The yield of higher hydrocarbons is very low. This reflects the fact that in TPDE the primary reaction products are swept from the reactor with very short contact times (~1.4 s).[13] Although the C balance (based on the collection of the above gases) is usually quite good (>90%), in a few cases it is not, most notably for $Rh_6(CO)_{16}$.[15] This could be due to the formation of heavier products (including oxygenates) which are not detected.[16] However, due to the low pressure and short contact times, a more likely explanation may be the formation of some type of Cads (adsorbed carbon) which is unreactive toward H_2.[17]

A notable feature of Table I is the large amounts of CH_4 which are formed, in six cases the conversion of CO to CH_4 exceeding 50%. The yield of CH_4 does not correlate with the activity of the respective metals for catalytic methanation.[18] For example, Ir, the least active of the group 8B metals for methanation, yields far more CH_4 than Ni, one of the most active metals. Examination of Figures 1–4 shows that the thermal stability of a supported complex is the prime factor in determining the quantity of CH_4 formed. Thus $Ni(CO)_4$, which decomposes at a very low temperature (Figure 1), has lost most of its CO before the temperature is high enough to give a reasonable rate of methanation (Figure 2).[19] In contrast, $Ir_4(CO)_{12}$ does not lose its CO until 125 °C (Figure 3).[21] TPDE in flowing H_2 (Figure 4) then yields a curve for CH_4 evolution which is remarkably similar to that for CO evolution in He (Figure 3). Similar correlations are found for the other catalysts.

The two complexes giving the most CH_4 (per complex) are $Ir_4(CO)_{12}$ and $Os_3(CO)_{12}$. These are the same two cluster complexes which were reported to be active for homogeneous catalytic methanation.[22] However, in those experiments the total yield of CH_4 was only about 4 CH_4/complex, whereas several times this amount is now seen to be formed in a purely stoichiometric reaction.[23] Hence, it is possible that the claimed catalytic reaction was in fact stoichiometric (or a heterogeneous reaction[24,25]) and the ability of some cluster complexes (but not mononuclear complexes) to homogeneously yield CH_4 may simply reflect their enhanced thermal stability.

TPDE in flowing H_2 increases the CH_4 yield by 25-fold over TPDE in flowing He.[8] In both He[8] and H_2 (Table I) it is found that the quantity of CH_4 formed is essentially independent of the nuclearity of a complex. This is contrary to some claims that multinuclear sites are necessary to effect the reduction of CO[26] but consistent with more recent work suggesting that mononuclear complexes can be active for methanation.[8,23] Recent data for the TPDE of $Mo(CO)_6/Al_2O_3$ in flowing He and H_2 indicate that sintering of mononuclear precursors to polynuclear sites is probably not a prerequisite for CH_4 formation.[8] (Several experiments in flowing H_2 at loadings between 0.0036 and 0.76% Mo show that the yield of C_2/Mo is independent of loading, again suggesting that multinuclear sites are not involved.) Hydrogenation is not preceded by the disproportionation of CO since the yield of CO_2 is extremely low. Further, in most cases dissociation of CO followed by hydrogenation of Cads is unlikely, since the CH_4 is often formed in a temperature region in which CO is evolved if the TPDE is carried out in flowing He. Hence, it is most likely in these systems that the direct hydrogenation of coordinated CO to CH_4 is occurring at discrete subcarbonyl sites.

In addition to the substantial yields of CH_4 during TPDE in flowing H_2, it is seen (Table I) that the reaction often occurs at temperatures well below that required for catalytic methanation (200–350 °C).[18] An interesting corollary to this result is that a good catalyst for methanation should result if a metal can react with CO to re-form a carbonyl (or subcarbonyl) complex, since a catalytic cycle is now formed. Two of the more active catalysts, Ni and Fe, are in fact the metals which most readily form carbonyls from CO, whereas many of the catalytically less active metals (Ir, Mn, and Cr) do not undergo this reaction.[18,27] However, the most active metal for methanation, Ru, only very slowly forms a carbonyl by exposure to CO under severe conditions, although it was suggested that this may be due to adsorption of $Ru(CO)_5$ which inhibits further reaction.[27] Hydrogenation of carbonyl-like intermediates has been considered as a mechanism for methanation and Fischer–Tropsch synthesis,[28] but currently favored is the dissociation of CO followed by hydrogenation of Cads.[29] Thus, although the facile hydrogenation of coordinated CO is now demonstrated, it is nuclear if this process is important during catalytic methanation. Catalytic methanation over supported carbonyl complexes is currently being studied.

Acknowledgment. Support of this research by the Department of Energy is gratefully acknowledged.

(13) Hydrocarbon synthesis has been reported for several carbonyl cluster complexes supported on *wet* Al_2O_3 and heated in sealed ampules at approximately 300 °C for ~10^4 s.[14] (H_2 is generated by the water gas shift reaction.)

(14) Smith, A. K.; Theolier, A.; Basset, J. M.; Ugo, R.; Commereuc, D.; Chauvin, Y. *J. Am. Chem.* Soc. **1978**, *100*, 2590.

(15) $Rh_6(CO)_{16}$ also gave a particularly poor C balance for reaction in sealed ampules.[14]

(16) Ichikawa, M. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2273.

(17) TPDE in flowing H_2 of $Mn_2(CO)_{10}$ yielded some CH_4 at temperatures higher than for CO evolution in a sweep gas of He, suggesting some hydrogenation of Cads. However, due to the generally good C balances and the fact that TPDE in H_2 did not significantly improve the C balances compared to TPDE in He, it appears that usually only small quantities of Cads can be formed, and it must be fairly unreactive toward H_2.

(18) Vannice, M. A. *J. Catal.* **1975**, *37*, 449.

(19) These results are in agreement with less detailed data previously published for $Ni(CO)_4/Al_2O_3$.[20]

(20) Bjorkland, R. B.; Burwell, R. L., Jr. *J. Colloid Interface Sci.* **1979**, *70*, 383.

(21) For this experiment the $Ir_4(CO)_{12}$ was dispersed at 125 °C during which time 0.2 CO/complex was evolved.

(22) Thomas, M. G.; Beier, B. F.; Muetterties, E. L. *J. Am. Chem. Soc.* **1976**, *98*, 1296.

(23) The homogeneous reactions were run at 140 °C in toluene solution and gave a turnover frequency of 1×10^{-5} s^{-1}. At 140 °C the extrapolated turnover frequencies for the stoichiometric hydrogenations of $Ir_4(CO)_{12}$ and $Os_3(CO)_{12}$ are also ~1×10^{-5} s^{-1}.

(24) Bradley, J. S. *J. Am. Chem. Soc.* **1980**, *101*, 7419.

(25) Doyle, M. J.; Kouwenhoven, A. P.; Cornelis, A.; Oort, B. V. *J. Organomet. Chem.* **1979**, *174*, C55.

(26) Muetterties, E. L. *Science* **1977**, *196*, 839.

(27) Wender, I.; Pino, P. "Organic Synthesis Via Metal Carbonyls"; Interscience: New York, 1968; Vol. 1, Chapter 1.

(28) Anderson, R. B. *Catalysis* **1956**, *4*, 29.

(29) Biloen, P.; Helle, J. N.; Sachtler, W. M. H. *J. Catal.* **1979**, *58*, 95.

A Strategy for the Total Synthesis of Jatrophone: Synthesis of Normethyljatrophone

Amos B. Smith, III,*† Michael A. Guaciaro, Steven R. Schow, Peter M. Wovkulich, Bruce H. Toder, and Tse Wai Hall

The Department of Chemistry
The Laboratory for Research on the Structure of Matter
and The Monell Chemical Senses Center
The University of Pennsylvania
Philadelphia, Pennsylvania 19104
Received October 1, 1980

Jatrophone (**1**), an architecturally interesting macrocyclic diterpene first isolated in 1970 by the late Professor Kupchan from extracts of *Jatropha gossypiifolia* L. (Euphorbiacae),[1] merits consideration as a synthetic target in that it displays *significant* inhibitory activity against a variety of cell lines, including sarcoma 180, Lewis lung carcinoma, P-388 lymphocytic leukemia, and Walker 256 intramolecular carcinsarcoma.[2] Indeed, extracts of this plant had long been employed in the treatment of cancerous growths.[2]

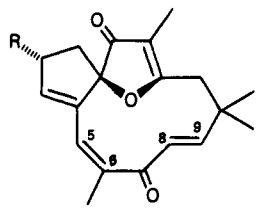
The structure of jatrophone was based on both chemical and X-ray crystallographic studies.[1] Central to the derived structure

†Camille and Henry Dreyfus Teacher–Scholar, 1978–1983; recipient of a National Institutes of Health (National Cancer Institute) Career Development Award, 1980–1985.

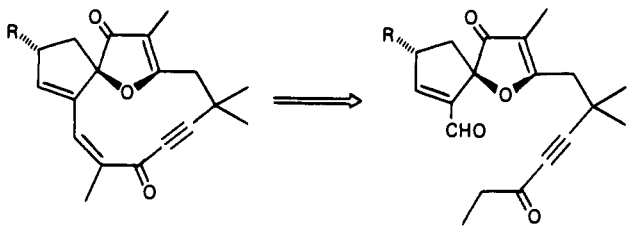
(1) S. M. Kupchan, C. W. Sigel, M. J. Matz, J. A. Saenz Renauld, R. C. Haltiwanger, and R. F. Bryan, *J. Am. Chem. Soc.*, **92**, 4476 (1970); S. M. Kupchan, C. W. Sigel, M. J. Matz, C. J. Gilmore, and R. F. Bryan, *ibid.*, **98**, 2295 (1976).

(2) J. L. Hartwell, *Lloydia*, **32**, 153 (1969).

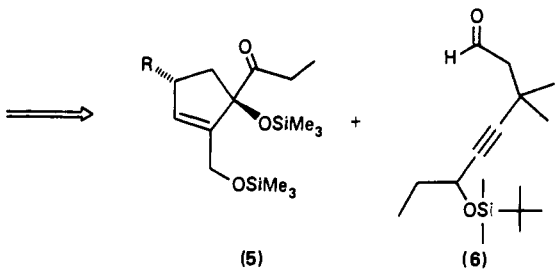
0002-7863/81/1503-219$01.00/0



Jatrophone, R = CH_3 (1)
Normethyljatrophone, R = H (2)



(3) (4)



(5) (6)

(a): R = CH_3
(b): R = H

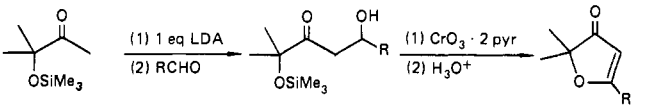
are the spiro-3(2*H*)-furanone, the macrocyclic ring, and the cross-conjugated trienone functionalities.

Recently, we have made considerable progress toward the development of a viable synthetic strategy for the elaboration of jatrophone. We now wish to announce completion of the synthesis of normethyljatrophone (**2**), the alicyclic backbone of this novel diterpene. Our strategy for both jatrophone and the normethyl system calls for the initial convergent elaboration of a spirofuranone carbocyclic array (**4**). With all necessary carbons in place, closure of the macrocyclic ring (e.g., aldol condensation) followed by conversion of the C(8,9) acetylene to a trans olefin would then complete the synthesis. The strategic selection of an acetylene functionality at C(8,9) was seen as the cornerstone of this approach in that it was anticipated that the linear nature of this functionality would provide the configurational control required at C(5,6). That is, examination of molecular models of **3** reveals that the *Z* configuration at C(5,6) should be considerably more stable than the corresponding *E*. Alternatively, models of jatrophone (**1**) suggested that both configurational isomers at C(5,6) are feasible molecular systems, the natural *Z* isomer being only slightly less strained. For final conversion of the acetylene linkage to the required trans olefin, we anticipated exploiting chromous sulfate, recently shown in our laboratory to effect cleanly the stereospecific reduction of α-oxoacetylenes to the corresponding trans enone derivatives.[3]

(3) Although chromous sulfate reduction of acetylenic alcohols to the corresponding trans allylic alcohols has been known for some time [see J. Inanaga, T. Katsuki, S. Takimoto, S. Ouchida, K. Inoue, A. Nakano, M. Aiga, N. Okukado, and M. Yamaguchi, *Chem. Lett.*, 1021 (1979); C. E. Castro and R. D. Stephens, *J. Am. Chem. Soc.*, **86**, 4358 (1964)], reduction of α-acetylenic ketones is novel. In that regard we have demonstrated that i undergoes stereospecific reduction to ii in 53% yield.

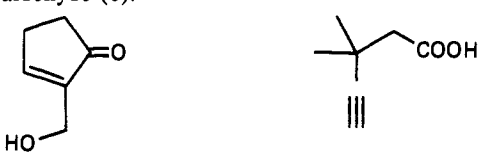
(i) (ii)

Central to the above scenario was the availability of an efficient, and hopefully general, method for the construction of the 3-(2*H*)-furanone ring system; unfortunately no such approach was available at the outset of our work. In fact, the chemistry of this increasingly important heterocycle has been little explored.[4] Convinced that the most plausible route to 3(2*H*)-furanone derivatives would involve the acid-catalyzed cyclization–dehydration of an appropriately substituted α-hydroxy 1,3-diketone, we directed our attention to model studies of the aldol-oxidation strategy illustrated in eq 1. We note in advance that this approach proved quite advantageous (vide infra).[5]



(1)

With a viable route to the central structural element, the 3-(2*H*)-furanone ring, secure, we initiated work on the normethyl system. Our strategy here begins with the elaboration of hydroxy ketone **5b** and aldehyde **6**. To this end, the readily available α-(hydroxymethyl)cyclopentenone **7**[6] was converted to **5b** in 42% overall yield (five steps) via the dithiane adduct. Specifically, the *tert*-butyldimethylsilyl ether of **7** was treated with lithioethyldithiane followed by hydrolysis ($CH_3I/CaCO_3/CH_3CN/H_2O$). Subsequent removal of the *tert*-butyldimethylsilyl group (aqueous AcOH/THF) afforded a keto diol which was silylated to give **5b**.[7] Aldehyde **6** in turn was prepared from 3,3-dimethyl-4-pentynoic acid (**8**)[8] in 55% yield via a straightforward sequence. The dianion derived from **8** (2.4 equiv of LDA/4.6 equiv of HMPA, −78 °C) was treated with excess propanal; protection of the resultant hydroxy acid as the bis(*tert*-butyldimethylsilyl) derivative followed by $LiAlH_4$ reduction in ether and Collins oxidation[9] afforded the desired aldehyde (**6**).[7]



(7) (8)

With ample quantities of both **5b** and **6** in hand, we executed the aforementioned 3(2*H*)-furanone synthetic protocol. To our delight, condensation of **5b** with **6**, followed by oxidation with

(4) For a recent detailed study on the synthesis and reactions of simple 3(2*H*)-furanones see A. B. Smith, III, P. A. Levenberg, P. J. Jerris, R. M. Scarborough, Jr., and P. M. Wovkulich, *J. Am. Chem. Soc.*, in press.

(5) We have, for example, prepared in good to excellent yield a wide variety of 5-alkyl-5-aryl- and 5-alkenyl-2,2-dimethyl-3(2*H*)-furanones via this approach; see ref 4.

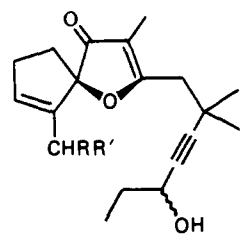
(6) S. J. Branca and A. B. Smith, III, *J. Am. Chem. Soc.*, **100**, 7767 (1978); A. B. Smith, III, M. A. Guaciaro, and P. M. Wovkulich, *Tetrahedron Lett.*, 4661 (1978).

(7) (a) The structure assigned to each new compound was in accord with its infrared and 220-, 250-, or 360-MHz NMR spectra. Analytical samples of all new compounds, obtained by recrystallization or chromatography (LC or TLC), gave satisfactory C and H combustion analysis within 0.4% and/or appropriate parent ion identification by high-resolution mass spectrometry. (b) All yields recorded here are based upon isolated material which was >97% pure. The 250-MHz ^1H NMR spectral data ($CDCl_3$) for representative intermediates are recorded below. **13**: NMR δ 1.33(s, 3 H), 1.45(s, 3 H), 1.73(s, 3 H), 1.80(d, J = 2 Hz, 1 H), 2.00–2.70(m, 5 H), 2.90(d, J = 14 Hz, 1 H), 5.37(m, 1 H), 6.00(m, 1 H). **14**: δ 1.16(s, 3 H), 1.24(s, 3 H), 1.70(s, 3 H), 1.88(d, J = 2 Hz, 3 H), 2.02–2.70(m, 4 H), 2.32(d, J = 14 Hz, 1 H), 2.64(d, J = 14 Hz, 1 H), 5.62(d, J = 14 Hz, 1 H), 5.86(d, J = 14 Hz, 1 H), 5.94(m, 1 H), 6.08(m, 1 H). **2**: δ 1.26(s, 3 H) 1.38(s, 3 H), 1.76(s, 3 H), 1.90(d, J = 2 Hz, 3 H), 5.80(m, 1 H), 5.94(m, 1 H), 6.00(d, J = 16 Hz, 1 H), 6.66(d, J = 16 Hz, 1 H). **1**: 1.08(d, J = 7 Hz, 3 H), 1.24(s, 3 H), 1.36(s, 3 H), 1.74(s, 3 H), 1.88(br s, 3 H), 1.88(dd, J = 7 and 12 Hz, 1 H), 2.16(dd, J = 7 and 12 Hz, 1 H), 2.40(d, J = 14 Hz, 1 H), 2.88(d, J = 14 Hz, 1 H), 2.98(m, 1 H), 5.78(m, 2 H), 5.98(d, J = 15 Hz, 1 H), 6.44(d, J = 15 Hz, 1 H).

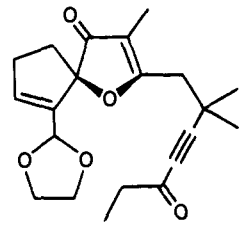
(8) O. K. Behrens, J. Corse, D. E. Huff, R. G. Jones, Q. F. Soper, and C. W. Whitehead, *J. Biol. Chem.*, **175**, 771 (1948).

(9) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

Collins reagent (12 equiv), acid-catalyzed deprotection, and cyclization–dehydration (10% HCl/THF, 5 h, room temperature), afforded spirofuranone **9a** as a mixture of diastereomers. The



(**9a**): R = R′ = O
(**9b**): R = R′ = OCH_2CH_2O

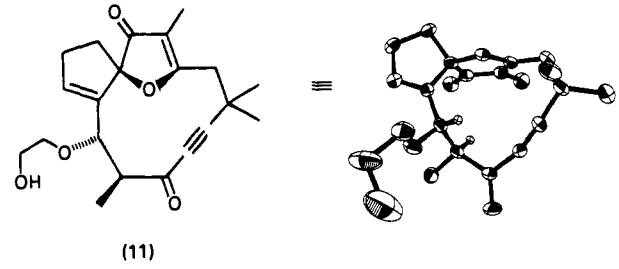


(**10**)

overall yield of **9a** based on **5a** after purification (medium-pressure LC, hexane/ethyl acetate, 2:1) was 68%. Fortunately for our purposes (vide infra) the allylic silyl ether underwent oxidation to the corresponding aldehyde during the Collins procedure.[9] Final conversion to keto aldehyde **4b**,[4] a crystalline solid (mp 91.5–92.5 °C), was accomplished again through the agency of Collins reagent.

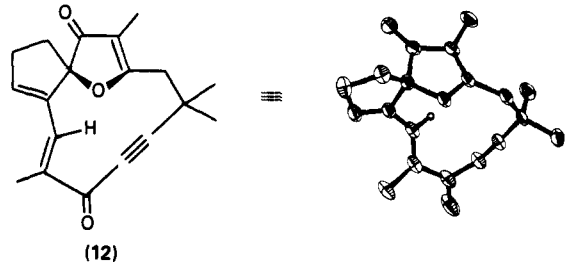
With this efficient *convergent* approach to keto aldehyde **4b** available, the stage was set to explore the key aldol cyclization (i.e., **4b** → **3b**). Unfortunately, all attempts to effect a *direct* cyclization to the desired eleven-membered ring system employing a wide variety of different acidic and basic reagents met with complete failure. Success was finally achieved via a somewhat less direct approach. Consider for the moment the events required for the successful cyclization of **4b**. First, chemospecific generation of the enol or enolate of the C(7) ketone and not the aldehyde is required.[10] Second, the enolate (enol) must undergo *irreversible* addition to the aldehyde. Ideal here would be the availability of an internal protecting or trapping agent. The latter stringent requirement appeared to be ideally fulfilled by the Mukaiyama[11] $TiCl_4$-promoted condensation of acetals with enol silyl ethers. To this end, ketal **9b** prepared from **9a** (100%, $HOCH_2CH_2OH$, TsOH, C_6H_6, $-H_2O$, 24 h) was oxidized (85%, Collins reagent)[9] to keto acetal **10**, which in turn was converted to the corresponding enol silyl ether (LDA/THF, −73 °C, 2.2 equiv of Me_3SiCl). Without isolation, the long sought after cyclization was effected with $TiCl_4$ (2.0 equiv, CH_2Cl_2, −78 °C, 5 min). Two diastereomeric products (47%, 2:1) resulted, the major (**11**) proving to be crystalline (mp 156–157 °C). To demonstrate beyond doubt that the macrocyclic ring was intact, we completed a single-crystal X-ray analysis; the result of that study is illustrated below.[12]

Elimination of the elements of ethylene glycol and conversion of the acetylene to a trans olefin were now all that were required



(**11**)

to complete normethyljatrophone, the first major plateau in our jatrophone synthetic program. Toward this end, both the major (**11**) and minor isomers were found to eliminate cleanly ethylene glycol upon exposure to toluenesulfonic acid in benzene, affording the same crystalline solid (mp 185–186 °C) in 79% yield. The ^1H NMR spectrum (250 MHz) of the elimination product revealed a substantial downfield shift for the C(5) vinyl proton. This result, clearly *inconsistent* with the chemical shift expected on the basis of analogy to jatrophone (δ 5.80 vs. 7.20 in $CDCl_3$), suggested that we had in fact generated the less stable *E* isomer (**12**).[7] X-ray crystallographic analysis, demonstrated this to be

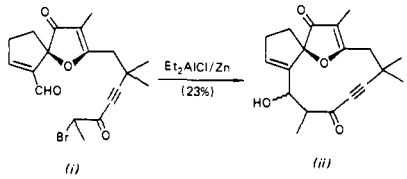


(**12**)

the case.[12] Significantly for our purposes, furanone (**12**) was found to undergo slow isomerization to the more stable *Z* isomer (**13**)[7] upon prolonged exposure to the above elimination conditions (2 weeks, 88%).

We had now arrived at the final step necessary for completion of our synthetic goal. The planned one-step conversion of the acetylene functionality to the desired trans olefin with chromous ion was, however, thwarted, presumably due to transannular reactions.[13] Fortunately, acetylene (**13**) could be selectively cis hydrogenated ($PdSO_4$/pyridine)[14] to *cis*/*Z*-**14**,[7,15] which in turn was promptly isomerized (KI/AcOH, room temperature, 30 min)[16] to normethyljatrophone (**2**)[7] (71% yield from **12**), the latter obtained as a beautiful crystalline solid (mp 135–136 °C). That normethyljatrophone was in hand derived from careful comparison

(10) To control generation of the specific ketone enolate, we initially selected the "Reformatsky-like" aldol condensation conditions recently introduced by Yamamoto; see K. Maruoka, S. Hashimoto, Y. Kitagawa, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, **99**, 7705 (1977); also see J. Tsuji and T. Mandai, *Tetrahedron Lett.*, 1817 (1978). To this end bromo aldehyde i was prepared from **9b** and subjected to the Yamamoto conditions.



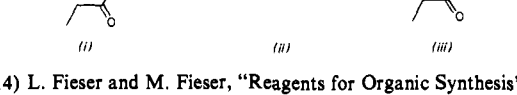
(i) (iii)

While successful, the above strategy does not eliminate the possibility of reversal of the aldol reaction; the latter, of course, would contribute to the modest yield of observed cyclization (i.e., 23%). Indeed, isolation of keto aldehyde **4b**, as a major side product, is suggestive that a reverse aldol process may be occurring under the Yamamoto conditions. Furthermore, we found aldol ii to be remarkably unstable, reverting to **4b** with ease!

(11) T. Mukaiyama and M. Yayashi, *Chem. Lett.*, 15 (1974); K. Banno and T. Mukaiyama, *Chem. Lett.*, 741 (1975); T. Mukaiyama and A. Ishida, *Chem. Lett.*, 312 (1975).

(12) Unpublished results of B. H. Toder, a graduate student, in our laboratory; a detailed account will be published in due course.

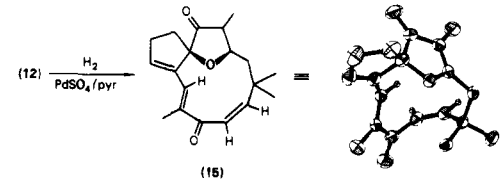
(13) That trans annular reaction plays a significant role in the reaction of chromous sulfate with **13** derives from the observed cyclization of model system i to ii. The latter was contaminated by a small amount of iii. Additional examples of this transformation will be reported in due course.



(i) (ii) (iii)

(14) L. Fieser and M. Fieser, "Reagents for Organic Synthesis", Wiley, New York, 1967, p 566.

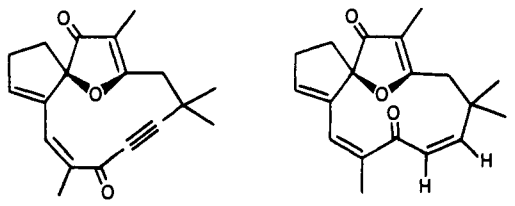
(15) Interestingly, hydrogenation ($PdSO_4$/pyridine) of **12** afforded furanone **15** (mp 212–213 °C) which proved to be stable to cis–trans isomerization. The structure of **15** was assigned by X-ray crystallographic analysis.[12]



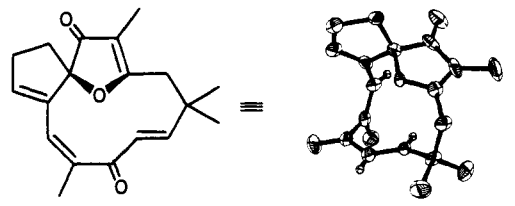
(15)

(16) We thank Dr. William Schreiber, International Flavors and Fragrances, for bringing this procedure to our attention.

of the 250-MHz ^1H NMR spectral data of the normethyl system with that of authentic jatrophone[7,17] as well as by completion of a single-crystal X-ray analysis; that result is illustrated below.[12]



(13) (14)



Normethyljatrophone

In summation, the total synthesis of normethyljatrophone has been achieved in 15 steps and in 5.6% overall yield from cyclopentenone (**7**). Four X-ray crystallographic analyses were completed during this venture, thereby confirming the structure of **11**, **12**, **15** and that of normethyljatrophone (**2**). Studies to improve the overall sequence, as well as to effect the total synthesis of jatrophone paralleling the above strategy, will be reported in due course.

Note Added in Proof. *Since acceptance of the manuscript, we have successfully completed the first stereocontrolled total synthesis of both (+)-jatrophone (**1**) and that of its epimer (+)-epijatrophone, exploiting the synthetic strategy outlined above; **5a** and its epimer served, respectively, as starting materials. A complete account of this effort will be forthcoming in the near future.*

Acknowledgment. It is a pleasure to acknowledge the support of this investigation by the National Institutes of Health (National Cancer Institute) through Grant No. CA-22807. In addition, we thank Mr. S. T. Bella of the Rockefeller University for the microanalyses and the Middle Atlantic Regional NMR Facility (NIH No. RR542) at the University of Pennsylvania where the 220- and 360-MHz spectra were recorded.

(17) We thank Dr. Matthew Suffness of the National Cancer Institutes and Dr. Jeffrey Cordell, University of Illinois, Chicago Circle—Medical Center, for providing us with a generous sample of jatrophone.

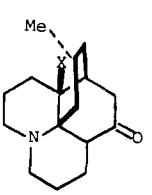
Total Synthesis of (±)-Lycodoline

Clayton H. Heathcock* and Edward F. Kleinman

Department of Chemistry, University of California Berkeley, California 94720

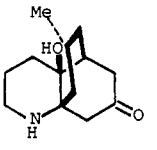
Received September 5, 1980

Lycodoline (**1**, "alkaloid L.8") is the second most widely occurring of the lycopodium alkaloids.[1] It was first isolated in 1943 by Manske and Marion from *L. annotinum* Linn[2] and its structure was established in 1961 by Ayer and Iverbach.[3] In an attempted synthesis, Horii and co-workers succeeded in preparing tricyclic amino ketone **2**[4] but were unable to add the final ring.[5] Because



1: X = OH

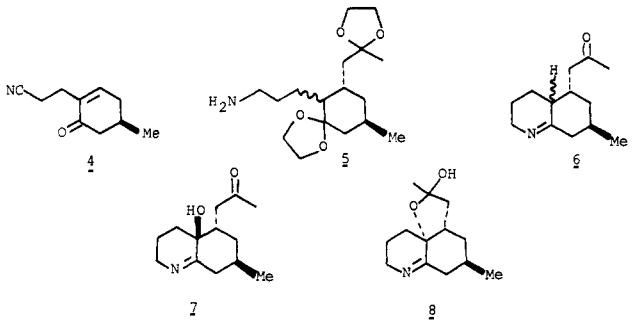
3: X = H



2

of the close structural resemblance between lycodoline and lycopodine (**3**), we have examined the use of intermediates employed in our lycopodine synthesis[6] for construction of alkaloid **1**. However, the presence of the sensitive tertiary alcohol function in lycodoline precludes the use of the acidic conditions required to effect the key Mannich cyclization in the synthesis of **3**.[6] In this communication, we report an interesting solution to this problem, which has culminated in the first total synthesis of (±)-lycodoline.

Amino diketal **5**, available in three steps (58% overall yield) from cyano enone **4**,[6] is treated briefly with 10% aqueous HCl, and the resulting solution is made basic with NaOH. The unstable



4 **5** **6** **7** **8**

octahydroquinoline (**6**) is extracted with ethyl acetate, and the resulting solution is treated with oxygen gas and then hydrogen and Pd/C to obtain a mixture of alcohol **7** (mp 164–65 °C, 43%) and hemiketal **8** (oil, 4%). This interesting autoxidation finds precedent in the work of Cohen and Witkop on the parent octahydroquinoline.[7] In the present case, it is noteworthy that the diastereomer having the angular oxygen and the neighboring acetonyl group trans predominates by a factor of 10:1. We postulate that this stereoselectivity arises from simple steric hindrance of approach of an oxygen molecule to the intermediate free radical.

The third ring is smoothly formed by heating a dilute solution of compound **7** (0.075 M) in a 5:1 mixture of toluene and 3-bromopropanol at reflux for 24 h. Neutralization of the resulting hydrobromide salt (which crystallizes from the hot solution) provides amino ketone **2** (mp 165–166 °C) in 85% yield. Many other attempts to accomplish this cyclization were unsuccessful. Since the product is a hydrobromide salt, a full equivalent of HBr is required. However, it appears to be crucial to the success of the reaction that the acid be added exceedingly slowly. Thus, if the hydrobromide salt of imine **7** is heated for 24 h in toluene, no cyclization occurs. 3-Bromopropanol functions as a source of HBr by slowly polymerizing under the reaction conditions. It is interesting to note that 3-bromopropanol is superior to 2-bromoethanol for this purpose.

(1) D. B. MacLean, *Alkaloids*, **14**, 347 (1973).
(2) R. H. Manske and L. Marion, *Can. J. Res., Sect. B*, **21**, 92 (1943).
(3) (a) W. A. Ayer and G. G. Iverbach, *Tetrahedron Lett.*, No. 3, 87 (1961); (b) W. A. Ayer and G. G. Iverbach, *Can. J. Chem.*, **42**, 2514 (1964).
(4) Z.-i. Horii, S.-W. Kim, T. Imanishi, and T. Momose, *Chem. Pharm. Bull.*, **18**, 2235 (1970).
(5) S.-W. Kim, Y. Bando, and Z.-i. Horii, *Tetrahedron Lett.*, 2293 (1978).
(6) C. H. Heathcock, E. Kleinman, and E. S. Binkley, *J. Am. Chem. Soc.*, **100**, 8036 (1978).
(7) L. A. Cohen and B. Witkop, *J. Am. Chem. Soc.*, **77**, 6595 (1955).

0002-7863/81/1503-222$01.00/0