3$. If freshly prepared it was suitable for the next step.

**16**: IR (neat) 1730, 1710, 1650 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.6–2.0 (m, 6 H), 2.1 (s, 3 H), 2.2–3.2 (m, 2 H), 3.7 (s, 3 H), 3.83 (d, 1 H, $J$ = 9 Hz), 5.05 (s, 1 H), 5.8 (s, 2 H), 5.9 (d, 1 H, $J$ = 9 Hz), 6.47 (s, 2 H), mass spectrum (70 eV), $m/e$ (relative intensity) 455 ($M^+$, 8), 415 (10), 343 (12), 315 (27), 298 (80), 284 (32), 266 (20), 254 (18), 214 (22), 166 (42), 150 (52), 149 (50), 137 (45), 115 (62), 85 (68), 79 (B), 69 (80); exact mass calcd for $C_{25}H_{29}NO_7$ 455.1944, found 455.1962.

**Methyl 3-Carbocephalotaxyl-3-hydroxy-7-oxooctanoate (18).** Active Zn metal was prepared as above (cf. preparation of **13**) from 47 mg of $ZnCl_2$ and 27 mg of potassium in 3 mL of THF. To it was added a mixture of 100 mg (0.000 219 mol) of freshly prepared ester **16** and 33 mg of methyl $\alpha$-bromoacetate. The reaction mixture was stirred at room temperature for 1 h and then at 40–50 °C for an additional hour. It was quenched and worked up in a manner identical with that used in the preparation of **13** to yield 105 mg (90.5%) of hydroxy ester **18** as a semisolid: IR ($CHCl_3$) 3400, 1730, 1720, 1710, 1640 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ (relevant signals only) 2.1 (s, 3 H), 3.70 (s, 3 H), 3.75 (s, 3 H), 3.8 (d, 1 H, $J$ = 9 Hz), 5.05 (s, 1 H), 5.75 (d, 1 H, $J$ = 9 Hz), 5.9 (s, 2 H), 6.6 (s, 2 H); mass spectrum (70 eV), $m/e$ (relative intensity) no $M^+$ detected due to cleavage to cephalotaxyl ($m/e$ 314.1392, found 314.1399), 368 (10), 315 (5), 314 (7), 298 (18), 282 (8), 266 (8), 254 (9), 240 (6), 229 (10), 150 (15), 129 (12), 115 (20), 97 (20), 91 (22), 81 (20), 77 (30), 69 (40), 55 (B); exact mass calcd for $C_{28}H_{35}NO_9$ 529.2311, found 529.2331 [measured at a lower ionization energy (20–30 eV)].

**Methyl 3-Carbocephalotaxyl-3,7-dihydroxy-7-methyloctanoate (2) (Homoharringtonine).** A Grignard was prepared from 270 mg of MeI and 45 mg of magnesium in 10 mL of THF. This solution (1 mL) was added to a solution of 100 mg (0.001 89 mol) of ester **22** in 2 mL of THF at −78 °C. The reaction temperature was raised to −20 °C and maintained for 30 min. It was then quenched with 10% tartaric acid, basified with $NaHCO_3$, and extracted with $CH_2Cl_2$. Evaporation gave 110 mg of crude product, which contained some of **18**, (10%), cephalotaxine (30%), and homoharringtonine (35%) (by HPLC, $MeOH/H_2O/Et_2N$ (20:80:1)). Preparative TLC (silica, $CHCl_3$/MeOH (85:15)) gave approximately 10 mg of **2** (10%): $^1H$ NMR ($CDCl_3$) $\delta$ (below 3.2) 3.56 (s, 3 H), 3.64 (s, 3 H), 3.8 (d, 1 H, $J$ = 9 Hz), 5.05 (s, 1 H), 5.82 (s, 2 H), 6.0 (d, 1 H, $J$ = 9 Hz), 6.54 (s, 1 H), 6.61 (s, 1 H). This spectrum was superimposable on that of an authentic sample.

**Cephalotaxyl 6,6-Dimethyl-5,6-dihydropyran-1-carboxylate (19).** Acid **11** (150 mg, 0.0096 mol) was dissolved in 2 mL of benzene containing 1 drop of pyridine and the mixture was cooled to 0 °C. Oxalyl chloride (0.25 mL) was added and the mixture was stirred for 6 h, whereupon all of the solvent was removed in vacuo and the acid chloride was taken up in 2 mL of dry $CH_2Cl_2$. To the acid chloride solution were added 100 mg of cephalotaxine, 90 mg (1.2 equiv) of pyridine, and 5 mg of 4-(dimethylamino)pyridine in 2 mL of $CH_2Cl_2$. The reaction mixture was allowed to stir overnight at room temperature. It was quenched on ice, and the aqueous layer was extracted with $CH_2Cl_2$, washed with $NaHCO_3$ and NaCl solutions, and dried over $Na_2SO_4$. Removal of solvent gave 110 mg of a semisolid, which was purified by preparative TLC ($CHCl_3$/MeOH (9:1)) to give 70 mg (77%) of **24**, in the highest esterification yield to date: IR (neat) 1710–1700, 1640 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.12 (s, 3 H), 1.19 (s, 3 H), 1.5 (br t, 1 H), 1.8 (m, 2 H), 2.0 (m, 2 H), 2.4 (dd, 2 H), 2.6 (m, 2 H), 3.0 (q, 1 H), 3.1 (m, 1 H), 3.3 (m, 1 H), 3.7 (s, 3 H), 3.80 (d, 1 H, $J$ = 9 Hz), 5.05 (s, 1 H), 5.53 (br t, 1 H), 5.80 (s, 1 H), 5.82 (s, 1 H), 5.92 (d, 1 H, $J$ = 9 Hz), 6.51 (s, 2 H); mass spectrum (70 eV), $m/e$ (relative intensity) 453 (10, $M^+$), 438 (2), 422 (6), 314 (22), 298 (B), 282 (20), 266 (40), 254 (20), 214 (22), 150 (60), 126 (40), 110 (52), 95 (58), 83 (55), 69 (55), 55 (B); exact mass calcd for $C_{26}H_{31}NO_6$ 453.2151, found 453.2163.

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**Registry No.** 1 (R = H), 24316-19-6; **2**, 26833-87-4; **8**, 84375-03-1; **8** ethyl ester, 42272-93-5; **10**, 87683-18-9; **11**, 76729-59-4; **12**, 76742-93-3; **13a**, 87683-19-0; **13b**, 87727-63-7; **14**, 81328-61-2; **15**, 84375-05-3; **16**, 84375-02-0; **18**, 84395-19-7; **19**, 87683-20-3; 2-cyclopropylpropan-2-ol, 930-39-2; 2-methyl-1-cyclopentenoic acid, 67209-77-2; ethyl cyclopropanecarboxylate, 4606-07-9; 4-methyl-3-pentenyl bromide, 2270-59-9; diethyl oxalate, 95-92-1.

**Supplementary Material Available:** Negative results and descriptions of side reactions connected to the preparation and functionalization of **8** (9 pages). Ordering information is given on any current masthead page.

(19) Harding, K. E.; Tseng, C. *J. Org. Chem.* **1978**, *43*, 3974. Rapson, W. S.; Robinson, R. *J. Chem. Soc.* **1935**, 1533.

(20) Adapted from: Dauben, W. G.; Wight, H. G.; Boswell, G. A. *J. Org. Chem.* **1958**, *23*, 1787.

(21) For a general description of ozonolyses performed in our laboratories, see: Hudlicky, T.; Short, R. P. *J. Org. Chem.* **1982**, *47*, 1522. The instrument used was a Purification Science Inc. instrument; range, 5–7 std $ft^3/h$ of $O_2$.