Table II. Incubation of ^{3}H-*all-trans*-Retinol Analogues with Bovine Pigment Epithelium Washed Homogenates at 37 °C for 1 h[a]

	retinol		retinyl palmitate	
substrate	% 11-cis	% recovery	% 11-cis	% recovery
5,6-DHATOL (3)				
without membranes	0.6	>99	/	<1
with membranes	3.7	19.8	1.2	80.2
7,8-DHATOL (4)				
without membranes	0.2	>99	/	<1
with membranes (n = 2)	3.9 ± 2.2	6.1 ± 2.6	0.6 ± 0.1	93.9 ± 2.6
9,10-DHATOL (5)				
without membranes	1.4	>99	/	<1
with membranes	4.3	30.5	2.5	69.5
vitamin A_2 (7)				
without membranes	0.1	>99	/	<1
with membranes (n = 2)	69.2 ± 1.2	18.3 ± 0.9	27.7 ± 3.9	81.7 ± 0.9
all-trans-retinol (1)				
without membranes	0.3	>99	/	<1
with membranes	52.1	26.5	25.1	73.5

[a] The preparation of bovine pigment epithelium washed membranes is described elsewhere;[2] 0.2 μCi of the 15-^{3}H-labeled substrate was incubated with 300 μL of the bovine pigment epithelium washed membranes and 15 μL of 10% BSA (as retinol carrier) for 1 h at 37 °C. The retinoids were extracted and analyzed by standard methods.[1] The formation of retinal is not significant in this membrane preparation. DHATOL refers to dihydro-*all-trans*-retinol.

the rhodopsin (porphyropsin) is based on the vitamin A_2 system.[9]

Acknowledgment. This work was supported by United States Public Health Service Research Grants EY 04096 and GM 36564 from the National Institutes of Health.

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A Highly Efficient, Practical Approach to Natural Taxol†

Jean-Noël Denis and Andrew E. Greene*

Université Joseph Fourier de Grenoble, LEDSS, Bât.52 38041 Grenoble Cedex, France

Daniel Guénard, Françoise Guéritte-Voegelein,* Lydie Mangatal, and Pierre Potier

Institut de Chimie des Substances Naturelles du CNRS 91190 Gif-sur-Yvette, France

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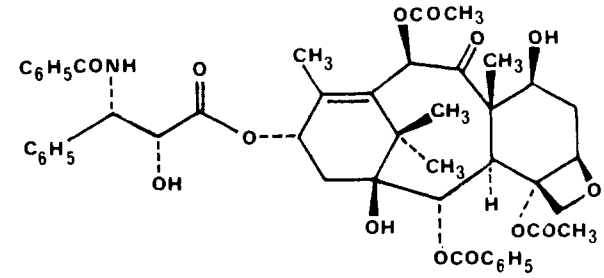
Taxol (**1**)[1] is an exceptionally promising cancer chemotherapeutic agent with an unusually broad spectrum of potent antileukemic and tumor-inhibiting activity.[2] Taxol is active in vivo against P-388, P-1534, and L-1210 mouse leukemias, B-16 melanocarcinoma, Lewis lung carcinoma, sarcoma 180, and CX-1 colon, LX-1 lung, and MX-1 breast xenographs.[1-3] The bark



Taxol (1)

from several species[4] of yew (genus *Taxus*, family Taxaceae), very slow-growing evergreens,[5] currently supplies taxol; the isolation procedure, however, is difficult, low-yielding,[6] and, obviously, fatal to the source, which is threatened. There is widespread concern that, ironically, "if taxol proves effective...the yew population could be so severely depleted that there would not be enough trees left to make treatment successful"[7] and that "alternative sources will need to be found to cater for the increased demand".[8] The National Cancer Institute has recently contracted for 27 000 kg of yew bark.[8]

The structural novelty of this complex, highly functionalized diterpene together with its exciting therapeutic potential has engendered worldwide a prodigious effort toward its total synthesis.[9] Taxol is quite possibly the number one target today of synthetic organic chemists. The various strategies revealed to date appear, however, to be of little practical value in that even if successful they would probably be incapable of furnishing the natural product in more than trace amounts.

In contrast, an efficient partial synthesis of taxol from an easily and permanently accessible taxol congener would provide an attractive solution to this serious supply problem. We report in this communication a direct synthesis of taxol through the successful implementation of such an approach.

10-Deacetyl baccatin III (**2**, Scheme I) can be readily extracted in high yield from the leaves of *Taxus baccata* L.[10] It is important to recognize that the yew leaves are quickly regenerated, hence through prudent harvesting large amounts of **2** can be continually

† Dedicated to the memory of Professor Pierre Crabbé.

(1) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325-2327.

(2) Taxol (NSC-125973) is currently in phase II clinical trials in the United States. It is the only plant product known to promote the assembly of microtubules and inhibit the tubulin disassembly process and, thus, appears to be the prototype of a new class of cancer chemotherapeutic agents. See: Suffness, M.; Cordell, G. A. In *The Alkaloids, Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: Orlando, FL, 1985; Vol. XXV, Chapter 1.

(3) Douros, J.; Suffness, M. In *Recent Results in Cancer Research*; Carter, S. K., Sakurai, Y., Umezawa, H., Eds.; Spinger-Verlag: Berlin, 1981; Vol. 76, pp 169-170. Lomax, N. R.; Narayanan, V. L. *Chemical Structures of Interest to the Division of Cancer Treatment*; U.S. Government Printing Office: Washington, D.C., 1983; Vol. III, p 17. Engel, S. I.; Schwartz, E. L.; Strauman, J. J.; Wiernik, P. H. *Proc. Am. Assoc. Cancer Res.* **1985**, *26*, 158. Zee-Cheng, R. K.-Y.; Cheng, C. C. *Drugs of the Future* **1986**, *11*, 45-48.

(4) (a) Miller, R. W.; Powell, R. G.; Smith, C. R., Jr.; Arnold, E.; Clardy, J. *J. Org. Chem.* **1981**, *46*, 1469-1474. (b) Sénilh, V.; Blechert, S.; Colin, M.; Guénard, D.; Picot, F.; Potier, P.; Varenne, P. *J. Nat. Prod.* **1984**, *47*, 131-137. (c) Magri, N. F.; Kingston, D. G. I. *J. Org. Chem.* **1986**, *51*, 797-802. (d) See, also: Sénilh, V. Ph.D. Dissertation, Université de Paris-Sud, Orsay, 1984, and references cited therein.

(5) The yew is one of the slowest growing trees in the world, growing at less than one-tenth the rate of the Douglas fir.[7]

(6) The reported yields of taxol from various species of yew range from 40 to 165 mg/kg.[4]

(7) New York Times, May 3, 1987, p 29.

(8) Suffness, M. National Cancer Institute, personal communication.

(9) For a compilation of references through 1986, see: Berkowitz, W. F.; Amarasekara, A. S.; Perumattam, J. J. *J. Org. Chem.* **1987**, *52*, 1119-1124. For more recent work, see: Swindell, C. S.; Patel, B. P.; deSolms, S. J. *J. Org. Chem.* **1987**, *52*, 2346-2355. Hua, D. H.; Gung, W.-Y.; Ostrander, R. A.; Takusagawa, F. *J. Org. Chem.* **1987**, *52*, 2509-2517. Lin, J.; Nikaido, M. M.; Clark, G. *J. Org. Chem.* **1987**, *52*, 3745-3752. Wender, P. A.; Snapper, M. L. *Tetrahedron Lett.* **1987**, *28*, 2221-2224. Pettersson, L.; Frejd, T.; Magnusson, G. *Tetrahedron Lett.* **1987**, *28*, 2753-2756. Swindell, C. S.; Patel, B. P. *Tetrahedron Lett.* **1987**, *28*, 5275-5278. Bonnert, R. V.; Jenkins, P. R. *J. Chem. Soc., Chem. Commun.* **1987**, 1540-1541. Shea, K. J.; Haffner, C. D. *Tetrahedron Lett.* **1988**, *29*, 1367-1370. Trost, B. M.; Fray, M. J. *Tetrahedron Lett.* **1988**, *29*, 2163-2166.

(10) Chauvière, G.; Guénard, D.; Picot, F.; Sénilh, V.; Potier, P. *C. R. Seances Acad. Sci., Ser 2* **1981**, *293*, 501-503. We are currently obtaining **2** in yields of ca. 1 g/kg of fresh leaves. (It should be noted that **2** is far less active than taxol.[1]) For previous transformations of **2**, including an alternative approach to taxol, see references 12a,b and Colin, M.; Guénard, D.; Guéritte-Voegelein, F.; Potier, P. French Patent 2 601 676, 1986.

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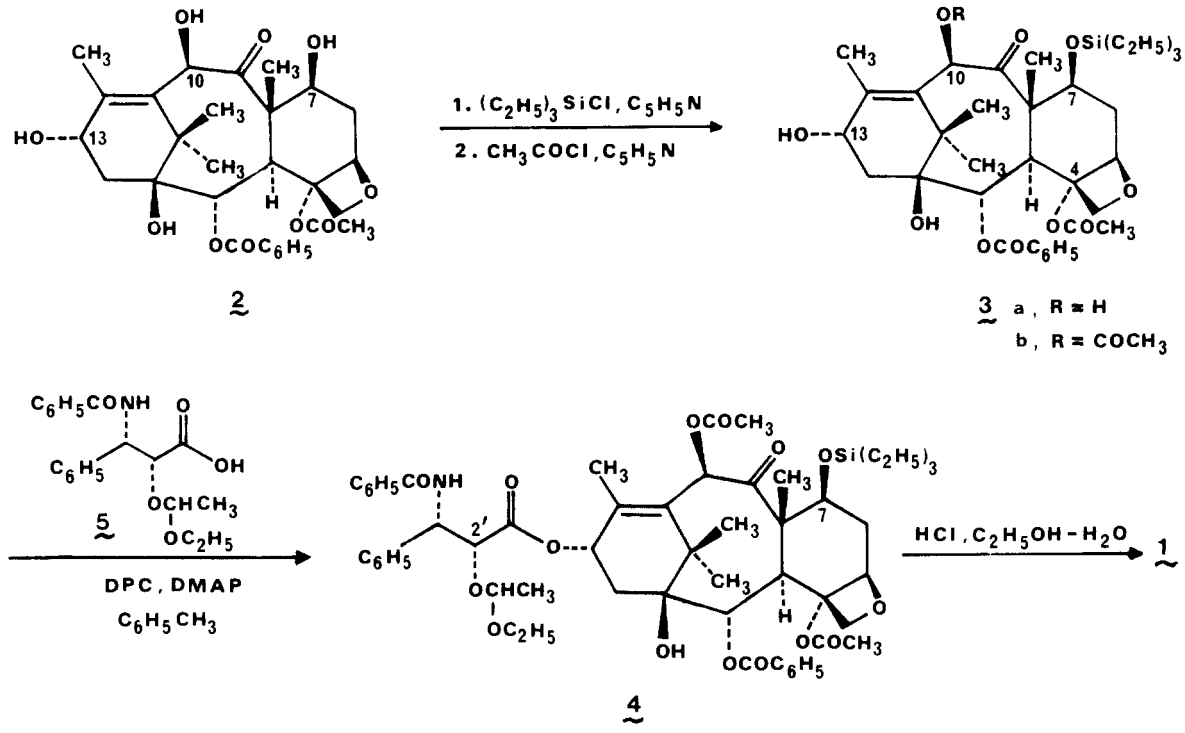
Scheme I



supplied with negligible effect on the yew population. The structural similarity of 10-deacetyl baccatin III to taxol belies, however, the difficulty of effecting the desired conversion. The sensitivity of this tetraol (hexaol derivative) to both acid[4d,11] and base[4a,12] and its folded architecture combine to render its transformation to taxol, in fact, highly problematical. The required differentiation of the similarly reactive C-7 and C-10 hydroxyl functions and the selective esterification of the difficultly accessible C-13 hydroxyl group[12] with the bulky (suitably protected) *N*-benzoylphenylisoserine side chain of taxol, in practice, could be successfully achieved only with specific protecting groups and under specially developed reaction conditions, as described below.

Controlled acetylation of 10-deacetyl baccatin III (**2**, Scheme I) under a variety of reaction conditions yielded the 7-acetyl derivative and not baccatin III as the principal product; consequently, the alternative strategy of effectively protecting the C-7 hydroxyl prior to acetylation was examined. Fortunately, parallel behavior was observed on triethylsilylation[13] and under carefully optimized conditions (20 equiv of $(C_2H_5)_3SiCl$, 50 mL of pyridine/mmol of **2**, 23 °C, Ar, 20 h) 7-triethylsilyl 10-deacetyl baccatin III (**3a**) could be reproducibly obtained in 84–86% yield after purification.[14] Acetylation of **3a** (5 equiv of CH_3COCl, 25 mL of pyridine/mmol of **3a**, 0 °C, Ar, 48 h) then cleanly provided in 86% yield 7-triethylsilyl baccatin III (**3b**),[14] identical in every respect with a sample prepared from natural baccatin III[4b] by triethylsilylation.

Molecular mechanics calculations[15] as well as inspection of molecular models indicated that the C-13 hydroxyl group is situated in the skeletal concavity of **3b** and, furthermore, is able to form a stabilizing hydrogen bond with the C-4 acetate (^{13}CHOH....O=COC^4 distance = 2.50 Å), and thus it was feared that the required esterification at C-13 might prove exceedingly difficult, if not impossible, to effect. In reality, this concern turned out to be well founded. None of the various esterification procedures that are generally successful with hindered substrates was able to produce, even to a modest degree, the desired coupling. Subsequent extensive investigation, however, led to the development of a powerful protocol, which proved effective: 7-triethylsilyl baccatin III (**3b**) in the presence of 6 equiv of readily available, optically pure (2*R*,3*S*)-*N*-benzoyl-O-(1-ethoxyethyl)-3-phenylisoserine (**5**),[16] 6 equiv of di-2-pyridyl carbonate (DPC), and 2 equiv of 4-(dimethylamino)pyridine (DMAP) in toluene solution (0.02M in **3b**) at 73 °C for 100 h produced the C-2′,C-7-protected taxol derivative **4** in 80% yield.[14,17] Concomitant removal of the carefully chosen protecting groups at C-2′ and C-7 in **4** could be cleanly accomplished with 0.5% HCl in ethanol at 0 °C for 30 h to give in 89% yield[14] taxol, having melting point, rotation, and spectral (IR, NMR, FABMS) and chromatographic (TLC, HPLC) characteristics indistinguishable from those of an authentic sample of the natural product.

We expect that the above-described methodology will be highly useful to the numerous groups that are currently pursuing taxol through total synthesis. More significantly, though, the synthesis presented in this paper should serve to alleviate the shortage of taxol and thereby greatly facilitate its clinical evaluation and application in cancer chemotherapy.

Acknowledgment. We thank Professor Bonnier, Professor Lhomme, and Dr. Luche for their interest in this work and Gey

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(12) See: (a) Sénilh, V.; Guéritte, F.; Guénard, D.; Colin, M.; Potier, P. *C. R. Seances Acad. Sci., Ser 2* **1984**, *299*, 1039–1043. (b) Guéritte-Voegelein, F.; Sénilh, V.; David, B.; Guénard, D.; Potier, P. *Tetrahedron* **1986**, *42*, 4451–4460. (c) Magri, N. F.; Kingston, D. G. I.; Jitrangsri, C.; Piccariello, T. *J. Org. Chem.* **1986**, *51*, 3239–3242.

(13) The trimethylsilyl group could also be selectively introduced at C-7, but it proved unstable to the subsequent esterification conditions. The *tert*-butyldimethylsilyl group could not be cleanly introduced.

(14) Yields refer to chromatographically (SiO_2) purified, homogeneous substances. **3a**: mp 256–257 °C (CH_2Cl_2–pentane); $[\alpha]^{23}_D$ −24° (*c* 0.4, CH_3OH). **3b**: mp 253–254 °C (CH_2Cl_2–pentane); $[\alpha]^{23}_D$ −49° (*c* 0.4, CH_3OH). **4**: mp 169–173 °C (CH_2Cl_2–pentane); $[\alpha]^{23}_D$ −34° (*c* 0.4, CH_3OH).

(15) Program "SCRIPT" (Roussel-Uclaf).

(16) See: Denis, J.-N.; Greene, A. E.; Serra, A. A.; Luche, M.-J. *J. Org. Chem.* **1986**, *51*, 46–50. A methoxymethyl protecting group at C-2′ could not be removed following esterification. The more acid-sensitive ethoxyethyl group, while inherently unstable due to the adjacent (acidic) carboxyl group, was sufficiently resistant to permit **5** to be isolated and used in the esterification. (At −20 °C in toluene, **5** can be kept for several days without appreciable change.) Cf.: Begley, M. J.; Cameron, A. G.; Knight, D. W. *J. Chem. Soc., Chem. Commun.* **1984**, 827–829. Walkup, R. D.; Cunningham, R. T. *Tetrahedron Lett.* **1987**, *28*, 4019–4022.

(17) Based on 50% conversion. At 85% conversion, the yield is 60%. This procedure is a substantial modification of Kim's general esterification method (Kim, S.; Lee, J. I.; Ko, Y. K. *Tetrahedron Lett.* **1984**, *25*, 4943–4946), *which failed to produce any 4 at all* under the published reaction conditions. In that C-13 cinnamoylation also proceeds in remarkably high yield (>90% isolated yield), this procedure appears to be general.

and Lavaitte for their help in recording the high field NMR spectra. Financial support for this program from the CNRS, "La Ligue Nationale Française contre le Cancer", and "L'Association pour la Recherche sur le Cancer" is gratefully acknowledged.

Supplementary Material Available: IR, ^{1}H NMR, MS, and microanalytical data on **3a**, **3b**, and **4** (2 pages). Ordering formation is given on any current masthead page.

Adiabatic Photochemistry of *o,o'*-Dibenzenes

Nien-chu C. Yang,* Taehee Noh, Hong Gan, Sherin Halfon, and Bruce J. Hrnjez

Department of Chemistry, University of Chicago
Chicago, Illinois 60637
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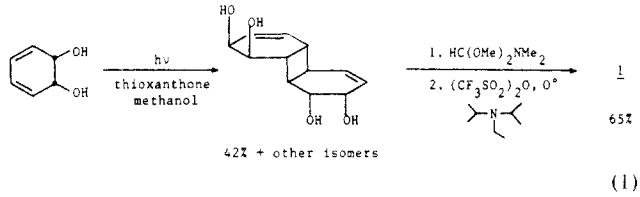
The 4n-subset of benzene dimers is a group of energy-rich compounds which are expected to exhibit interesting physical and chemical properties.[1-6] Among the *o,o'*-dimers the anti isomer **1** has been known for some time,[1-4] while the syn isomer **2** has been synthesized recently in our laboratory.[6] Although the preliminary studies on the properties of **1** have been reported by several groups,[1-4] detailed studies of its properties have been hindered by its limited supply. In this communication, we wish to report a new efficient synthesis of **1**, a more detailed study of its thermal and photochemical decomposition, and a comparison of the results from the two isomeric *o,o'*-dibenzenes. We have found that the photochemical decomposition of **1** and **2** is adiabatic, yielding excited benzene efficiently. Since the photolyses of **1** and **2** may be induced with light longer than 300 nm where benzene exhibits no detectable absorption, the result demonstrates that the high-energy content of **1** and **2** may be utilized to excite the reaction product, benzene, with light of lower energy than that normally needed for the direct irradiation.

Since **1** undergoes fairly rapid thermolysis at 40°,[1] the key step in our new synthesis is based on the efficient deoxygenation of 1,2-diols under mild conditions, a procedure developed in our laboratory.[7] The photosensitized dimerization[8] of the *cis*-3,5-cyclohexadienediol (Aldrich 30,152-3, **3**) yielded a mixture of dimers from which the desired tetraol **4** was isolated by recrystallization (42%). Tetraol **4** was then deoxygenated to **1** (65%) in 0.5-g lot.



(1)

Although it has been reported that both thermolysis and photolysis of **1** yield benzene as the product,[1] the kinetic parameters of thermolysis, other than an estimated value of $\Delta H^{\ddagger}$, have not been evaluated, and the nature of the electronic state of benzene formed in the photolysis is not known. Since there is a significant difference between the thermolytic behaviors of **1** and **2**, the kinetic parameters of thermolysis of **1** were analyzed in two different solvents, cyclohexane and acetone. Furthermore, in the conversion of photoexcited **1** or **2** to an excited benzene and a ground-state benzene (reaction 2), the orbital symmetry is conserved in this energetically favorable process.[9] Therefore, the photolyses of **1** and **2** to benzene are likely to be adiabatic ones following the current concept of adiabatic photochemical reactions.[9] The results are tabulated in Table I.

Table I

	anti-o,o'-dibenzene	*syn-o,o'*-dibenzene[a]
	Thermal Decomposition (in Cyclohexane)	
$\Delta H^{\dagger}$	24.9 ± 1.4 kcal·mol^{-1} (23.6 ± 0.3 kcal·mol^{-1})[b]	22.5 ± 1.3 kcal·mol^{-1}
$\Delta S^{\dagger}$	0.1 ± 2.4 eu (−3.4 ± 1.0 eu)[b]	−14.0 ± 2.2 eu
$\Delta G^{\dagger}$ (298 K)	24.8 ± 1.7 kcal·mol^{-1} (24.6 ± 1.4 kcal·mol^{-1})[b]	26.7 ± 2.0 kcal·mol^{-1}
	Photochemical Decomposition[c]	
Φ-[compd]	1.04 ± 0.09[d]	1.01 ± 0.14[d]
ΦC_6H_6*	0.32 ± 0.03[e]	0.41 ± 0.03[f]

[a] The values of activation parameters are from ref 6. [b] The values are from acetone solution. [c] Concentration of dibenzenes, 1.5–2.0 × 10^{-5} M in cyclohexane, $\lambda_{excitation}$, 300 nm. [d] The average of six separate determinations. [e] The average of three separate determinations. [f] The average of two separate determinations.

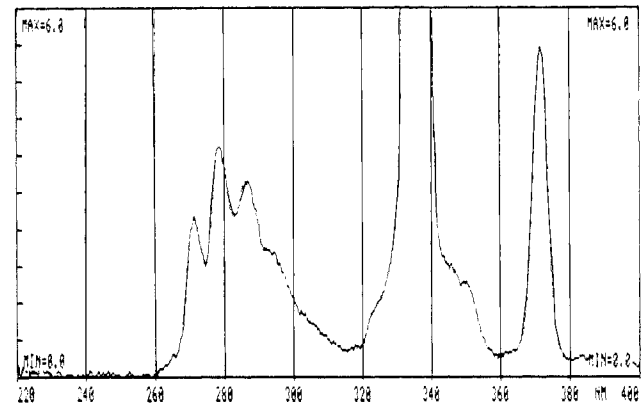
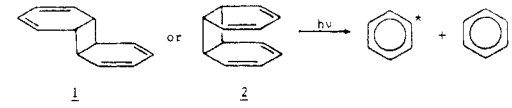


Figure 1. Formation of excited benzene as monitored by its fluorescence from the photolysis of **1**, $\lambda_{excitation}$ 335 nm, the peak at 374 nm is the Raman band of cyclohexane solvent.



(2)

We have found that the thermolysis of **1** proceeds with little or no activation entropy. This is not surprising for such a highly exoergic process, but it is very different from that of **2** which proceeds with an appreciably negative activation entropy.[6] Therefore, this observation is in agreement with our suggestion that the thermolyses of **1** and **2** are likely to proceed via very different reaction pathways.[6]

The efficiency of photolysis of **1** and **2** is determined with the aid of the ferrioxalate actinometry[10] and the formation of excited benzene from **1** and **2** monitored with a Perkin-Elmer MPF-66 spectrofluorimeter. Interestingly, the photolyses of both **1** and **2** proceed with unit quantum efficiency and yield excited benzene

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