cooling, followed by chloroform extraction.

Notably, only two of the three dimethylamino ligands underwent nitration to give a 200% yield, rather than all three giving the maximum possible 300% yield of the desired product. Further study will reveal the fate of the currently unaccounted for dimethylamino ligand.

The implications of this observation for explosive technology are significant. A phosphorus-based scaffold might be feasible as an incipient polynitramine framework, with use of variations on the reaction described here. Elaborations of this methodology are being investigated.

Experimental Section

Caution! This procedure produces traces of N,N-dimethylnitrosamine, a known carcinogen.

Hexamethylphosphoramide (50 g, 0.28 mol) was added dropwise to a stirred mass of 600 g (400 mL) of 100% nitric acid in a 1-L flask cooled by an ice bath. The rate of addition was carefully regulated to prevent the reaction mixture from ever heating beyond 10 °C; the addition time was approximately 90 min. After the addition was complete, the reaction mixture was allowed to warm to room temperature over an additional 90 min. Workup was carried out by quenching the reaction mixture into 1 kg of ice, neutralizing with 400 g of NaOH with ice cooling of the diluted mixture, and extracting with 3 × 200 mL of chloroform. Drying, filtering, and concentrating, followed by crystallization from carbon tetrachloride, gave 50 g (200%) of *N,N*-dimethylnitramine, mp 53–55 °C. The mother liquor yielded 3 g (12%) of dimethylnitrosamine, a yellow liquid with nonequivalent methyls in its NMR spectrum. *N,N*-Dimethylnitramine does not pose a significant explosion hazard under normal laboratory conditions. It should be kept from exposure to extreme heat (>150 °C).

Acknowledgment. We wish to thank the Army Research Office (Contract No. DAAC03-86-K-0030) and the Air Force Office of Scientific Research (Contract No. F49620-85-K-00006) for support of this research.

Registry No. $[(CH_3)_2N]_3P{=}O$, 680-31-9; $HONO_2$, 7697-37-2; $(CH_3)_2NNO_2$, 4164-28-7.

Communications

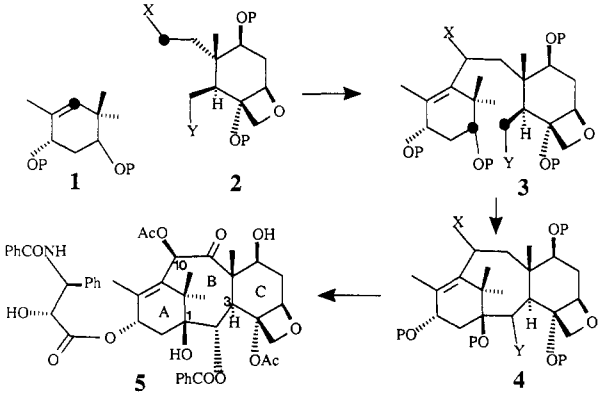
A Convergent Approach to the Taxane Class of Compounds

Summary: A short A + C → AC → ABC route to the taxane class of compounds is described which features a Claisen-rearrangement-mediated stereocontrolled ring closure of the central eight-membered ring in the key AC → ABC step.

Sir: From a synthetic perspective, the taxane diterpenes[2] constitute one of the most demanding classes of compounds as a consequence of both a high level of structural complexity and abundant stereochemical detail. For these reasons, no naturally occurring member of the taxane class of compounds has yielded to total synthesis despite an extraordinary amount of activity in this area[3] and the desire to secure a reliable synthetic source of the highly promising antitumor antileukemic agent taxol **5**[4] and/or its analogues.

Most of the synthetic effort to date has not dealt with stereochemical issues but, instead, has primarily concentrated on elaboration of the taxane carbon framework.[3] We believe that a viable taxane synthesis should accommodate the introduction of most of the stereogenic centers *before* the ring system is assembled. An idealized strategy which conceptualizes this point is depicted in Scheme I. The fully substituted six-membered A and C rings, **1** and **2**, respectively, of taxol are first constructed and then

Scheme I



joined in two separate carbon,carbon bond-forming steps to provide the highly substituted taxane derivative **4**, which requires only modest functional group manipulation to arrive at taxol **5**.[5] The stereocontrolled ring closure of the eight-membered ring, cf. **3** → **4**, represents the most significant challenge in this approach. We describe herein a general solution to this problem which can eventually be incorporated into a more defined plan for the synthesis of taxol similar to that adumbrated in Scheme I.

We have previously demonstrated that our methodology for the preparation of carbocycles, the Claisen rearrangement mediated ring contraction of macrocyclic lactones, is applicable to the preparation of eight-membered rings and, moreover, to strained ring systems.[6] Hence, the

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(2) Lythgoe, B. *The Alkaloids*; Manske, R. H. F., Ed.; Academic: New York, 1968; Vol. X p 597. (b) Miller, R. W. *J. Nat. Prod.* **1980**, *43*, 425.

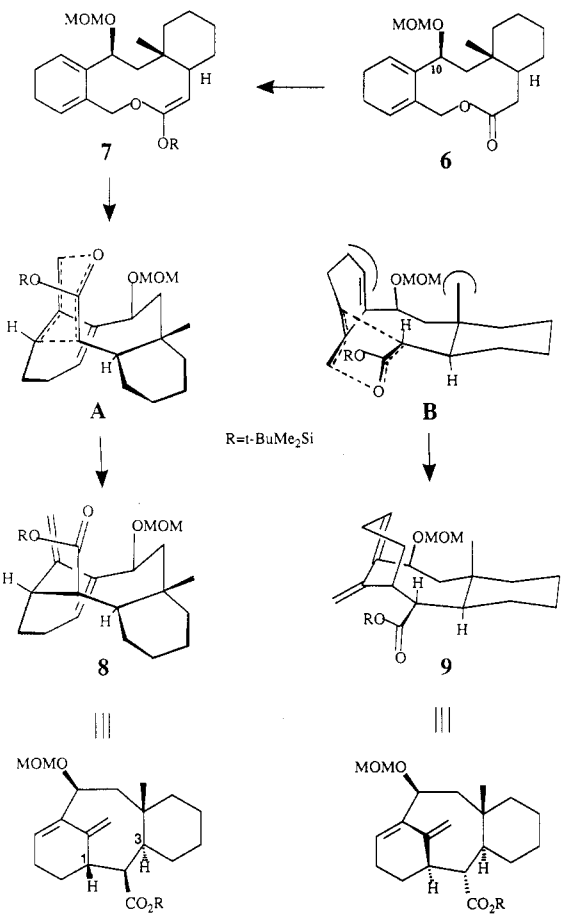
(3) For very recent work, see: (a) Wender, P. A.; Snapper, M. L. *Tetrahedron Lett.* **1987**, *28*, 2221. (b) Pettersson, L.; Frejd, T.; Magnusson, G. *Ibid.* **1987**, *28*, 2753. (c) Kraus, G. A.; Thomas, P. J.; Hon, Y.-S. *J. Chem. Soc., Chem. Commun.* **1987**, 1849. (d) Swindell, C. S.; Patel, B. P. *Tetrahedron Lett.* **1987**, *28*, 5275. (e) Berkowitz, W. F.; Amarasekara, A. S.; Perumattam, J. J. *J. Org. Chem.* **1987**, *52*, 1119. (f) Bonnert, R. V.; Jenkins, P. R. *J. Chem. Soc., Chem. Commun.* **1987**, 1540. (g) Swindell, C. S.; Patel, B. P.; deSolms, S. J. *J. Org. Chem.* **1987**, *52*, 2346. For an exhaustive list of work prior to 1987, see ref 3 of ref 3d.

(4) Miller, R. W. *J. Nat. Prod.* **1980**, *43*, 425.

(5) Other research groups have recognized the advantages of this type of approach, although the closure of the eight-membered ring has not been accomplished in most of the examples, see: (a) Kitagawa, I.; Shibuya, H.; Fujioka, H.; Kajiwara, A.; Tsujii, S.; Yamamoto, Y.; Takagi, A. *Chem. Lett.* **1980**, 1001. (b) Andriamialisoa, R. Z.; Fetizon, M.; Hanna, I.; Pascard, C.; Prange, T. *Tetrahedron* **1984**, *40*, 4285. (c) Shibuya, H.; Tsujii, S.; Yamamoto, Y.; Miura, H.; Kitagawa, I. *Chem. Pharm. Bull.* **1984**, *32*, 3417. (d) Reference 3b. The Kende approach is the exception, see: Kende, A. S.; Johnson, S.; Sanfilippo, P.; Hodges, J. C.; Jungheim, L. N. *J. Am. Chem. Soc.* **1986**, *108*, 3513.

0022-3263/88/1953-4141$01.50/0

Scheme II



exploitation of this method as a solution to the aforementioned taxane ring construction problem seemed quite feasible. Specifically, it was envisioned that the lactone **6** (Scheme II) could be converted to a ketene acetal **7**, which would then rearrange to provide the taxane derivative **8**. It should be noted that two chair-like transition states for the Claisen rearrangement, A and B, are conceivable. However, examination of molecular models clearly indicated that the desired transition-state A should be greatly preferred over transition-state B which suffers from a serious steric interaction between the cyclohexadienyl ring and the angular methyl substituent. Thus, only the carboxylate **8**, which possesses the correct relative stereochemistry at C(1) and C(3) necessary for a taxane total synthesis, rather than the diastereomer **9** should be obtained from the Claisen rearrangement.

A concise synthesis of the lactone **6** precursor, hydroxy acid **15**, is shown in Scheme III. Treatment of hydrazone **10**[7] with *t*-BuLi (3 equiv, −78 → −10 °C, THF) generated dianion **11**, which was coupled with the aldehyde **12**[9] to

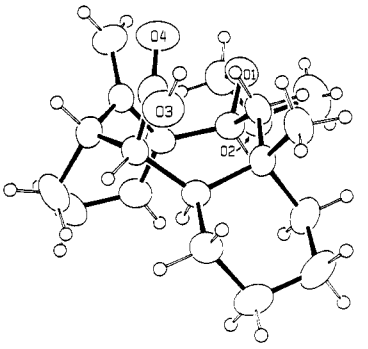
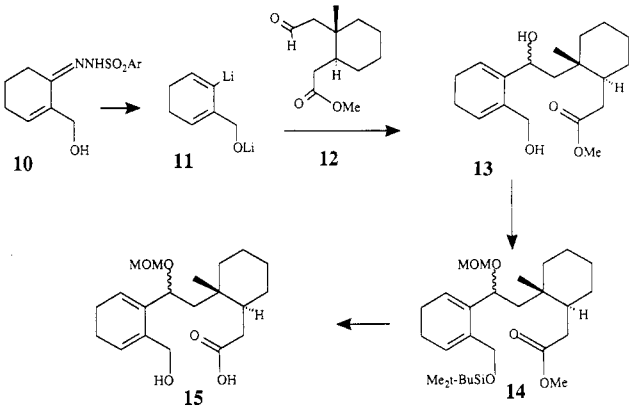


Figure 1.

Scheme III



provide a 1:1 diastereomeric mixture of diols **13** in 56% yield after column chromatography.[12] Selective silylation of the primary hydroxyl of **13** (1.05 equiv of *t*-BuMe$_2$SiCl, 1.1 equiv of NEt$_3$ 0.05 equiv of DMAP, CH$_2$Cl$_2$, 2 h, 84%)[13] followed by protection of the remaining secondary hydroxyl as the methoxymethyl ether (4 equiv of ClCH$_2$OCH$_3$, 5 equiv of EtN(*i*-Pr)$_2$, 0.05 equiv of DMAP, CH$_2$Cl$_2$, 2 h, 96%) afforded the fully protected ester **14**. Selective deprotection of **14** (1.2 equiv of Bu$_4$NF, THF, 27 °C, 0.5 h; 74%) and saponification (3 M KOH, MeOH, 25 °C, 12 h; 97%) furnished the desired hydroxy acid **15**. Lactonization of this hydroxy acid according to the Mukaiyama protocol[14] (5 equiv of *N*-methyl-2-chloropyridinium iodide, 10 equiv of NEt$_3$, CH$_3$CN, 85 °C, 24 h; 63%) furnished the desired lactone stereoisomer **6** and its easily separable C(10) stereoisomer[15] (taxane numbering) after column chromatography.

Silylation of the lactone **6** enolate (2.5 equiv of LDA, 3.1 equiv of *t*-BuMe$_2$SiCl, 2.5 equiv of HMPA, THF) gave rise to a single silyl ketene acetal, presumably the *E* stereoisomer **7**.[6a] We were pleased to observe smooth rearrangement of the ketene acetal **7** to a single silyl ester **8** upon thermolysis in refluxing toluene (8 h). The stereochemical assignment for the rearrangement product was suggested by the transition state analysis described earlier and was confirmed by single-crystal X-ray analysis[16] of the

(6) (a) Funk, R. L.; Abelman, M. M.; Munger, J. D. *Tetrahedron* **1986**, *42*, 2831. (b) Funk, R. L.; Abelman, M. M. *J. Org. Chem.* **1986**, *51*, 3247. (c) Funk, R. L.; Munger, J. D. *Ibid.* **1985**, *50*, 707. (d) Funk, R. L.; Olmstead, T. A. *J. Am. Chem. Soc.* **1988**, *110*, 3298.

(7) Prepared from the ethylenedioxy ketal of 2-(hydroxymethyl)-2-cyclohexen-1-one[8] upon subjection to triisopropylbenzenesulfonyl hydrazide (1.2 equiv) in the presence of oxalic acid (0.05 equiv) in MeOH (0 °C, 3 h; 77%).

(8) Smith, A. B., III, Branca, S. J.; Pilla, N. N.; Guaciaro, M. A. *J. Org. Chem.* **1982**, *47*, 1855.

(9) Prepared by conversion of 3,4,4a,5,6,7,8,8aβ-octahydro-4aα-methyl-2(1*H*)-naphthalenone[10] to a 8:1 regioisomeric mixture of Δ^2 and Δ^1 methyl enol ethers, respectively, according to the procedure of Wohl[11] (2 equiv of HC(OCH$_3$)$_3$; 0.05 equiv of pTsOH, 25 → 140 °C; 88%), which were ozonized (O$_3$, catalytic NaHCO$_3$, 1:1 CH$_2$Cl$_2$/MeOH; 93%) to give **12** contaminated by the inseparable ester aldehyde derived from the Δ^1 enol ether.

(10) Casadevall, A.; Casadevall, E.; Lasperas, M. *Bull. Soc. Chim. Fr.* **1968**, *11*, 4506.

(11) Wohl, R. *Synthesis* **1974**, 38.

(12) All new compounds reported herein exhibited satisfactory spectral (IR, NMR), analytical, and/or high-resolution mass spectral characteristics.

(13) Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, *20*, 99.

(14) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49.

(15) This isomer was contaminated by ~30% of its corresponding diolide as indicated by mass spectral analysis and saponification of the mixture to provide only one hydroxy acid **15** stereoisomer (α-OMOM). Consequently, the rearrangement of this isomer was not investigated.

derived carboxylic acid as shown in the ORTEP structure in Figure 1 (mp 189.5–190.5 °C, 82% overall yield from **6**).

In conclusion, we have developed an exceptionally short synthesis of the taxane ring system founded on the A + C → AC → ABC approach conceptualized in Scheme I. In particular, we have accomplished the first *stereocontrolled* ring closure of the central eight-membered ring in the key AC → ABC step by exploiting our versatile Claisen-rearrangement-based methodology for the preparation of carbocycles. The synthesis and connection of more highly functionalized A and C rings suitable for the synthesis of taxol is now justified and is in progress.

Acknowledgment. We appreciate the financial support provided by the National Institutes of Health (Grant GM 28663), Eli Lilly and Company, and the Alfred P. Sloan Foundation. High-field (360 MHz) ^{1}H NMR and ^{13}C NMR spectra were obtained on a spectrometer purchased with funds provided, in part, by the National Science Foundation (Grant CHE-80-24328). Mass spectra were obtained through the National Science Foundation Regional Mass Spectroscopy Center at the University of Nebraska (Grant CHE-82-11164).

Supplementary Material Available: X-ray crystallographic data for compound 8 (R = H) (9 pages). Ordering information is given on any current masthead page.

(16) Crystal data: $C_{20}H_{30}O_4$; M 334.46; monoclinic, space group $P2_1/c$; a = 13.255 (3) Å, b = 9.956 (4) Å, c = 13.870 (7) Å, β = 94.00 (3)°, V = 1825.9 Å^3; Z = 4; D_{calcd} = 1.217 g cm^{-3}; Mo Kα radiation, λ = 0.71073 Å, μ = 0.78 cm^{-1}; 1957 observed reflections [$I > 3\ \sigma(I)$] collected on an Enraf-Nonius CAD-4 diffractometer using a $\omega/2\theta$ scan method and variable scan speed to a θ_{max} = 25°; the structure was solved by direct methods and refined by full-matrix least-squares calculations to a conventional R = 0.038 (R_w = 0.047).

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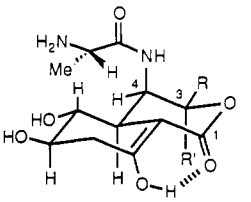
Stereoselective Total Synthesis of the Antitumor Antibiotic (-)-Bactobolin

Summary: The first total synthesis of the biologically active microbial metabolite bactobolin (**2**) has been achieved. An efficient, stereoselective route to **2** in 16 steps from previously prepared α-keto lactone **3** is outlined.

Sir: Actinobolin (**1**)[1] and bactobolin (**2**)[2] are members of a small class of microbial natural products[3] which show broad spectrum antibiotic activity[4] as well as significant inhibitory effects against various leukemias.[3,5] Bactobolin



1 R = Me, R' = H
2 R = $CHCl_2$, R' = Me

is the more interesting of the two compounds due to its superior antitumor activity[6] and its more complex structure bearing an unusual dichloromethyl group. Several groups have reported approaches to the total synthesis of actinobolin (**1**),[7] including one from these laboratories.[8] We now describe the first total synthesis of bactobolin (**2**) utilizing an efficient variation of the strategy which we previously applied to **1**.[8]

In analogy with our actinobolin synthesis[8] a key step was the anticipated stereoselective reduction of a C-4 imine to introduce the amino substituent. However, the choice of an appropriate protecting group for nitrogen was not straightforward and proved to be frustrating and quite time consuming. Based upon early studies,[9] we knew that *N*-acyl protection was not compatible with several transformations within our synthetic approach.[10] It was finally determined that the [β-(trimethylsilyl)ethyl]sulfonyl (SES) group[11] was suitable. Thus, racemic α-keto lactone **3**[8] (Scheme I) was converted to an *N*-sulfonyl imine with the *N*-sulfinyl compound[12] derived from β-(trimethylsilyl)-

(1) Isolation and structure: Haskell, T. H.; Bartz, Q. R. *Antibiot. Annu.* **1959**, 505. Antotz, F. J.; Nelson, D. B.; Herald, D. L., Jr.; Munk, M. E. *J. Am. Chem. Soc.* **1970**, *92*, 4933. Wetherington, J. B.; Moncrief, J. W. *Acta Crystallogr., Sect. B* **1975**, *B31*, 501.

(2) Isolation and structure: Kondo, S.; Horiuchi, Y.; Hamada, M.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1979**, *32*, 1069. Ueda, I.; Munakata, T.; Sakai, J. *Acta Crystallogr., Sect. B* **1980**, *B36*, 3128. Munakata, T.; Ikeda, Y.; Matsuki, H.; Isagai, K. *Agric. Biol. Chem.* **1983**, *47*, 929.

(3) For some additional closely related compounds, see: Okumoto, T.; Kontani, M.; Hoshino, H.; Nakanishi, M. *J. Pharmacobio-Dyn.* **1980**, *3*, 177.

(4) (a) Pittillo, R. F.; Fisher, M. W.; McAlpine, R. J.; Thompson, P. E.; Ehrlich, J. *Antibiot. Annu.* **1959**, 497. (b) Hunt, D. E.; Navia, J. M.; Lopez, H. *J. Dent. Res.* **1971**, 371. (c) Munakata, T. *Yakugaku Zasshi* **1981**, *101*, 138.

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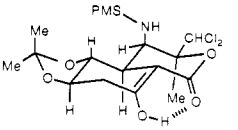
(7) (a) Yoshioka, M.; Nakai, H.; Ohno, M. *J. Am. Chem. Soc.* **1984**, *106*, 1133. Yoshioka, M.; Nakai, H.; Ohno, M. *Heterocycles* **1984**, *21*, 151. (b) Rahman, M. A.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1985**, *107*, 5576. (c) Askin, D.; Angst, C.; Danishefsky, S. *J. Org. Chem.* **1985**, *50*, 5005. Askin, D.; Angst, C.; Danishefsky, S. *Ibid.* **1987**, *52*, 622. (d) Kozikowski, A. P.; Konoike, T.; Nieduzak, T. R. *J. Chem. Soc., Chem. Commun.* **1986**, 1350. Kozikowski, A. P.; Nieduzak, T. R.; Konoike, T.; Springer, J. P. *J. Am. Chem. Soc.* **1987**, *109*, 5167.

(8) Garigipati, R. S.; Tschaen, D. M.; Weinreb, S. M. *J. Am. Chem. Soc.* **1985**, *107*, 7790.

(9) Tschaen, D. M. Ph.D. Thesis, The Pennsylvania State University, 1984.

(10) (*p*-Methylbenzyl)sulfonyl (PMS) nitrogen protection, as was used for actinobolin,[7a,8] proved unrewarding. PMS-protected bactobolamine i was prepared by a variation of the total synthesis described in this paper, but despite intensive effort this group could not be removed without destruction of the molecule.



i

(11) Weinreb, S. M.; Demko, D. M.; Lessen, T. A.; Demers, J. P. *Tetrahedron Lett.* **1986**, *27*, 2099.

(12) Bussas, R.; Kresze, G.; Munsterer, H.; Schwobel, A. *Sulfur Rep.* **1983**, *2*, 215.

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