Supplementary Material Available: Tables of atomic positional and thermal parameters, interatomic distances and angles, and a list of observed and calculated structure factors (17 pages). Ordering information is given on any current masthead page.

Synthesis of the Taxane Ring System

Robert A. Holton

Department of Chemistry
Virginia Polytechnic Institute and State University
Blacksburg, Virginia 24061

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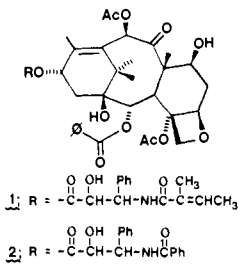
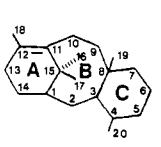
The taxane family of diterpenes[1] has attracted interest in both the biological and chemical communities. Cephalomannine (**1**) and taxol (**2**) have been found to exhibit significant antitumor properties.[2] The structural complexity of these molecules presents a formidable synthetic challenge, and some preliminary synthetic studies have recently been described.[3]

We have embarked upon a taxane synthesis program featuring three sequential objectives: (1) an efficient synthesis of the tricyclic taxane ring system **3**, (2) total synthesis of a modestly functionalized naturally occurring taxane such as taxusin (**4**), and (3) synthesis of the fully functionalized molecules **1** and **2**. We describe herein the realization of the first of these objectives.



1; R = -C-CH-CH-NHC-C=CHCH$_3$ (O OH Ph O CH$_3$)

2; R = -C-CH-CH-NHCPh (O OH Ph O)



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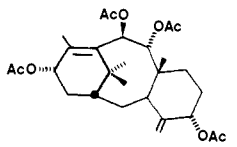

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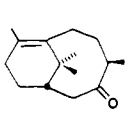
Our initial plan for the synthesis of the taxane ring system involved annulation of ring C onto hydroxy ketone **5** using standard methodology. Preparation of **5** was envisioned to provide a significant challenge. We considered the fragmentation of either **6** or **7** to hold promise for this purpose. The structural similarity of **6** and patchouli alcohol led us to discover that Buchi's elegant synthesis of the natural product[4] suggested a readily available fragmentation substrate.



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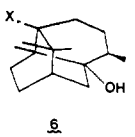

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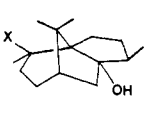

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Therefore, following the Buchi procedure, β-patchouline oxide (**8**)[5] was converted (BF_3·Et_2O) to the tertiary alcohol **9** in 65% yield.[6] Hydroxyl-directed epoxidation[7] of **9** gave an unstable substance which underwent fragmentation in situ to provide keto alcohol **10**.[8-10] The **9** → **10** conversion was found to proceed quantitatively[6] under the following conditions: first, treatment of a methylene chloride solution of **9** with *t*-BuOOH (1.0 mol equiv) and Ti(O-*i*-Pr)$_4$[11] (1.0 mol equiv) at 0 °C for 1 h then addition of dimethyl sulfide (5 mol equiv) followed by warming the solution to reflux for 5–8 h.

Unexpectedly, attachment of ring C proved to be troublesome. Hydroxy ketone **10** was first converted to MOM ether **11**[8] (CH_3OCH_2Cl, EtN(*i*-Pr)$_2$, CH_2Cl_2, O °C, 12 h, 98%).[6] Treatment of **11** with BMDA/TMSCl/Et_3N[12] gave exclusively the desired more-substituted enol ether,[13] which, upon treatment with methyllithium in DME followed by trimethylsilyl methyl vinyl ketone[14] at -78 → 0 °C, was converted to diketone **12**[8] as a single stereoisomer[13] in 93% yield[6] from **11**.

Aldol condensation of **12** was found to be most difficult. None of the commonly used conditions for the transformation (employing sodium or potassium counterions) gave a cyclized product.

(1) For a recent review, see: Miller, R. W. *J. Nat. Prod.* **1980**, *43*, 425.

(2) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325. Miller, R. W.; Powell, R. G.; Smith, C. R., Jr. *J. Org. Chem.* **1981**, *46*, 1469 and references contained therein.

(3) Several approaches to the synthesis of various versions of the taxane ring system have been reported: (a) Intramolecular Diels–Alder approaches: Sakan, K.; Craven, B. M. *J. Am. Chem. Soc.* **1983**, *105*, 3732. Brown, P. A.; Jenkins, P. R.; Fawcett, J.; Russell, D. R. *Chem. Commun.* **1984**, 253. Shea, K. J., David, P. D. *Agnew. Chem., Int. Ed. Engl.* **1983**, *22*, 419. (b) Anionic oxy-Cope approach: Martin, S. F.; White, J. B.; Wagner, R. *J. Org. Chem.* **1982**, *47*, 3192. (c) Fragmentation approach: Trost, B. M.; Hiemstra, H. *J. Am. Chem. Soc.* **1982**, *104*, 886.

(4) Buchi, G.; MacLeod, W. D., Jr. *J. Am. Chem. Soc.* **1962**, *84*, 3205. Buchi, G.; Erickson, R. E.; Wakabayashi, K. *Ibid.* **1961**, *83*, 927. Dobler, M.; Dunitz, J. D.; Gubler, G.; Weaver, H. P.; Buchi, G.; Padilla, J. *Proc. Chem. Soc.* **1963**, 383. Buchi, G.; MacLeod, W. D., Jr.; Padilla, J. *J. Am. Chem. Soc.* **1964**, *86*, 4438.

(5) Prepared from patchouli alcohol in 95% overall yield via a two-step procedure: (a) I_2, benzene; (b) *m*-CPBA, CH_2Cl_2. Alternately, epoxide **8** is available in bulk from International Flavors and Fragrances, Inc., under the trade name Patchino.

(6) All yields refer to isolated, chromatographically and spectrally homogeneous substances.

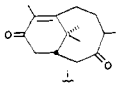
(7) Sharpless, K. B.; Verhooeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63 and references contained therein.

(8) Elemental composition of this substance has been verified by combustion analysis within 0.3% of theory or high-resolution mass spectroscopy; some analytical samples were purified by Dr. S. B. Hendi.

(9) Spectral data (taxane numbering): ^{1}H NMR (250 MHz, CD_3OD) δ 0.92 (3 H, *J* = 5.8 Hz, H-19), 0.93 (3 H, s, H-17), 1.35 (3 H, s, H-16), 1.57 (3 H, s, H-18), 1.68 (1 H, dd, J_{gem} = 11.5, J_{vic} = 5.3 Hz, H-2), 1.78 (2 H, m, H-9), 1.84 (1 H, dd, J_{gem} = 15, J_{13-14} = 3.4 Hz, H-4α), 1.96 (1 H, dddd, H-1), 2.15 (1 H, ddq, H-8), 2.45 (2 H, dd, dd, H-10α,β), 2.74 (1 H, ddd, J_{gem} = 15, J_{14-1} = 7.5, J_{13-14} = 10 Hz, H-14β), 2.87 (1 H, dd, J_{gem} = 11.5, J_{1-2} = 1 Hz, H-2), 4.14 (1 H, dd, *J* = 10, ~3 Hz, H-13).

(10) Reactions similar to this novel fragmentation have been encountered by Professor S. Dev in the course of his elegant pursuit of longifolene chemistry; see: Dev, S. *Acc. Chem.* **1981**, *14*, 82 and references contained therein. One noteworthy feature of the fragmentation leading to **10** is the syn periplanar orientation of the breaking bonds. In ancillary studies we have found that the syn periplanar relationship between breaking bonds is required for facile fragmentation in a related bridged bicyclic system: Holton, R. A.; Kennedy, R. M. *Tetrahedron Lett.*, in press.

(11) We have found Ti(O-*i*-Pr)$_4$ to be most effective for this transformation. Use of more acidic catalysts generally led to poorer results due to premature fragmentation of **9**. For example, substitution of VO(AcAc) for Ti(OiPr)$_4$ led to the production of **10** (83% yield)[6] contaminated by diketone **i** (17% yield). Oxidation of **10** to **i** is a very facile process and can be avoided



i

only under carefully controlled reaction conditions. Oxidation of **10** with Jones reagent affords **i** quantitatively.

(12) Krafft, M. E.; Holton, R. A. *Tetrahedron Lett.* **1983**, *24*, 1345.

(13) Hydrolysis of this enol ether led to a 1:1 mixture of **11** and its C8 epimer. These could be separated by careful flash chromatography. Assignment of C8 stereochemistry in **11**, the C8 epimer of **11**, and **12** is based on a ^{1}H NMR study utilizing europium shift reagent. Upon addition of Eu(fod)$_3$ to a $CDCl_3$ solution of **11**, downfield shifts of proton resonances were observed consistent with primary complexation of shift reagent with C13 allylic oxygen. Protons attached to C19 β methyl were observed to shift upfield slightly. Shifts observed upon addition of Eu(fod)$_3$ to a $CDCl_3$ solution of the C8 epimer of **11** were again consistent with primary complexation as the C13 oxygen. However, in this case, a significant downfield shift of C19 methyl resonance was observed. A similar study involving **12** again showed Eu(fod)$_3$ complexation at C13 oxygen, and in this case the C19 methyl resonance shifted slightly upfield. This result supports structure **12** and is inconsistent with an epimeric formulation at C8.

(14) Stork, G.; Ganem, G. *J. Am. Chem. Soc.* **1947**, *96*, 6181.

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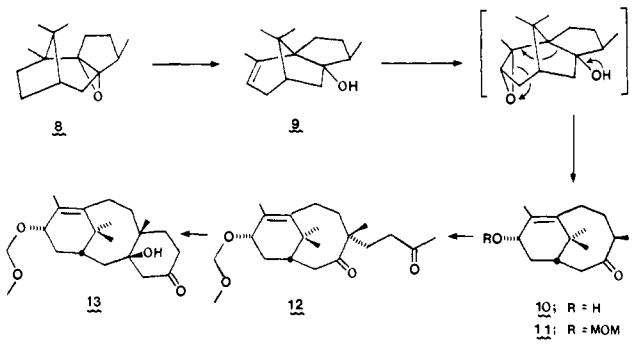
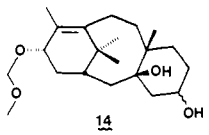
Treatment of **12** with KO-*t*-Bu in either *tert*-butyl alcohol or benzene at reflux resulted in retro Michael reaction to produce a mixture of **11** and its C8 epimer.[13] Cyclization of **12** to **13**[8]



8 9 13 12 10; R = H 11; R = MOM

could be carried out using a magnesium counterion: treatment of **12** with either BMDA[12] or bromomagnesium isopropylcyclohexylamide (BMICA)[15] (THF, -78 °C) gave **13** in 90% yield.[6] We have found **13** to be of modest stability, easily undergoing retroaldolization to **12** under mildly acidic or basic conditions.

To circumvent this problem, diketone **12** was treated with BMDA in THF at -78 °C for 30 min. Addition of excess Red-Al directly to the mixture at -78 °C afforded diol **14**[8] in high yield.



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This provides a stable taxane derivative which can be utilized for further study.[16,17]

Formation of ketol **13**, embodying all of the skeletal features of the taxane diterpenes, *completes the first synthesis of this ring system. This synthesis requires five chemical steps* from readily available, optically active starting material **8** *and proceeds in 53% overall yield.*

The simplicity and efficiency of this process serve to underscore the viability of our fragmentation strategy for taxane synthesis. Having completed construction of the taxane skeleton, we have now turned our attention to modification of the route outlined here to allow for introduction of oxygen functionality at C9 and C10. Realization of this modification should make possible a simple and direct synthesis of taxusin (**4**). The results of this endeavor will be reported in due course.

Acknowledgment. We are particularly grateful to Robert Molino, Synfleur, Inc., for a generous gift of patchouli oil which enabled us to embark on this investigation. We also thank Dr. William Schrieber, International Flavors and Fragrances, Inc., who brought to our attention the fact that Patchino is an IFF product and later provided a generous donation of this substance. We appreciate the help of Professor Koji Nakanishi and John Termini, Columbia University, in the detailed ^{1}H NMR analysis (250 mHz) of hydroxy ketone **10**. Professor Harry C. Dorn provided valuable assistance in the ^{13}C NMR and ^{1}H NMR analysis of compounds **9-13**. Finally, we acknowledge financial support of this program by the National Cancer Institute.

Registry No. 8, 38337-32-5; **9**, 56143-63-6; **10**, 91606-42-7; **11**, 91606-43-8; **12**, 91606-44-9; **13**, 91606-45-0; **14**, 91606-46-1; trimethylsilyl methyl vinyl ketone, 43209-86-5.

(15) Prepared by treatment of isopropylcyclohexylamine with methylmagnesium bromide in THF at 25 °C for 24 h.

(16) This operation was carried out in response to a suggestion by the editor. We are grateful to Professor Meyers for providing the impetus for this finding.

(17) We thank Professor W. C. Still, in whose laboratory the **12** → **14** conversion was accomplished, for his hospitality and generosity. Although these are many potential solutions to this problem, we thank Professor P. L. Stotter for suggesting the use of Red-Al in this context.

Proton-Carbon NOE Difference Spectroscopy Studies of Carbon Microenvironments, Internuclear Distances, and Hydrogen Bonding in Rifamycin S

Neri Niccolai,[†] Claudio Rossi,[†] Vittorio Brizzi,[‡] and William A. Gibbons*[§]

Institute of General Chemistry and Institute of Pharmaceutical Chemistry University of Siena, 53100 Siena, Italy Department of Pharmaceutical Chemistry School of Pharmacy, University of London London, England WC1N 1AX

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Proton-proton distance measurement[1] by (^{1}H:^{1}H) difference spectroscopy[2] and proton relaxation[3,4] are now well-established approaches for the study of conformation and dynamics of natural products[5] and biopolymers.[6] An alternative complementary approach was recently demonstrated on model compounds using (^{1}H:^{13}C) NOE difference spectroscopy.[7] This latter approach can (i) simultaneously delineate the carbon microenvironment and hence hydrogen bond pairs, (ii) yield proton-carbon distances, and (iii) provide criteria for distinguishing conformations of natural products and biopolymers.

Here we report the actual extension of this approach from model compounds to rifamycin S, a natural product whose ^{1}H and ^{13}C spectral assignments have been reported.[8,9]

The on-resonance carbon-13 spectrum (Figure 1A) obtained by selective saturation of the hydroxyl proton attached to C_8 and the corresponding (^{1}H:^{13}C) NOE difference spectrum (Figure 1C) obtained by subtraction showed four NOE enhancements of carbon resonances: the magnitudes of these NOEs and ^{13}C relaxation rates are given in Table I.

Qualitative Information from (^{1}H:^{13}C) NOEs: Carbon Skeleton Mapping, Sequencing, and Hydrogen Bonds. One large NOE is attributed to the geminal H-O-$^{13}C_8$ dipolar interaction and the two small NOEs at C_7 and C_9 to dihedral H-O-C-^{13}C dipolar interactions. The fourth NOE clearly delineates the acceptor $^{13}C_1$ carbonyl group "hydrogen bonded" to the donor C_8-O-H group. The detection of only four NOEs qualitatively delineates the carbon microenvironment of the proton irradiated, and the relative size of the $^{13}C_7$ and $^{13}C_9$ NOEs is proof that the hydroxyl proton does not significantly populate the conformation cis to the $^{13}C_7$ atoms. This is confirmed by the lack of NOEs to $^{13}C_{14}$. The corrollary to these is that by irradiating individual protons and summing the carbon microenvironments such as that of the C_8-O-H one can map the carbon skeletons of a natural product or biopolymer.

Quantitative Proton-Carbon Distances Measurement. A com-

[†] Institute of General Chemistry.
[‡] Institute of Pharmaceutical Chemistry.
[§] University of London.

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(3) (a) Noggle, J. H.; Schirmer, R. E. "The Nuclear Overhauser Effect"; Academic Press: New York, 1971; Chapter 3, pp 44-76. (b) Campbell, I. D.; Freeman, R. *J. Chem. Phys.* **1973**, *58*, 2666-2667. (c) Hall, L. D.; Hill, D. W. *J. Am. Chem. Soc.* **1976**, *98*, 1269-1270.
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(9) Fuhrer, H. *Helv. Chim. Acta* **1973**, *56*, 2377.
(10) Unpublished results.

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