in the reduction process and the quantum yield for net hydrogen transfer is one.

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C. G. Shaefer, K. S. Peters*
Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138
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Synthesis of (±)-Illudol

Sir:

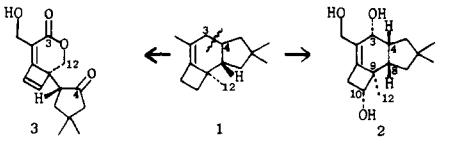
Among natural sesquiterpene alcohols, those possessing the Δ^6-protoilludane skeleton (**1**) have attracted attention as synthesis targets because of the unique methylene–cyclobutane structural feature.[1] Illudol (**2**), a member of this class, has recently been obtained by total synthesis.[2] Fomannosin (**3**) has been shown to arise through protoilludane precursors in nature[3] and has not yet been successfully synthesized.[4] The relation between illudol (**2**) and fomannosin (**3**) is indicated by the bond cleavage at C-3/C-4 (in **1**, and Scheme I) and reconnection at C-3/C-12 and provides an important suggestion for a strategy for the synthesis of fomannosin, currently under way in our laboratory.[5] The two carbons joining the four-membered and five-membered rings have the same configuration in both illudol and fomannosin. An appropriately functionalized protoilludane derivative provides a rigid skeletal framework for a stereocontrolled synthesis of fomannosin and illudol. We report here a short synthesis of the appropriate intermediate (**4**) and its conversion to illudol (**2**).

Illudol (**2**) has five contiguous chiral centers: two of them (C-3, C-10) bear hydroxyl groups where selective carbonyl reduction will control the configuration, one (C-4) is adjacent to a potential carbonyl group (C-3) and therefore easily epimerized, and the C-8/C-9 pair are to be controlled in the central carbon–carbon bond-forming step. This central operation is the Diels–Alder reaction of a cyclobutene (i.e., **5**) and a 1,3-diene (i.e., **6**). The ester substituent in **5** was expected to provide sufficient reactivity for cycloaddition, to provide the oxygen substituent required at C-12 in fomannosin (**3**), and to allow secondary orbital overlap leading to the required endo addition product (**4**).

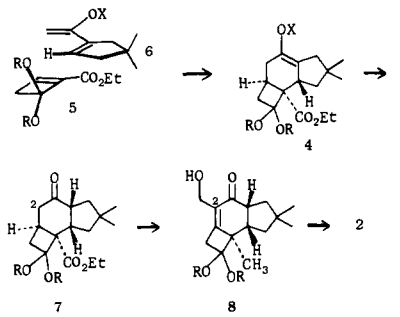
Scheme II presents the strategy for illudol, focusing on three critical stages: (a) cycloaddition to give **4**, (b) hydrolysis of the enol unit to give **7**, and (c) introduction of the hydroxymethyl group and double bond at C-2 to give **8**.

The highly functionalized cyclobutene **5** is of a type which has recently been prepared by Lewis acid catalyzed [2 + 2] cycloaddition of propiolic esters with electron-rich alkenes.[6] After initial studies using various Lewis acids, we found that a simple uncatalyzed thermal reaction (CH_2Cl_2, reflux, 29 h) of ethyl propiolate with 1,1-diethoxyethylene produced **5** in 65% yield.[7] The acetylcyclopentene **9**[7,8] served as precursor of the general diene, **6**. It was prepared in 80% overall yield from 4,4-dimethylcyclohexanone via addition of methylmagnesium bromide, dehydration, and ozonolysis to give 3,3-dimethyl-6-oxoheptanal which underwent acid-catalyzed aldol condensation and dehydration to give **9**; a small amount of the alternative aldol product was separated by distillation. Treatment of **9** with lithium diisopropylamide produced the enolate anion **6a** which was trapped in separate experiments with methyl *p*-toluenesulfonate (to give **6b**), chlorotrimethylsilane (to give **6c**),[7] and *tert*-butylchlorodimethylsilane (to give **6d**).[7] Extensive studies on the reaction of

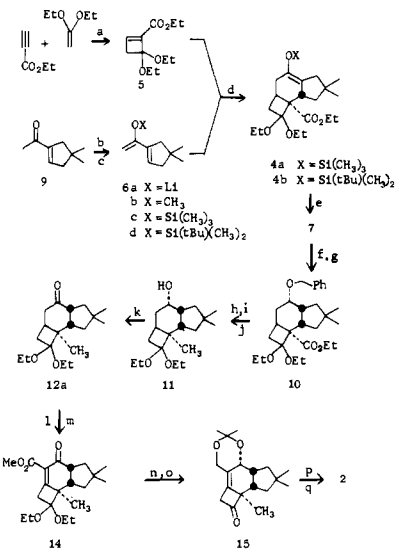
Scheme I. Biosynthesis Connection



Scheme II. Strategy for Illudol



Scheme III. Synthesis of Illudol[a]



[a] (a) 29 h, CH_2Cl_2, reflux, 65%; (b) $LiNR_2$, −78 °C; (c) CH_3OTs, $ClSi(CH_3)_3$, or $ClSi(t\text{-}Bu)(CH_3)_2$; (d) 48 °C, 10 days (sealed flask), 72%; (e) 3-Å molecular sieves, CH_3OH, 25 °C, 4.5 h, 96%; (f) $LiEt_3BH$, 0 °C, 3 min, 99%; (g) $PhCH_2Br$, NaH, 70 °C, 5 h, 92%; (h) $LiAlH_4$, 96%; (i) *n*-BuLi, THF, 25 °C, 5 min, followed by $ClPO(N(CH_3)_2)_2$, 25 °C, 5 h, 82%; (j) Li, $EtNH_2$, THF, *t*-BuOH, 0 °C, 0.5 h, 94%; (k) CrO_3, pyridine, CH_2Cl_2, 87%; (l) $LiNR_2$, THF, −78 °C, followed by CO_2 (gas, excess), followed by neutralization and CH_2N_2; (m) $LiNR_2$, THF, −78 °C, followed by H_2O_2, 25 °C, 0.5 h, 38% overall; (n) $NaAl(OR)_2H_2$, C_6H_6, 25 °C, 14 h (ref 2); (o) $C_7H_6SO_3H$, acetone, 25 °C (ref 2); (p) $NaAl(OR)_2H_2$, C_6H_6, 25 °C (ref 2), (q) HCl–THF.

(1) Illudol was first reported in 1967: T. C. McMorris, M. S. R. Nair, and M. Anchel, *J. Am. Chem. Soc.*, **89**, 4562 (1967).
(2) T. Matsumoto, K. Miyano, S. Kagawa, S. Yu, J. Ogawa, and A. Ichibara, *Tetrahadron Lett.*, 3521 (1971).
(3) D. E. Cane and R. S. Nachbar, *J. Am. Chem. Soc.* **100** 3208 (1978).
(4) Two syntheses of dihydrofomannosin derivatives (cyclobut*ane*) have been reported: (a) K. Miyano, F. Ohfune, S. Azuma, and T. Matsumota, *Tetrahedron Lett.*, 1545 (1974); (b) H. Kosugi and H. Uda, *Bull. Chem. Soc. Jpn.* **53**, 160 (1980).
(5) The biogenetic relationship between illudol and fomannosin was proposed to us by Professor D. Arigoni (ETH, Zurich) during seminar discussions at Cornell in 1974 and led to the strategy developed here.
(6) For examples, see: (a) B. B. Snider, D. J. Rodini, R. S. E. Conn, and S. Sealfon, *J. Am. Chem. Soc.*, **101**, 5283 (1979); (b) R. D. Clark and K. G. Untch, *J. Org. Chem.*, **44**, 248 (1979). Simple thermal [2 + 2] cycloaddition of enamines with propiolate esters also produces cyclobutene-2-carboxylates: (c) C. F. Huebner, L. Dorfman, M. M. Robison, E. Donoghue, W. G. Pierson, and P. Strachan, *ibid.* **28**, 3134 (1963); (d) K. C. Braunnock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *ibid.*, **29**, 818 (1964).
(7) Characterization data for this compound are included in the supplementary material.
(8) K. Von Auwers and E. Lange, *Liebigs Ann. Chem.*, **409**, 149 (1915).

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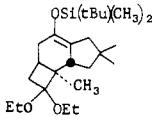
6b with acrylate derivatives, with and without Lewis acid and metal catalysts,[9] failed to produce more than traces of Diels-Alder adducts. This lack of reactivity of diene **6b** was particularly forbidding in light of the tendency of cyclobutene derivatives to rearrange thermally to 1,3-dienes.[10]

However, using the enolsilyl ethers **6c** or **6d**, reaction of **5** proceeded efficiently under minimum temperature conditions (48 °C, 10 days) to produce 1:1 adducts in 70-75% yield and >95% selectivity after purification by column chromatography.[11] Structures **4a** and **4b** were assigned to the adducts based on spectral data.[7] However, the stereochemical assignment was secure only after conversion to illudol, which requires the configuration shown in **4**.

Hydrolysis of **4a** or **4b** under standard conditions (fluoride anion or basic hydrolysis) produced a mixture of the desired cis ring fusion isomer **7** and the corresponding trans isomer, in similar amounts.[12] However, desilylation of **4a** could be achieved under very mild conditions (3-Å molecular sieves, methyl alcohol, 25 °C, 4.5 h) to give exclusively the cis product, **7** (95% yield).[7] This selective hydrolysis could not be obtained from the more stable silyl ether, **4b**. Selective reduction of **7** with lithium triethylborohydride followed by protection of the secondary hydroxyl group as the benzyl ether (to give **10**)[7] allowed application of Ireland's procedure for converting ester units to methyl groups.[13] The lithium metal reduction (Scheme III, step i) also served to remove the benzyl protecting group. Oxidation produced the key intermediate **12a**[7] in 56% overall yield from **4a**.

An alternative preparation of **12** without the use of the benzyl protecting group was developed through application of Ireland's reduction method directly on the *tert*-butyldimethylsilyl ether **4b**. The reduced compound **13** was obtained in 74% yield by using



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carefully selected conditions.[7,14] Then desilylation with fluoride anion gave a mixture of **12a** and the corresponding trans isomer, **12b**, which were separated by chromatography. Equilibration of the trans isomer in dilute sodium methoxide/methyl alcohol gave a mixture of **12a**/**12b** (60/40) from which **12a** was again isolated. The combined yield of **12a** after two equilibrations was 89%, resulting in an overall yield of **12a** from **4b** of 65%.

Functionalization of C-2 in **12a** was accomplished by carboxylation of the kinetic enolate anion with carbon dioxide and methylation with diazomethane (Scheme III). By means of a selenoxide elimination,[15] the strained double bond exocyclic to the four-membered ring was introduced to give **14** in 37% overall yield from **12a**.[7] Intermediate **14** was used in the earlier synthesis of illudol,[2] and we followed that pathway to produce a sample of (±)-illudol which was identified by comparison with material from nature (Scheme III).[16] Efforts are under way to convert intermediate **4** into fomannosin (**3**).

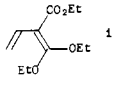
Acknowledgment. We are pleased to acknowledge preliminary work by Dr. Utpal Chakraborty and Professor Leonard Keller (Florida International University) and financial support from the National Institutes of Health. A grant from the National Science Foundation to the Princeton Chemistry Department provided the JEOL-MX90Q NMR spectrometer which was used in this work. S.T. thanks the Ministry of Education (Japanese Government) for financial support.

Supplementary Material Available: Characterization data on all new compounds (5 pages). Ordering formation is given on any current masthead page.

(9) For a review of the role of catalysis in the Diels-Alder reaction, see: J. Sauer, *Angew. Chem., Int. Ed. Eng.*, **6**, 16 (1967).

(10) For discussion and examples, see: R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Academic Press, New York, 1971, p 48 ff. The cyclobutene derivative **5** has a half-life of ~1 h/90 °C. Cyclobutenes are not common participants in Diels-Alder reactions. For discussion and recent examples, see: V. V. Plemenkov and V. P. Kostin, *J. Org. Chem. USSR (Engl. Transl.)*, **15**, 1086 (1979), and references therein.

(11) The adducts were homogeneous within the limits of ^{13}C NMR analysis. Reaction of **5** at higher temperatures was less efficient, giving a byproduct which has been tentatively characterized as diene i.



i

(12) The cis isomer **7** was converted to a mixture of **7** and the corresponding trans ring fusion isomer (~60:40, favoring **7**) upon treatment with sodium methoxide in methyl alcohol.

(13) R. E. Ireland, D. C. Muchmore, and U. Hengartner, *J. Am. Chem. Soc.*, **94**, 5098 (1972).

(14) The combination of sodium counterion (instead of Li) and 1,2-dimethoxyethane as solvent (instead of tetrahydrofuran) was important in the formation of the phosphorodiamidate, in order to avoid cleavage of the enol silyl ether. Similarly, under the standard[13] conditions (0 °C, Li/$EtNH_2$) for cleavage of primary phosphorodiamidates, substantial desilylation occurred. But at −78 °C, reaction using the same reagents was complete within 2 h with no significant desilylation.

(15) H. J. Reich, F. Chow, and S. K. Shah, *J. Am. Chem. Soc.*, **101**, 6638 (1979), and references therein.

(16) We are grateful to Dr. M. Anchel of the New York Botanical Garden for providing a sample of natural (−)-illudol.

(17) Fellow of the John Simon Guggenheim Foundation, 1978-1979.

(18) On leave from the Department of Chemistry, University of Tokyo, Komaba, Meguro, Tokyo, Japan 153.

* Address correspondence to Princeton University.

M. F. Semmelhack,*[17] Shuji Tomoda,[18] K. M. Hurst

Department of Chemistry, Princeton University
Princeton, New Jersey 08544
Department of Chemistry, Cornell University
Ithaca, New York 14853

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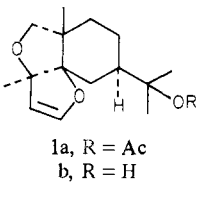
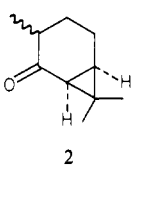
A Convenient, Stereospecific Synthesis of (−)-Phytuberin from (−)-2-Carone[1]

Sir:

\Phytuberin (**1a**) is a sesquiterpene stress metabolite which has been isolated from fungal-infected potato tubers by Coxon and co-workers.[2] Its structure was established by spectroscopic methods and by an X-ray crystallographic structure determination on its 2,3-dihydro derivative. A lengthy biogenetic-like synthesis of **1a** from α-cyperone, which established the absolute stereochemistry of the compound, was reported recently by Masamune and co-workers.[3,4] We wish to report a convenient, seven-step synthesis of **1a** from (−)-2-carone (**2**) which allowed preparation



1a, R = Ac
b, R = H



2

of the natural product in 11% overall yield.

The cyclohexanone derivative **3** was obtained in a highly stereospecific manner. Alkylation of the lithium 2,3-enolate of **2** prepared under thermodynamic conditions by using lithium di-

(1) This research was supported by a grant (NSF 7810044) from the National Science Foundation for which we are grateful.

(2) Coxon, D. T.; Price, K. R.; Howard, B.; Curtis, R. F. *J. Chem. Soc., Perkin Trans. 1* **1977**, 53.

(3) Murai, A.; Ono, M.; Abiko, A.; Masamune, T. *J. Am. Chem. Soc.* **1978**, *100*, 7751.

(4) For the proposed biogenetic pathway to phytuberin, see Stossel, A.; Stothers, J. B.; Ward, E. W. B. *Can. J. Chem.* **1978**, *56*, 645.

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