δ 0.9 (6 H, t, CH_2CH_3), 1.2 (19 H, br s, R_2CH_2, R_3CH), 3.7 (3 H, m, R_2CHOH, RCH_2OH); IR 3400 cm^{-1}.

Anal. Calcd for $C_{14}H_{30}O_2$: C, 72.98; H, 13.12; mol wt, 230. Found: C, 72.81; H, 12.92; mol wt, 230 (MS).

A solution of 500 mg of the mixture of **3a** and **3b**, 2.5 mL of acetic anhydride, and 0.75 mL of pyridine was kept for 24 h at room temperature under anhydrous conditions. Workup gave 512 mg of the monoacetyl derivative: bp (Kugelrohr) 162–168 °C (0.2 torr); n^{24}_D 1.4430° [lit.[21] for 2-pentyl-3-acetoxynonyl heptanoate, bp 160–164 °C (1.0 torr); $n^{18.5}_D$ 1.4484°].

Anal. Calcd for $C_{23}H_{44}O_4$: C, 71.83; H, 11.52. Found: C, 72.05; H, 11.68.

Oxidation of 3a and 3b. A mixture of **3a** and **3b** (390 mg) was dissolved in acetone (250 mL) and Jones reagent[28] was added dropwise, with stirring, until a yellow color persisted. The chromium salts were filtered, most of the acetone was removed at reduced pressure, water was added, and the resulting solution was extracted with ether. Drying over sodium sulfate and removal of solvent gave 368 mg of material. Thin-layer chromatographic analysis indicated the presence of two compounds, which were separated by chromatography on silica gel into 73 mg (18%) of a carboxylic acid and 285 mg (76%) of neutral 2-pentyl-3-oxononyl heptanoate (**8**): bp (Kugelrohr) 138–142 °C (0.1 torr); n^{24}_D 1.4440°; ^1H NMR δ 0.9 (9 H, t, CH_2CH_3), 1.3 (24 H, m, CH_2), 2.1–2.8 (5 H, m, $CH_2C{=}O$, $CHC{=}O$), 4.1 (2 H, d, CH_2OCO); IR 1735, 1720 cm^{-1} (ester and ketone C=O).

Anal. Calcd for $C_{21}H_{40}O_3$: C, 74.07; H, 11.84; mol wt, 340. Found: C, 73.76; H, 11.96; mol wt, 340 (MS).

The acid (**9a**) was treated with diazomethane and characterized as its methyl ester, methyl 2-pentyl-3-(heptanoyloxy)nonanoate (**9b**): bp (Kugelrohr) 143–147 °C (0.2 torr); n^{24}_D 1.4410°; ^1H NMR δ 0.9 (9 H, t, CH_2CH_3), 5.0 (1 H, m, RCHOCO); IR 1735 cm^{-1} (ester C=O).

Anal. Calcd for $C_{22}H_{42}O_4$: C, 71.31; H, 11.42; mol wt, 370. Found: C, 71.18; H, 11.42; mol wt, 370 (MS).

2-Pentyl-3-(bromoacetoxy)nonyl heptanoate (**4a**) and its isomer (**4b**) could not be obtained analytically pure. GC of the sample at 245 °C showed both isomers, in a ratio of 3:1, principally **4a**, as established by the ^1H NMR spectrum. The sample had the following: bp (Kugelrohr) 187–193 °C (0.15 torr); n^{24}_D 1.4558°; IR 1735 cm^{-1}; ^1H NMR δ 0.9 (9 H, t, CH_2CH_3), 1.3 (27 H, br s, R_2CH_2, R_3CH), 2.2 (2 H, t, $CH_2C{=}O$), 3.8 (2 H, s, $COCH_2Br$), 4.1 (2 H, d, $RCH_2OC{=}O$), 5.0 (1 H, m, $R_2CHOC{=}O$). Saponification[21] gave heptanoic acid and 2-pentyl-1,3-nonanediol (**7**); bromoacetic acid was not recovered in the workup.

Anal. Calcd for $C_{23}H_{43}BrO_4$: mol wt, 462. Found: mol wt, 462 (MS).

2-Pentyl-3-acetoxynonyl heptanoate (**5a**) and its isomer (**5b**), a mixture, had the following: bp (Kugelrohr) 162–166 °C (0.1 torr); n^{24}_D 1.4427° [lit.[21] bp 160–164 °C (0.1 torr); $n^{18.5}_D$ 1.4484°]; IR 1740 cm^{-1}; ^1H NMR δ 0.9 (9 H, t, CH_2CH_3), 1.3 (27 H, br s, R_2CH_2, R_3CH), 2.0 (3 H, s, $OCOCH_3$), 2.2 (2 H, t, $CH_2C{=}O$), 4.0 (2 H, m, $RCH_2OC{=}O$), 4.9 (1 H, m, $R_2CHOC{=}O$). GC of the sample at 195 °C showed both possible isomers in a ratio of 6:1; the ^1H NMR spectrum indicated the principal isomer to be **5a**.

Anal. Calcd for $C_{23}H_{44}O_4$: C, 71.83; H, 11.52; mol wt, 384. Found: C, 71.79; H, 11.53; mol wt, 384 (MS).

Saponification[21] gave heptanoic acid and 2-pentyl-1,3-nonanediol (**7**); acetic acid was not recovered in the workup.

2-Pentyl-3-[(3-hydroxynonanoyl)oxy]nonyl heptanoate (**6a**), presumably mixed with its positional isomer **6b**, had the following: bp (Kugelrohr) 208–214 °C (0.006 torr); n^{24}_D 1.4532°; IR 3450, 1735 cm^{-1}; ^1H NMR δ 0.9 (12 H, t, CH_2CH_3), 1.3 (37 H, br s, R_2CH_2, R_3CH), 2.3–2.4 (2 H, m, $CH_2C{=}O$), 3.9 (1 H, m, R_2CHOH), 4.0 (2 H, d, $RCH_2OC{=}O$), 5.0 (1 H, m, $R_2CHOC{=}O$).

Anal. Calcd for $C_{30}H_{58}O_5$: C, 72.24; H, 11.72; mol wt, 498. Found: C, 71.72; H, 11.55; mol wt, 498 (MS).

Saponification[21] gave 2-pentyl-1,3-nonanediol (**7**) and two carboxylic acids, which were separated by chromatography into heptanoic acid and 3-hydroxynonanoic acid, mp 58–59 °C (lit.[26] 57–59 °C).

Acknowledgment. This work was supported in part by a grant from the National Institute of Allergy and Infectious Diseases (AI 04769).

Registry No. **1**, 26257-80-7; **2**, 3021-89-4; **2** DNP, 10385-38-3; **3a**, 49562-88-1; **3b**, 55109-59-6; **4a**, 82352-12-3; **4b**, 82352-13-4; **5a**, 82352-14-5; **5b**, 82374-04-7; **6a**, 82352-15-6; **6b**, 82352-16-7; **7**, 55109-63-2; **8**, 82352-17-8; **9a**, 82352-18-9; **9b**, 82352-19-0; heptanal, 111-71-7; ethyl bromoacetate, 105-36-2; heptanoic acid, 111-14-8; 3-hydroxynonanoic acid, 40165-87-5.

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Jatrophone Analogues: Synthesis of *cis*- and *trans*-Normethyljatropholactones

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This, a full account, discloses an efficient, convergent synthesis of two novel analogues of the macrocyclic antitumor diterpene jatrophone (**1**). We term these analogues *cis*- and *trans*-normethyljatropholactone (**2** and **3**, respectively). Our approach in each case begins with the bis(trimethylsilyloxy) ketone **7** and the requisite acetylenic or trans ester–aldehyde, **8** or **12a**. Application of our previously developed 3(2*H*)-furanone synthetic protocol consisting of aldol condensation of the lithium enolate derived from **7** with the respective ester–aldehydes **8** or **12a**, followed by oxidation (Collins reagent) and acid-catalyzed cyclization–dehydration, affords spirofuranone **6c** and **14c**, respectively, in 52% and 45% overall yields. Sodium borohydride reduction, ester hydrolysis, and closure of the macrolide by employing the conditions of Mukaiyama (i.e., 1-methyl-2-chloropyridinium iodide-/Et_3N/CH_3CN) in the case of spirofuranone **14a** leads directly to *trans*-normethyljatropholactone (**3**), while completion of *cis*-normethyljatropholactone (**2**) requires first semihydrogenation; the latter was accomplished by employing $PdSO_4$ in pyridine as the catalyst. The overall yields of **2** and **3**, based on **7**, were 23% and 21%, respectively.

In connection with a synthetic program which recently culminated in the sucessful stereocontrolled total synthesis of (±)-jatrophone (**1a**),[2] its epimer (**1b**),[2] and (±)-normethyljatrophone (**1c**),[3] we have prepared two architec-

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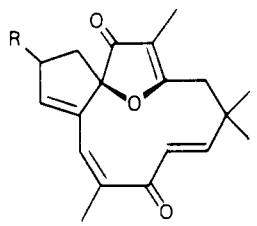
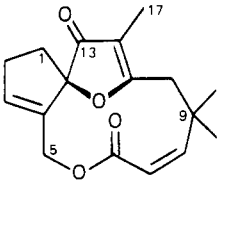


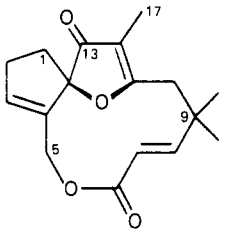
1

(a) Jatrophone, R = α-Me
(b) Epijatrophone, R = β-Me
(c) Normethyljatrophone, R = H



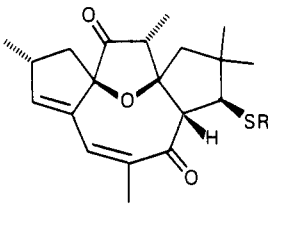
2

cis-Normethyljatropholactone



3

trans-Normethyljatropholactone



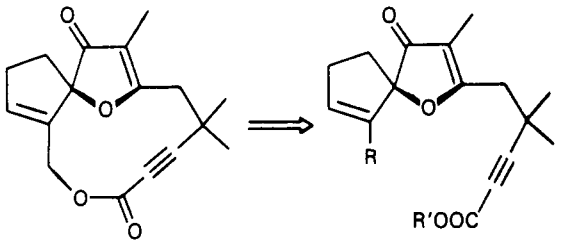
4

(a) R = *n*-Pr
(b) R = protein

turally related analogues which we term *cis*- and *trans*-normethyljatropholactone (**2** and **3**, respectively). We record here a full account of the synthesis of these analogues. Our interest in such systems stemmed from the Kupchan observation[4] that jatrophone, when treated in neutral or buffered solution with a variety of thiols, including cysteine hydrochloride and the free thiols of proteins such as bovine serum alubumin and DNA-dependent RNA polymerase, led to the formation of unstable adducts possessing the general structure **4**. This reactivity was suggested by Kupchan to be responsible for the pronounced antileukemic activity (P-388 lymphocytic leukemia) and cytotoxicity (KB cell cultures) displayed by jatrophone.[2a] It was anticipated that the availability of such synthetic analogues, in conjunction with jatrophone, epijatrophone, and normethyljatrophone, would allow further exploration of their relative antitumor properties as well as definition of the site(s) of reactivity with model biologic nucleophiles.

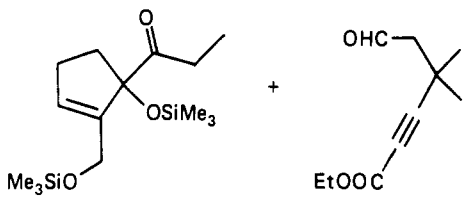
Results and Discussion

From the retrosynthetic perspective, acetylenic macrolide **5** appeared to be an ideal advanced intermediate from which both **2** and **3** could in turn be elaborated via the stereocontrolled reduction of the acetylenic linkage. Central to this strategy was the prospect of exploiting our recently developed 3(2*H*)-furanone synthetic protocol[5] for construction of spirofuranone **6a**; subsequent macrocyclic lactonization would then afford **5**.



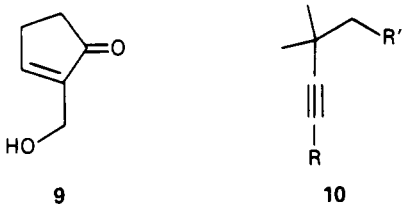
5 6

(a) R = CH_2OH; R' = H
(b) R = CH_2OH; R' = Et
(c) R = CHO; R' = Et



7 8

This scenario calls initially for construction of the silyl protected keto alcohol **7** and acetylenic aldehyde **8**, the former prepared previously from α-(hydroxymethyl)-cyclopentenone (**9**).[2b,6] The requisite aldehyde (**8**) was



9 10

(a) R = H; R' = COOH
(b) R = H; R' = CH_2OH
(c) R = COOH; R' = CH_2OH
(d) R = COOEt; R' = CH_2OH

prepared from readily available acetylenic acid **10a**.[7] Reduction with $LiAlH_4$ to the corresponding alcohol **10b**, followed by generation of the dianion with 2.2 equiv of *n*-BuLi in THF at -40 °C for 2 h and then addition of solid

(1) Camille and Henry Dreyfus Teacher Scholar, 1978–1983; National Institutes of Health (National Career Institute) Career Development Awardee.

(2) (a) Structure: Kupchan, S. M.; Sigel, C. W.; Matz, M. J.; Saenz Renauld, R. C.; Haltiwanger, R. C.; Bryan, R. F. *J. Am. Chem. Soc.* **1970**, *92*, 4476. Kupchan, S. M.; Sigel, C. W.; Matz, M. J.; Gilmore, C. J.; Bryan, R. F. *Ibid.* **1976**, *98*, 2295: (b) Synthesis: Smith, A. B., III; Schow, S. R.; Guaciaro, M. A.; Wovkulich, P. M.; Toder, B. H.; Malamas, M.; Hall, T. W., unpublished results.

(3) Smith, A. B., III; Guaciaro, M. A.; Schow, S. R.; Wovkulich, P. M.; Toder, B. H.; Hall, T. W. *J. Am. Chem. Soc.* **1981**, *103*, 219.

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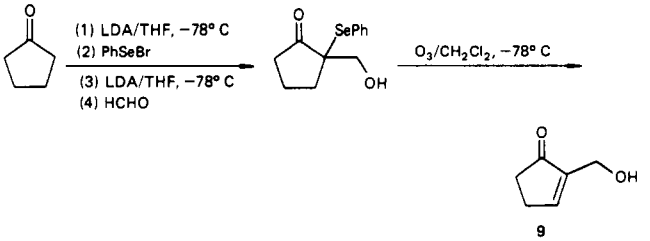
(6) Initially, 2-(hydroxymethyl)-2-cyclopentenone (**9**) was prepared via the keto vinyl anion equivalent methodology developed in our and Swenton's laboratory. See: Branca, S. J.; Smith, A. B., III *J. Am. Chem. Soc.* **1978**, *100*, 7767. Smith, A. B., III; Guaciaro, M. A.; Wovkulich, P. M. *Tetrahedron Lett.* **1978**, 4661. Also see: Manning, M. J.; Raynolds, P. W.; Swenton, J. S. *J. Am. Chem. Soc.* **1976**, *98*, 5008. Raynolds, P. W.; Manning, M. J.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 4467. An alternate more economical preparation of (**9**) is outlined below: unpublished results of Mr. M. Malamas of our laboratory.



9

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Table I. High-Field (250 MHz) ^{1}H NMR Data for *cis*- and *trans*-Normethyljatropholactone (2 and 3) and (*Z*,*E*)- and (*E*,*Z*)-Normethyljatrophone (1c and 11, Respectively)[a]

H[b]	chemical shift			
	2	3	1c	11
1-H_a	2.37 (ddd, 13.4, 8.2, 6.0)	2.29 (ddd, 14.1, 7.1, 6.7)	2.15 (dd, 13.1, 8.1)	2.35 (m)
1-H_b	2.13 (ddd, 13.4, 7.4, 3.0)	2.04 (ddd, 14.1, 7.1, 3.3)	1.85 (dd, 13.1, 6.4)	2.10 (m)
2-H_a	2.62 (m)	2.58 (m)	2.4 (m)	2.40 (m)
2-H_b	2.62 (m)	2.58 (m)	2.2 (m)	2.40 (m)
3-H	6.14 (br s)	6.55 (br s)	5.8 (m)	6.08 (m)
5-H_a[c]	4.98 (dq, 13.9, 1.1)	4.72 (dq, 13.8, 1.3)	5.67 (m)	6.94 (m)
5-H_b[c]	4.65 (dq, 13.9, 2.3)	4.27 (d, 13.8)		
7-H	5.72 (d, 13.6)	5.91 (d, 16.1)	5.86 (d, 16.4)	5.62 (d, 14.0)
8-H	5.84 (d, 13.6)	6.53 (d, 16.1)	6.35 (d, 16.4)	5.68 (d, 14.0)
10-H_a	2.25 (d, 13.6)	2.31 (d, 12.9)	2.29 (d, 14.9)	2.32 (d, 13.2)
10-H_b	2.78 (d, 13.6)	2.78 (d, 12.9)	2.77 (d, 14.9)	2.64 (d, 13.2)
15-CH_3[d]	1.42 (s)	1.34 (s)	1.24 (s)	1.16 (s)
16-CH_3[d]	1.30 (s)	1.21 (s)	1.13 (s)	1.24 (s)
17-CH_3	1.64 (s)	1.75 (s)	1.62 (s)	1.70 (s)

[a] Chemical shifts are given in parts per million downfield from $(CH_3)_4Si$ (δ), with multiplicities and coupling constants (in hertz) in parentheses. [b] Numbering for **1c** and **11** has been altered so that corresponding carbons in **2**, **3**, **1c**, and **11** have the same number. [c] Assignments for 5-H_2 could not be made with confidence in regard to stereochemistry. [d] Assignments for 15-CH_3 and 16-CH_3 may be reversed in **2**, **3**, and **11**.

Table II. High-Field (62.9 MHz) ^{13}C NMR Data for *cis*- and *trans*-Normethyljatrolactone (2 and 3) and Normethyljatrophone (1c)[a]

carbon[b,d]	chemical shift		
	2	3	1c
1 (t)	34.2	35.4	33.5
2 (t)	30.6	30.6	30.4
3 (d)	122.2	117.9	123.1
4 (s)	135.6	136.4	137.8
5 (t)	61.1	62.5	140.6
6 (s)	165.6	168.8	201.1
7 (d)	135.8	144.8	128.2
8 (d)	146.6	152.4	158.7
9 (s)	38.8	39.6	36.3
10 (f)	40.4	42.8	40.9
11 (s)	184.3	184.1	182.8
12 (s)	112.1	112.4	112.0
13 (s)	204.8	205.1	203.7
14 (s)	98.5	98.7	98.8
15 (q)[c]	34.5	29.0	30.0
16 (q)[c]	26.4	24.0	26.5
17 (q)	6.24	6.55	5.66

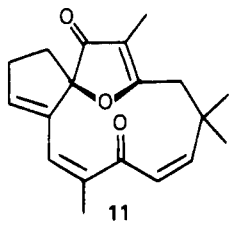
[a] Chemical shifts are reported in parts per million downfield from $(CH_3)_4Si$ (δ). [b] Numbering for **1c** has been altered so that corresponding carbons in **2**, **3**, and **1c** have the same number. [c] Assignments for carbons 15 and 16 in **2** and **3** may be reversed. [d] Multiplicity is given in parentheses.

CO_2, afforded after an acidic workup acid **10c** in 80% yield. This acid was then esterified with EtOH and oxidized with pyridinium chlorochromate[8] to afford the desired aldehyde **8** in 94% yield.

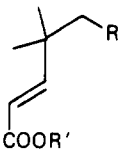
With ample quantities of both **7** and **8** in hand, we executed the 3(2*H*)-furanone synthetic protocol. To this end, the lithium enolate of **7**, generated via addition of 1.3 equiv of LDA in THF at −78 °C, was condensed with aldehyde **8** in THF. Without purification the derived aldol was subjected first to Collins oxidation (ca. 13 equiv)[9] and then to acid-catalyzed cyclization–dehydration to afford spirofuranone **6c** in 51% overall yield.

With an efficient, convergent approach to **6c** available, the stage was next set for macrocyclic ring closure. Reduction of **6c** with 1.1 equiv of $NaBH_4$ in MeOH at −23 °C for 10 min followed by hydrolysis with K_2CO_3 in methanol–water (2:1) gave acid **6a** in 77.4% yield for the two steps. Lactonization employing Mukaiyama's procedure[10] (i.e., 1-methyl-2-chloropyridinium iodide/Et_3N/CH_3CN, high dilution) then afforded the pivotal intermediate, macrolide **5**, in 58% yield.

At this point all that remained to complete the synthesis of *cis*- and *trans*-normethyljatropholactone was the stereoselective reduction of the C(7,8) acetylenic linkage. As anticipated, semihydrogenation employing $PdSO_4$ in pyridine[11] afforded *cis*-normethyljatropholactone (**2**) as a crystalline solid, mp 101–103 °C (ether–hexane). That in fact **2** was in hand derives from careful comparison of the high-field ^{1}H and ^{13}C NMR spectra of **2** with those of **1a–c**, as well as with that of **11**, the latter prepared in connection with our normethyljatrophone synthesis (see Tables I and II).[3]



11



12

(a) R = CHO; R' = Et
(b) R = CH_2OH; R' = H
(c) R = CH_2OH; R' = Et

Turning next to the conversion of macrolide **5** to *trans*-normethyljatropholactone (**3**), we initially anticipated exploiting the well-known propensity of chromous sulfate to effect the stereoselective trans reduction of α-acetylenic acids and esters.[12] This one-step plan, however, was thwarted presumably due to transannular reactions.[3] Undaunted by lack of initial success, we considered next isomerization of *cis*-normethyljatropholactone (**2**) to the desired trans isomer. Such a strategy, of course, was not

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(9) Collins, J. E.; Hess, W. W.; Frank, F. J. *Tetrahedron Lett.* **1968**, 3363.
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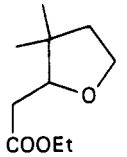
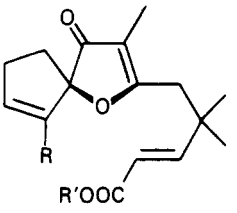
novel; it was this approach that we had exploited to great advantage in our jatrophone synthesis.[2b,3] However, to our dismay all attempts to effect the required isomerization by employing numerous acids, light (with and without I_2), and/or transition-metal catalysts under a wide variety of time, temperature, and solvent regimes proved fruitless.

Our only alternative at this point, aside from abandoning the goal of *trans*-normethyljatropholactone, was to prepare trans aldehyde ester **12a** and then to subject this intermediate to the 3(2*H*)-furanone synthetic protocol. Toward this end, reduction of the previously prepared hydroxy acid **10c** with aqueous chromous sulfate for 24 h at room temperature proceeded as anticipated to yield **12b** in 78% as the sole product. Characteristic of the desired trans olefinic geometry, the 250-MHz NMR spectrum displayed two doublets at δ 5.95 and 6.50 having a coupling constant of 16.2 Hz. Fischer esterification[13] then gave alcohol **12c** in 92% yield, contaminated with 8% of tetrahydrofuran **13**, the latter arising via a facile 5-exo-trigonal cyclization[14] of ester **12c**.[15] Subsequent Collins oxidation of **12c** then led to aldehyde **12a**.



13



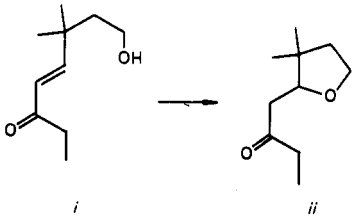
14

(a) R = CH_2OH; R' = H
(b) R = CH_2OH; R' = Et
(c) R = CHO; R' = Et

Execution of the 3(2*H*)-furanone synthetic protocol [(a) aldol condensation, (b) Collins oxidation, (c) cyclization–dehydration] as employed above led to spirofuranone **14c** in 45% overall yield. Reduction of the aldehyde functionality with sodium borohydride in methanol (**14c** → **14b**) followed by saponification and macrolactonization of the resultant hydroxy acid (**14a**) again a la Mukaiyama afforded *trans*-jatropholactone (**3**) as a crystalline solid [mp 168–170 °C (ether–hexane)], the overall yield from spirofuranone **14c** being 42%. Indicative of the trans geometry the olefinic resonances display as two doublets (δ 5.91 and 6.53) with the characteristic trans coupling of 16.1 Hz.

In summation, an economic convergent synthesis of two analogues of jatrophone has been achieved in 20% and 19% yields (**2** and **3**, respectively) based on **7**. Biological screening data as well as NMR studies to correlate the solution conformation vis-à-vis the bioactivity will be presented in due course.

(13) Fischer, E. *J. Physiol. Chem.* **1901**, *33*, 151.
(14) Baldwin, j. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *Ibid.* **1976**, 736. Baldwin, J. E. *Ibid. 1976*, 738. Baldwin, J. E.; Thomas, R. C.; Kruse, K. I.; Siverman, L. *J. Org. Chem.* **1977**, *42*, 3846.
(15) Interestingly, the propensity with which the analogous hydroxy enone i displayed for this 5-exo-trigonal cyclization (i → ii) precluded its utilization as an intermediate in our jatrophone approach: unpublished results of Dr. S. R. Schow of this laboratory.



i *ii*

Experimental Section

Materials and Methods. Melting points were taken on a Thomas-Hoover capillary melting apparatus and are corrected. Boiling points are uncorrected. All solvents were distilled prior to use. Solutions were dried over $MgSO_4$. Unless specified otherwise, IR and ^1H NMR spectra were obtained for CCl_4 solutions, the former on a Perkin-Elmer Model 337 spectrophotometer and the latter on either a Varian A-60A (60 MHz), a Varian T60A (60 MHz), or a Bruker WP 250 (250 MHz) spectrometer. ^{13}C NMR spectra were obtained in $CDCl_3$ on either a JEOL PS-100 (25 MHz) or a Bruker WP-250 FT (62.9 MHz) spectrometer; signal multiplicities were determined via off- resonance decoupling. The internal standard for ^1H and ^{13}C NMR experiments was Me_4Si. For those compounds containing the TBDMS protecting group, an external reference of either Me_4Si or $CHCl_3$ (δ 7.24) for $CDCl_3$ solutions was used. High-resolution mass spectra were obtained at the University of Pennsylvania Mass Spectrometry Service Center on a Hitachi Perkin-Elmer RMH-2 high-resolution double-focusing electron-impact spectrometer or a VG micromass 70/70H high-resolution double-focusing electron impact–chemical ionization spectrometer, the latter using isobutane as the reagent gas and each interfaced with a Kratos DS-50-S data system. Preparative thin-layer chromatography (TLC) was performed on 500- or 1000-μm precoated silica gel plates with fluorescent indicator supplied by Analtech, Inc. Visualization was accomplished with UV light. Flash column chromatography and medium-pressure liquid chromatography were performed with silica gel 60 (0.04–0.063 mm) supplied by E. M. Merck.

Preparation of 3,3-Dimethyl-4-pentyn-1-ol (10b). To a mixture of 100 mL ether and 3.056 g (80.52 mmol) of lithium aluminum hydride under a nitrogen atmosphere at 0 °C was added 5.06 g (40.16 mmol) of 3,3-dimethyl-4-pentynoic acid in 30 mL of ether over a 30-min period. The mixture was stirred for 2 h after the addition. Solid sodium sulfate decahydrate was added to quench the reaction, and the resultant solid was filtered and washed thoroughly with ether. Concnetrated in vacuo afforded 4.28 g of a colorless oil, which was distilled (Kugelrohr, ~3 mm, 49 °C) to give 4.21 g (93.5%) of a colorless oil: IR ($CHCl_3$) 3635, 3430 (br), 2980, 2880 (s), 2120 (w), 1260 (br), 1065, 1095 (w), 630 (w), cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 1.26 (s, 6 H), 1.72 (t, J = 7 Hz, 2 H), 2.16 (s, 1 H), 2.30 (br s, 1 H), 3.85 (t, J = 7 Hz, 2 H); mass spectrum, m/e 112.0823 (M^+; calcd for $C_7H_{12}O$ 112.0888).

Preparation of Ethyl 4,4-Dimethyl-6-hydroxy-2-hexynoate (10d). To a mixture of 250 mL of THF and 12.47 g of acetylenic alcohol **10b** (111.3 mmol) under a nitrogen atmosphere at −42 °C (acetonitrile/CO_2) was added dropwise 131 mL (256.15 mmol) of *n*-BuLi. The mixture was stirred 2 h at −42 °C after completion of the *n*-butyllithium addition. Solid carbon dioxide was then added to the solution, and the thick solution was stirred for 0.5 h followed by acidification with 6 N hydrochloric acid. The aqueous layer was extracted four times with ether and the solution dried. Concentration in vacuo gave 15.7 g of a colorless oil that crystallized upon standing; the latter was employed in the next step without purification.

A mixture of 100 mL of absolute ethanol, 6.8 g (43.58 mmol) of hydroxy acid **10c**, and 1 mL of concentrated sulfuric acid was stirred at room temperature for 64 h. Dilution in water and extraction with ether afforded 7.95 g of colorless oil. Purification via flash column chromatography (5:1 hexane/ethyl acetate) afforded 7.86 g (98%) of colorless oil: IR ($CHCl_3$) 3630–3450 (br), 2980, 2930 (s), 2210 (s), 1690 (s), 1260 (br), 905 (w) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 1.30, (s, 6 H), 1.30 (t, J = 7.0 Hz, 3 H), 1.78 (t, J = 7.25 Hz, 2 H), 2.79 (br s, 1 H), 3.83 (t, J = 7.25 Hz, 2 H), 4.23 (q, J = 7.0 Hz, 2 H); mass spectrum, m/e 184.1100 (M^+; calcd for $C_{10}H_{16}O_3$ 184.1100).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.20; H, 8.70. Found: C, 65.04; H, 8.79.

Preparation of Ethyl 4,4-Dimethyl-6-oxo-2-hexynoate (8). To a mixture of 160 mL dry methylene chloride and 26.35 g (122.28 mmol) pyridinium chlorochromate under a nitrogen atmosphere at room temperature was added 9.02 g (49.02 mmol) of ester **10d** in 50 mL of methylene chloride. The mixture was stirred for 3.5 h at room temperature, diluted in 800 mL ether, and filtered

through Florisil (100–200 mesh). Removal of the solvent in vacuo and distillation (Kugelrohr, ~1 mm, 110–120 °C) gave 8.47 g (93.9%) of a colorless oil: IR ($CHCl_3$, 2980, 2930 (s), 2210 (m), 1700 (s), 1260 (br), 1040 (br), 850 (w) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 1.31 (t, J, = 7.25 Hz, 3 H), 1.40 (s, 6 H), 2.54 (d, J = 2.0 Hz, 2 H), 4.24 (q, J = 7.25 Hz, 2 H), 9.86 (t, J = 2.0 Hz, 1 H); mass spectrum, m/e 182.0715 (M^+; calcd for $C_{10}H_{14}O_3$ 182.0709).

Preparation of *trans*-Ethyl 4,4-Dimethyl-6-hydroxy-2-hexenoate (12c). To a mixture of 46 mL of degassed water (nitrogen purge for 2 h) and 4.2 g (26.92 mmol) of hydroxy acid **10c** was added under a nitrogen atmosphere at room temperature 229 mL of 0.4 M $CrSO_4$ over a 30-min period. The reaction solution first became green and then 10 min later turned dark. The mixture was stirred for 12 h at room temperature. The dark reaction solution was then basified with aqueous KOH and vacuum filtered from chromic hydroxide. The filtrate was next acidified (concentrated H_2SO_4) to pH 1 and extracted with ethyl acetate. The organic extracts were dried over sodium sulfate, filtered, and conentrated in vacuo to afford 3.31 g (78.6%) of **12b** as a colorless oil which was used without purification.

A mixture of 100 mL of absolute ethanol, 7.4 g (46.83 mmol) of **12b**, and 0.5 mL of concentrated sulfuric acid was stirred at room temperature for 50 h. Dilution in water and extraction with ether afforded 8.53 g (98%) of a colorless oil. Purification via flash column chromatography (10:1 hexane/ethyl acetate) afforded 7.89 g (90.6%) of **12c** as a colorless oil: IR (CCl_4) 3630, 3400 (br), 2980, 2930 (s), 1700, 1650 (s), 1300, 1200 (br), 1035 (br), 995 (w), 870 (w) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 1.1 (s, 6 H), 1.30 (t, J = 7.0 Hz, 3 H), 1.71 (t, J = 7.75 Hz, 2 H), 2.30 (s, 1 H), 3.62 (t, J = 7.75 Hz, 2 H) 4.21 (q, J = 7.0 Hz, 2 H), 5.76 (d, J = 16.2 Hz, 1 H) 6.95 (d, J = 16.2 Hz, 1 H); mass spectrum, m/e 186.1311 (M^+; calcd for $C_{10}H_{18}O_3$ 186.1290).

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.51; H, 9.67. Found: C, 64.42; H, 9.69.

Preparation of Ethyl *trans*-4,4-Dimethyl-6-oxo-2-hexenoate (12a). To a mixture of 120 mL of methylene chloride and 19.03 g (88.28 mmol) of pyridinium chlorochromate under a nitrogen atmosphere at room temperature was added 6.6 g (34.94 mmol) of ester **12c** in 40 mL of methylene chloride. The mixture was stirred for 3.5 h at room temperature, diluted in 700 mL of ether, and filtered through Florisil (100–200 mesh). Removal of solvent in vacuo and distillation (Kugelrohr, ~1 mm, 115–130 °C) gave 6.07 g (93%) of **12a** as a colorless oil: IR (CCl_4) 2980, 2930 (s), 1700 (s), 1250 (br), 1030 (br) 850 (w) cm^{-1}, NMR (250 MHz, $CDCl_3$) δ 1.25 (s, 6 H), 1.32, (t, J = 7.0 Hz, 3 H), 2.48 (d, J = 2.1 Hz, 2 H), 4.24 (q, J = 7.0 Hz, 2 H), 5.81 (d, J = 16.2 Hz, 1 H), 6.90 (d, J = 16.2 Hz, 1 H), 9.75 (t, J = 2.1 Hz, 1 H); mass spectrum, m/e 184.1093 (M^+ calcd for $C_{10}H_{16}O_3$ 184.1100).

Preparation of Spirofuranone (6c). To a solution of 0.62 mL (4.38 mmol) of diisopropylamine in 3 mL of THF containing a few crystals of 2,2'-dipyridylamine as an indicator at 0 °C under a nitrogen atmosphere was added 2.40 mL (3.41 mmol, 1.42 M solution) of n-butyllithium. The resultant deep red solution was stirred 30 min at 0 °C and then cooled to −78 °C. After 5 min bis(silyloxy) ketone **7** (765 mg, 2.44 mmol) in THF (3 mL) was added over a period of 5 min. The red mixture was stirred 2 h, and then 896 mg (4.92 mmol) of aldehyde **8** in mL of THF was added over a 50-s period. The color of the reaction mixture changed to orange-brown; stirring was continued for 2 min, and then saturated ammonium chloride (2 mL) was added. The mixture was diluted with 3 mL of water and extracted thoroughly with ether. The combined extracts were washed with water and brine. Removal of solvent in vacuo gave 1.34 g of yellow oil which was employed in the next step without purification.

To a solution of 7.49 mL (92.61 mmol) of pyridine in 100 mL of methylene chloride was added 4.41 g (44.1 mmol) of chromium trioxide (CrO_3). After the mixture was stirred 20 min at room temperature under a nitrogen atmosphere, the above hydroxyl ketone (1.34 g) in 5 mL of CH_2Cl_2 was added and the stirring continued for 3 h. The organic layer was decanted from the black residue and the latter washed with ether. Conventional workup and removal of solvent in vacuo gave 1.09 g of a light brown oil, which was taken up in 50 mL THF with 25 mL of 10% HCl and stirred at room temperature under a nitrogen atmosphere for 48 h. The mixture was then saturated with solid NaCl and diluted with ether. The organic layer was washed and dried. Removal of the solvent in vacuo gave 657 mg of a viscous yellow oil which was purified via medium-pressure liquid chromatography [hexane/ethyl acetate (2:1)] to afford 409.1 mg (50.8% from **7**) of **6c** as a pale yellow oil: IR (CCl_4) 2995, 2930 (s), 2210 (s), 1700 (s), 1630 (s), 1250 (br), 1035 (m), 920 (s) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 1.30 (t, J = 7.3 Hz, 3 H), 1.38 (s, 3 H), 1.39 (s, 3 H), 1.79 (s, 3 H), 2.27 (m, 1 H), 2.44 (m, 1 H), 2.70 (s, 2 H), 2.80 (m, 2 H), 4.20 (q, J = 7.0 Hz, 2 H), 7.33 (m, 1 H), 9.64 (s, 1 H); mass spectrum; m/e 330.1403 (M^+; calcd for $C_{19}H_{22}O_5$ 330.1467).

Preparation of Spirofuranone 6b. To a mixture of 4 mL of methanol and 244 mg (0.74 mmol) of spirofuranone **6c** under a nitrogen atmosphere at −23 °C (CCl_4/CO_2) was added 27.97 mg (0.74 mmol) of sodium borohydride. The mixture was stirred for 15 min at −23 °C before the pH was adjusted to 7 with dilute aqueous HCl. The mixture was extracted with ether, and the organic extract was dried and concentrated in vacuo to afford 219.6 mg of a viscous colorless oil which was purified via medium-pressure liquid chromatography [hexane/ethyl acetate (2:1)] to afford 203 mg (83.2%) of **6b** as a colorless oil: IR 3500, 3400 (br), 2980, 2930 (s), 2220 (m), 1700 (s), 1630 (s), 1260, 1100 (br), 1030 (m), 750 (br) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 1.29 (t, J = 7.0 Hz, 3 H), 1.40 (s, 3 H), 1.43 (s, 3 H), 1.74 (s, 3 H), 2.21 (m, 1 H), 2.40 (m, 1 H), 2.57 (m, 2 H), 2.71 (s, 2 H), 4.03 (m, 2 H), 4.20 (q, J = 7.0 Hz, 2 H), 6.21 (t, J = 1.8 Hz, 1 H); mass spectrum, m/e 332.1620 (M^+; calcd for $C_{19}H_{24}O_5$ 332.1624).

Preparation of Spirofuranone 6a. To a solution of 5 mL of MeOH, 2 mL of H_2O and 170 mg (0.512 mmol) of spirofuranone **6b** at room temperature was added a concentrated aqueous K_2CO_3 solution, adjusting the pH of the reaction mixture to 10.5–11.0. The mixture was then stirred 15 h at room temperature under nitrogen and diluted with 5 mL of H_2O, and the pH was adjusted to 2. The mixture was extracted extensively with ether, and the organic fraction was dried and concentrated in vacuo to afford 144.7 mg (93.0%) of acid **6a**: IR 3450, 3300, 2500 (br), 2980, 2930 (s), 2220 (m), 1700, 1630 (s), 1450 (s), 1200 (s), 700 (br) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 1.37 (s, 3 H), 1.41 (s, 3 H), 1.70 (s, 3 H), 2.05 (m, 1 H), 2.40 (m, 2 H), 2.61 (m, 2 H), 2.81 (d, J = 13 Hz, 1 H), 4.05 (m, 2 H), 5.75 (br s, 1 H), 6.20 (t, J = 1.8 Hz, 1 H), COOH not observed.

Preparation of the Macrolide 5. To a solution consisting of 767 mg (3.0 mmol) of 1-methyl-2-chloropyridinium iodide in 73 mL of dry acetonitrile held at reflux was continuously and uniformly added a solution of 230 mg (0.75 mmol) of **6a** and 0.84 mL (6 mmol) of triethylamine in 65 mL of dry acetonitrile over a period of 9 h. After one additional hour at reflux, evaporation of the solvent under reduced pressure afforded a residue which was separated via silica gel column chromatography to afford 125.6 mg (57.8%) of **5** as a viscous colorless oil that crystallized upon standing: mp 125–127 °C; IR ($CHCl_3$) 2980, 2930 (s), 220 (m), 1700, 1630 (s), 1500, 1400 (m), 1180, 1200 (br) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 1.45 (s, 3 H), 1.49 (s, 3 H) 1.78 (s, 3 H), 2.20 (m, 1 H), 2.41 (m, 1 H), 2.60 (d, J = 13.2 Hz, 1 H), 2.65 (m, 2 H) 2.81 (d, J = 13.2 Hz, 1 H) 4.64 (s, 2 H), 6.47 (t, J = 1.9 Hz, 1 H); mass spectrum, m/e 286.1201 (M^+; calcd for $C_{17}H_{18}O_4$ 286.1205).

Preparation of *cis*-Normethyljatropholactone (2). A suspension of 10 mg of 5% palladium on barium sulfate in 2 mL of pyridine was stirred under hydrogen at atmospheric pressure for 30 min, whereupon 153 mg of macrolide **5** in 200 mL of pyridine was added and the stirring under hydrogen continued for 15 min. The reaction mixture was then filtered through Celite with a CH_2Cl_2 wash. Removal of the solvent in vacuo yielded **2** as a viscous yellow oil that crystallized upon standing. Recrystallization from hexane/ethyl ether (10:1) gave 144.7 mg (94.6%) of a white crystalline solid: mp 101–103 °C; IR ($CHCl_3$) 2980, 2930 (s), 1700, 1620 (s), 1220 (br), 1090 (m), 715 (br) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 1.30 (s, 3 H), 1.42 (s, 3 H), 1.64 (s, 3 H), 2.20 (m, 1 H), 2.28 (d, J = 13.6 Hz, 1 H), 2.35 (m, 1 H), 2.60 (m, 2 H), 2.75 (d, J = 13.6 H_3, 1 H), 4.71 (m, 1 H), 5.05 (m, 1 H), 5.72 (d, J = 13.3 Hz, 1 H), 5.85 (d, J = 13.3 Hz, 1 H), 6.14 (t, J = 1.5 Hz, 1 H); mass spectrum, m/e 288.1351 (M^+; calcd for $C_{17}H_{20}O_4$ 288.1361).

Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.80; H, 6.95. Found: C, 70.60; H, 7.03.

Preparation of Spirofuranone 14c. To a solution of 0.45 mL (3.27 mmol) of diisopropylamine in 2.5 mL of THF containing a few crystals of 2,2'-dipyridylamine as indicator at 0 °C under

a nitrogen atmosphere was added 1.88 mL (2.54 mmol, 1.35 M solution) of *n*-butyllithium. The resultant deep red solution was stirred 30 min at 0 °C and cooled to -78 °C. After 5 min bis(silyloxy) ketone **7** (507.2 mg, 1.62 mmol) in 3 mL of THF was added over a period of 5 min. The red mixture was stirred 2 h, and then 675.5 mg (3.67 mmol) of aldehyde **12a** in 1 mL of THF was added over a 50-s period. The color of the reaction mixture changed to orange-brown; stirring was continued for 2 min, and then saturated ammonium chloride (2 mL) was added. The mixture was diluted with 3 mL of water and extracted thoroughly with ether. The combined organic extracts were washed with water and dried. Removal of the solvent in vacuo gave 767 mg of yellow oil which was employed in the next step without purification.

To a solution of 5.6 mL (68.6 mmol) of pyridine in 65 mL of methylene chloride was added 3.25 g (32.5 mmol) of chromium trioxide (CrO_3). After the mixture was stirred 20 min at room temperature under a nitrogen atmosphere, the above hydroxy ketone (767 mg) in 5 mL of CH_2Cl_2 was then added and the stirring continued for 3 h. The organic layer was decanted from the dark residue, and the latter was washed with ether. A conventional workup and removal of solvent in vacuo gave 585 mg of a light brown oil, which was taken up in 40 mL of THF with 20 mL of 5% aqueous HCl and stirred at room temperature under a nitrogen atmosphere for 5 days. The mixture was then saturated with solid NaCl and diluted with ether. The organic layer was washed and dried, and the solvent was removed in vacuo to give 355 mg of a viscous yellow oil, which was purified via medium-pressure liquid chromatography [hexane/ethyl acetate (2:1)] to afford 241.3 mg (45% from **7**) of **14c** as a pale yellow oil: IR ($CHCl_3$) 2980, 2930 (s), 1700, 1630 (s), 1200, 1300 (br), 1040 (s), 920, 840 (m) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 1.12 (s, 6 H), 1.20 (t, J = 7.25 Hz, 3 H), 1.66 (s, 3 H), 2.10 (m, 1 H), 2.35 (m, 1 H), 2.51 (d, J = 10.25 Hz, 2 H), 2.81 (m, 2 H), 4.20 (q, J = 7.25 Hz, 2 H), 5.75 (d, J = 16.2 Hz, 1 H), 6.94 (d, J = 16.2 Hz, 1 H), 7.20 (t, J = 1.5 Hz, 1 H), 9.61 (s, 1 H); mass spectrum, m/e 332.1615 (M^+; calcd for $C_{19}H_{24}O_5$ 332.1693).

Preparation of Spirofuranone 14b. To a mixture of 4-mL of methanol and 290 mg (0.873 mmol) of spirofuranone **14c** under a nitrogen atmosphere at -23 °C (CCl_4/CO_2) was added 33.78 mg (0.893 mmol) of sodium borohydride. The mixture was stirred for 15 min at 23 °C before the pH was adjusted to 7 with dilute aqueous HCl. The mixture was extracted extensively with ether. The organic material was then dried and concentrated in vacuo to afford 275.3 mg of a viscous colorless oil which was purified via medium-pressure liquid chromatography [hexane/ethyl acetate (2:1)] to give 231.3 mg (79.5%) of **14b** as a colorless oil: IR ($CHCl_3$) 3450, 3400 (br), 2980, 2930 (s), 1700, 1625 (s), 1480 (m), 1200 (br), 1040 (s) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 1.15 (s, 6 H), 1.22 (t, J = 7.8 Hz, 3 H), 1.72 (s, 3 H), 2.10 (m, 1 H), 2.35 (m, 1 H), 2.60 (br m, 4 H), 3.96 (br d, J = 2 Hz, 2 H), 4.22 (q, J = 7.8 Hz, 2 H), 5.75 (d, J = 16.3 Hz, 1 H), 6.20 (br s, 1 H), 7.03 (d, J = 16.3 Hz, 1 H); mass spectrum, m/e 334.1746 (M^+; calcd for $C_{19}H_{26}O_5$ 334.1781).

Preparation of Spirofuranone 14a. To a solution of 8 mL of MeOH, 2 mL of H_2O, and 250 mg (0.748 mmol) of spirofuranone **14b** at room temperature was added a concentrated aqueous K_2CO_3 solution, adjusting the pH of the reaction mixture to 10.5–11.0. The mixture was stirred 12 h at room temperature under nitrogen and then diluted with 5 mL of H_2O, and the pH was adjusted to 7. The mixture was extracted extensively with ether, and the organic fraction was dried and concentrated in vacuo to afford 231.3 mg (91.5%) of **14a**: IR ($CHCl_3$) 3450–2500 (br) 2980–2930 (s) 1700 (s), 1450 (br), 1080 (m), 850 (m) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 1.15 (s, 3 H), 1.20 (s, 3 H) 1.65 (s, 3 H), 2.1 (m, 1 H), 2.35 (m, 2 H), 2.55 (m, 2 H), 2.70 (m, 1 H), 3.59 (br s, 1 H), 3.95 (m, 2 H), 5.18 (br s, 1 H), 5.75 (d, J = 16.2 Hz, 1 H), 6.10 (s, 1 H), 6.50 (d, J = 16.2 Hz, 1 H).

Preparation of *trans*-Normethyljatropholactone (3). To a solution consisting of 654 mg (2.55 mmol) of 1-methyl-2-chloropyridinium iodide in 65 mL of acetonitrile held at reflux was continuously and uniformly added a solution of 195 mg (0.64 mmol) of spirofuranone **14a** and 0.72 mL (5.12 mmol) of triethylamine in 55 mL of dry acetonitrile over a period of 9 h. After one additional hour at reflux evaporation of the solvent under reduced pressure followed via silica gel column chromatography afforded 138 mg of a viscous colorless oil that crystallized upon standing. Recrystallization [hexane/ethyl ether (10:1)] gave 104.0 mg (56.8%) of **3** as a white crystalline solid: mp 168–170 °C; IR 2980, 2930 (s), 1700, 1630 (s), 1460 (m), 1210 (m), 720 (br) cm^{-1}; NMR (250 MHz, $CDCL_3$) δ 1.21 (s, 3 H), 1.34 (s, 3 H), 1.75 (s, 3 H), 1.15 (m, 1 H) 2.28 (m, 1 H), 2.33 (d, J = 13 Hz, 1 H), 2.60 (m, 2 H), 2.80 (d, J = 13 Hz, 1 H), 4.31 (d, J = 14 Hz, 1 H), 4.75 (m, 1 H), 5.95 (d, J = 16.1 Hz, 1 H), 6.50 (d, J = 16.1 Hz, 1 H) 6.51 (t, J = 1.5 Hz, 1 H); mass spectrum, m/e 288.1359 (M^+; calcd for $C_{17}H_{20}O_4$ 288.1362).

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Cobalt-Mediated [2 + 2 + 2] Cycloadditions En Route to Natural Products: A Novel Total Synthesis of Steroids via the One-Step Construction of the B,C,D Framework from an A-Ring Precursor

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The first application of the cobalt-mediated intramolecular cyclization of α,δ,ω-diynenes to annulated cyclohexadienes in natural product synthesis is described by demonstrating its feasibility in a versatile and efficient steroid synthesis, including a new total synthesis of the Torgov intermediate, 3-methoxyestra-1,3,5(10),8,14-pentaen-17-one, via a new steroid, 3-methoxyestra-1,3,5(10),8(14),9-pentaen-17-one ethylene ketal. Several model reactions en route to *B*-homo-7-oxa steroids allow the delineation of some stereochemical details of the transition-metal-catalyzed [2 + 2 + 2] cycloaddition reaction.

We have recently developed methodology based on cobalt-mediated [2 + 2 + 2] cycloadditions of unsaturated substrates which yields annulated and complexed five-[1] and six-membered[2] rings. We believe that this strategy

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