Inside–Outside Stereoisomerism. 2.[1] Synthesis of the Carbocyclic Ring System of the Ingenane Diterpenes via the Intramolecular Dioxolenone Photocycloaddition[†]

Jeffrey D. Winkler*[2] and Kevin E. Henegar

Searle Chemical Laboratories, Department of Chemistry
The University of Chicago, Chicago, Illinois 60637

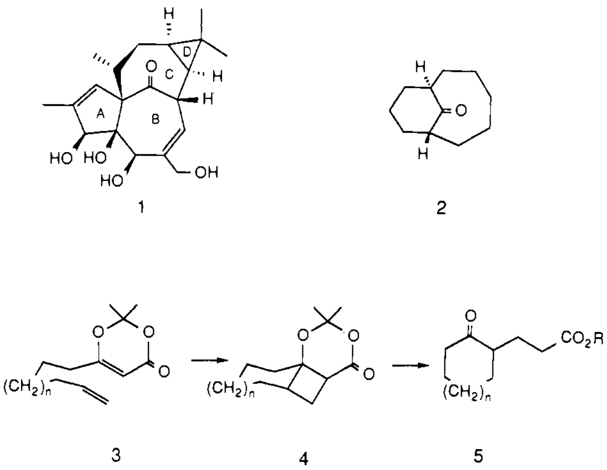
Paul G. Williard[3]

Department of Chemistry, Brown University
Providence, Rhode Island 02912

Received November 21, 1986

The ingenane diterpenes comprise a structrually novel group of highly oxygenated tetracyclic diterpene esters with a broad spectrum of biological activities, ranging from the tumor-promoting properties of some derivatives to the powerful antileukemic activity of others.[4,5] The isolation and pharmacology of these substances have been thoroughly reviewed.[6] Structural and absolute configurational assignments for the series follow from X-ray crystal structure analysis of the triacetate of ingenol (**1**) (Scheme I).[7,8] Central to the novel structure of the ingenanes and a structural feature which has thwarted all synthetic efforts to date[8–10] is the highly strained bicyclo[4.4.1]undecan-11-one (BC rings), which possesses the unusual inside–outside intrabridgehead stereochemical relationship.[11] We have recently described the first synthesis of *trans*-bicyclo[5.3.1]undecan-11-one (**2**), the smallest bicyclic ring system known to exhibit inside–outside intrabridgehead stereochemistry,[1] via the intramolecular dioxolenone photocycloaddition developed in our laboratories, i.e., **3** → **5**.[12] We report herein the first synthesis of the carbocyclic skeleton of the ingenane diterpenes, which contains the remarkable inside–outside intrabridgehead stereochemistry.

Scheme I



Scheme II

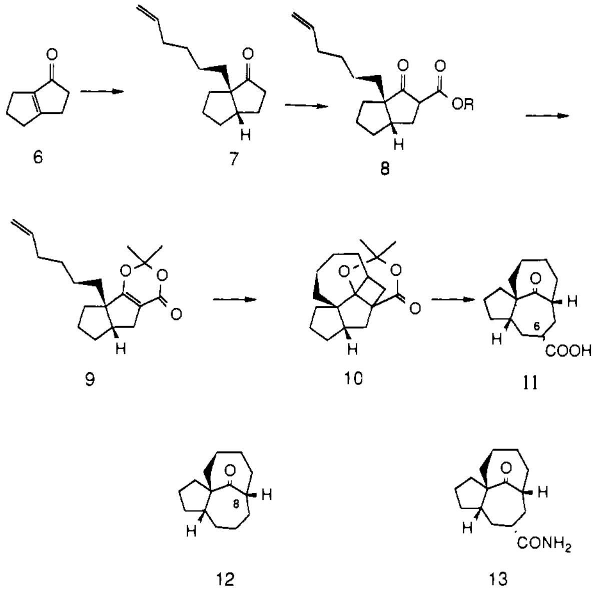


Chart I

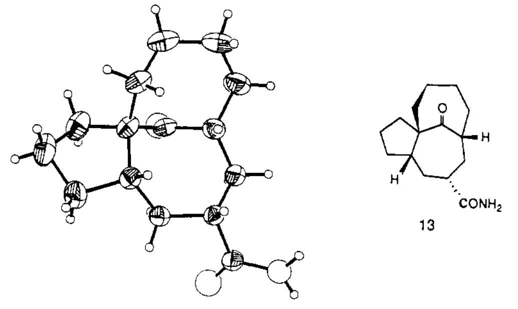
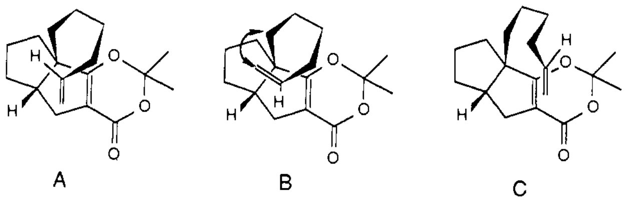


Chart II



The photosubstrate **9** was prepared as outlined in Scheme II.[13] Reductive alkylation of **6**[14] (Li^0, tetrahydrofuran, liquid ammonia) with 5-hexenyl iodide provided the *cis*-fused angularly alkylated bicyclooctane **7** in 58% yield. The next step in the sequence was the carboxylation of **7** to provide **8**. Attempted carboxylation of the enolate derived from **7** with carbon dioxide, dimethyl carbonate, di-*tert*-butyl dicarbonate, or *tert*-butyl cyanoformate was unsuccessful. However, treatment of the enolate derived from **7** (lithium diisopropylamide, tetrahydrofuran, 0 °C) with *p*-methoxybenzyl cyanoformate (1.3 equiv of cyanoformate, 1 equiv of hexamethylphosphoramide, −78 °C → room temperature)[15]

[†] Dedicated to Professor Gilbert Stork, an inspiring teacher and scholar to whom we are very grateful.

(1) For the preceding publication on inside–outside stereoisomerism, see: Winkler, J.; Hey, J; Williard, P. *J. Am. Chem. Soc.* **1986**, **108**, 6425.

(2) Fellow of the Alfred P. Sloan Foundation, 1987–1989. Recipient of a Merck Grant for Faculty Development, 1985–1987.

(3) Author to whom correspondence regarding X-ray structure of **13** should be addressed.

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0002-7863/87/1509-2850$01.50/0

led to the formation of the desired β-keto ester 8 (R = *p*-methoxylbenzyl) in 82% yield. Conversion of the *p*-methoxylbenzyl keto ester to photosubstrate **9** proceeded in 85% yield, using an excess of acetic anhydride (55 equiv) in 1:1 trifluoracetic acid/acetone (−78 °C → room temperature, 12 h). Irradiation of **9** (0.0075 M in 1:9 acetone/acetonitrile, Pyrex immersion well, 0 °C, 90 min) lead to the formation of a single photoadduct **10**[16] in 83% yield. Fragmentation of **10** (2 N potassium hydroxide, methanol, 40 °C, 4 h, 88% yield) provided keto acid **11** as a mixture of epimeric compounds, which could be interconverted as the corresponding methyl esters by using sodium methoxide in methanol. That the keto acids were epimeric at C-6 (ingenane numbering) could be demonstrated by Barton decarboxylation[17] of the separated keto acids to the same ketone **12**.[18] The chemical shift of the C-8 proton [δ 2.87 (m, 1 H)] and the infrared absorption for the carbonyl (1719 $\mathrm{cm^{-1}}$) in **12** were identical with the corresponding spectral data obtained for *trans*-bicyclo[4.4.1]undecan-11-one,[19] prepared in our laboratory in a similar manner, but unambiguous proof of the inside–outside intrabridgehead stereochemical relationship in **11** follows from the single-crystal X-ray analysis of ketoamide **13**[20] [derived from the major epimer of **11** via treatment of the derived acid chloride (thionyl chloride, toluene) with aqueous ammonium hydroxide]. As indicated in Chart I, the stereochemistry of the bicyclo[4.4.1]undecane (BC rings) of **13** is trans bridged.

The exclusive formation of the inside–outside isomer can be explained by examination of the diastereomeric transition states in Chart II. The seven-membered ring can be formed in the cycloaddition in either pseudochair (A or B) or pseudoboat (C) conformations.[21] In the first two cases, the double bond can approach in either a parallel or perpendicular sense.[22] The perpendicular approach, B, presents the indicated unfavorable nonbonded interactions which are not present in A. The alternate pseudoboat conformation C suffers transannular eclipsing interactions which are not present in A or B, so that A, which leads to the desired "inside–outside" conformation, should best represent the transition state leading to photocycloaddition.

In conclusion, the results described herein represent another example of the stereochemical consequences of the conformation of the nascent ring (seven-membered in the photocycloaddition of **9**) in the intramolecular photochemical cyclization.[1,12] The viability of the intramolecular dioxolenone photocycloaddition for the establishment of the critical inside–outside intrabridgehead stereochemistry of the ingenane diterpenes has now clearly been established, and the application of this methodology to the synthesis of this fascinating class of compounds is currently under way in our laboratory.

Acknowledgment. Support from the donors of the Petroleum Research Fund, administered by the American Chemical Society, the National Institutes of Health (CA40250 to J.D.W. and GM35982 to P.G.W.), an American Cancer Society Institutional Grant, and Merck, Sharp and Dohme is gratefully acknowledged. The NMR instruments used were funded in part by the NSF Chemical Instrumentation Program and by the NCI via the University of Chicago Cancer Research Center (CA 14599).

Supplementary Material Available: X-ray crystal stucture data, stereoview, and tables of atomic coordinates, bond lengths, bond angles, and anisotropic thermal parameters for the crystal structure of **13** (4 pages); table of crystal structure factor data of **13** (13 pages). Ordering information is given on any current masthead page.

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(16) Spectral data for **10**: IR ($\mathrm{CDCl_3}$) 1723 $\mathrm{cm^{-1}}$; ^{1}H NMR ($\mathrm{CDCl_3}$) δ 1.2–2.1 (m, 13 H), 1.63 (s, 3 H), 1.75 (s, 3 H), 1.9 (m, 1 H), 2.1 (m, 2 H), 2.35 (m, 3 H), 2.62 (m, 1 H); ^{13}C NMR δ 23.6, 25.25, 30.5, 30.67, 31.3, 33.43, 35.22, 35.48, 39.77, 40.72, 41.96, 43.10, 52.72, 61.35, 93.87, 108.04, 172.49.

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(18) Spectral data for **12**: IR ($\mathrm{CDCl_3}$) 1719 $\mathrm{cm^{-1}}$; ^{1}H NMR ($\mathrm{CDCl_3}$) δ 1.1–2.1 (m, 21 H), 2.87 (m, 1 H); ^{13}C NMR ($\mathrm{CDCl_3}$) δ 25.16, 25.96, 30.42, 30.45, 30.50, 30.59, 30.74, 34.98, 36.10, 41.07, 50.28, 54.22, 63.45, 216.90.

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(20) Data were collected on a Nicolet R3m/E crystallographic system. The structure was solved by the SHELXTL 4.1 programs. The ingenane skeleton crystallized in the centrosymmetric, monoonoclinic space group $P2_1/c$. The unit cell parameters were determined to be $a = 6.723$ (1) Å, $b = 15.852$ (6) Å, and $\beta = 91.86$ (2)°; $R = 0.0461$, $R_w = 0.0621$.

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Reductive Cleavage of Sulfonates. Deprotection of Carbohydrate Tosylates by Photoinduced Electron Transfer

John Masnovi,* Dolores J. Koholic, Robert J. Berki, and Roger W. Binkley

Department of Chemistry, Cleveland State University
Cleveland, Ohio 44115

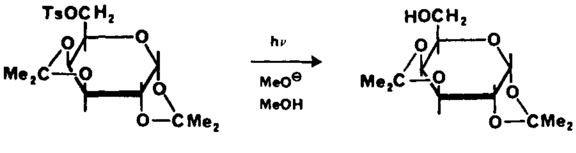
Received September 26, 1986

Esters of *p*-toluenesulfonic acid are used as protecting groups in carbohydrate chemistry.[1] This use is possible because tosylate displacement from carbohydrates usually requires forcing conditions; consequently, a variety of transformations can be conducted elsewhere in the molecule without altering the tosyloxy group.[2] Deprotection is accomplished with ease by photolysis in the presence of base.[3] The mechanism of this reaction has been proposed to involve homolytic cleavage of a S–O bond to form an alkoxy radical (eq 1).[4,5] Mechanistic studies have shown

$$\mathrm{CH_3C_6H_4SO_2OR} \xrightarrow{h\nu} \mathrm{CH_3C_6H_4SO_2OR^1} \xrightarrow{\mathrm{OH^-}} \mathrm{CH_3C_6H_4SO_2 + OR} \quad (1)$$

that bases such as hydroxide quench the excited singlet state of tosylates and improve the efficiency of reaction; however, the nature of the quenching interaction has not been explained.[5]

Recent studies in our laboratories have determined the role of hydroxide in this reaction and indicated a different mechanism for the photochemical process than that previously proposed.[4,5] Photolysis of 1,2:3,4-di-*O*-isopropylidene-6-*O*-(*p*-tolylsulfonyl)-α-D-galactopyranose (**1**) (10 mM) in alkaline (25 mM NaOH) methanol under nitrogen using a Corex optical filter (240 nm cut-off) affords the alcohol **2** quantitatively after aqueous workup (eq 2).[3] Amines also promote the reaction, and the efficiency of removal of the tosyloxy group depends upon the structure of the particular amine (Table I). No correlation is observed between the nucleophilicity of the bases and the efficiency of reaction; for example, the weakly nucleophilic diisopropylethylamine serves as one of the most effective bases. However, a qualitative correlation is found with the electron-donating ability of the amines (which is related to their ionization potentials[6]). Electron transfer



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