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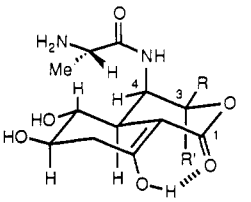
Stereoselective Total Synthesis of the Antitumor Antibiotic (-)-Bactobolin

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)-

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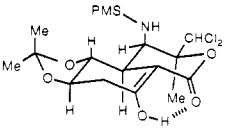
(10) (*p*-Methylbenzyl)sulfonyl (PMS) nitrogen protection, as was used for actinobolin,[7a,8] proved unrewarding. PMS-protected bactobolamine i was prepared by a variation of the total synthesis described in this paper, but despite intensive effort this group could not be removed without destruction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



i

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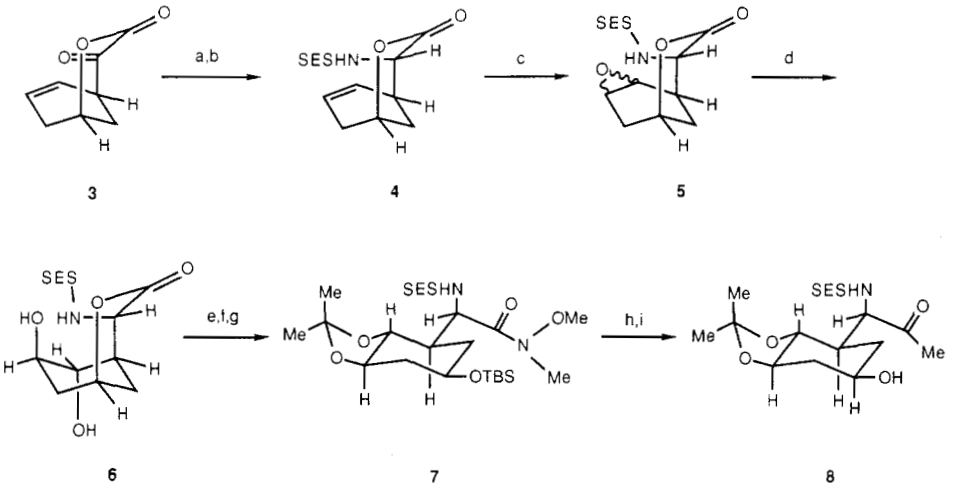
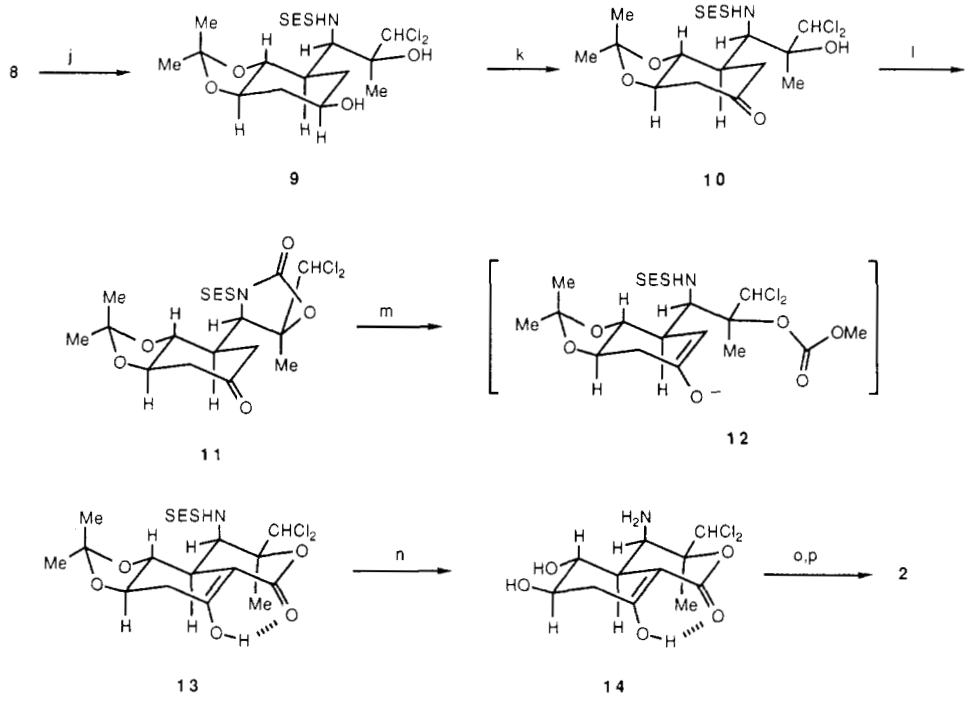
Scheme I[a]



[a] (a) $Me_3SiCH_2CH_2SO_2NSO$ (SESNSO)/BF_3Et_2O, $ClCH_2CH_2Cl$, 42 °C; (b) $NaCNBH_3$, *tert*-amyl alcohol; (c) mCPBA, CH_2Cl_2; (d) HCOOH; MeOH/Et_3N; (e) $Me_2AlNMe(OMe)$, THF; (f) $Me_2C(OMe)_2$/*p*-TsOH, DMF; (g) TBSOTf/2,6-lutidine, DMF, −15 °C; (h) MeMgBr, THF; (i) *n*-Bu_4NF, THF, room temperature.

Scheme II[a]



[a] (j) $Cl_2CHLi/CeCl_3$, Et_2O, −100 °C; (k) CrO_3/pyr, CH_2Cl_2; (l) MeOCOCl, Et_3N, 4-pyrrolidinopyridine; (m) NaOMe, MeOH; (n) *n*-Bu_4NF, THF, 52 °C; MeOH/HCl; (o) Cbz-L-alanine/DCC/Et_3N, DMF; (p) H_2/Pd–C, MeOH/HOAc, 0.5 N HCl.

ethanesulfonamide, and this intermediate was reduced stereoselectively with sodium cyanoborohydride to afford α-sulfonamido lactone **4** (80%). Epoxidation of **4** gave a 1.8:1 mixture of epoxide stereoisomers **5** (100%), which was solvolyzed to the diaxial diol **6**. The lactone functionality of **6** was opened with the aluminum amide reagent prepared from trimethyl aluminum and *N,O*-dimethylhydroxylamine,[13] and the resulting triol was protected as the silyl acetonide **7** (65% from **5**). Addition of methyl Grignard reagent to **7**[14] provided keto alcohol **8** (88%) after desilylation. Compound **8** possesses four of the five chiral centers of bactobolin, and the methyl ketone group provides a handle for introduction of the dichloromethyl group at C-3.

Addition of (dichloromethyl)lithium[15] to **8** afforded only intractable material. However, if the lithium reagent was first treated with an equivalent of cerium trichloride[16] addition to the ketone occurred smoothly to provide the *single stereoisomer* **9**, along with some unreacted **8**, presumably due to enolization of the methyl ketone (60% conversion, 90% yield). The structure of **9** was proven by its eventual conversion to bactobolin. The stereochemistry in **9** is consistent with a Cram chelation controlled addition

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of an organocerium reagent to α-sulfonamido ketone 8.

The next stage of the synthesis involved introduction of the carboxyl carbon (C-1) of the enol lactone function of 2. Alcohol 9 was first oxidized to ketone 10 (90%) (Scheme II). Not surprisingly, acylation of the tertiary hydroxyl group of 10 with a variety of phosgene-based reagents proved exceedingly difficult. However, it was eventually found that upon treatment of 10 with methyl chloroformate in triethylamine in the presence of 4-pyrrolidinopyridine, cyclic carbamate 11 was produced (80%). This compound is probably formed via initial acylation of the sulfonamide nitrogen, followed by intramolecular closure onto the hydroxyl group.

Exposure of 11 to methanolic sodium methoxide yielded the desired enol lactone 13 (70%). It would appear from inspection of models that direct C-acylation of an enolate derived from 11 is not possible. We believe that cyclic carbamate 11 is first opened by methoxide to carbonate 12. Moreover, the alkoxide base generates an equilibrating enolate mixture, of which only the regioisomer shown in 12 can undergo intramolecular acylation.

The SES protecting group of 13 was removed with fluoride[11] and acidification upon workup hydrolyzed the acetonide moiety (45–50%). The resulting racemic amino diol 14 was acylated with *N*-Cbz-L-alanine and the diastereomers were separated by preparative TLC on silica gel (30% isolated yield of each isomer). Hydrogenolysis of the Cbz group (80%) afforded (–)-bactobolin (2), which was identical with an authentic sample.[17,18] We have thus completed a totally stereoselective synthesis of bactobolin in sixteen steps from readily available α-keto lactone 3.

Acknowledgment. We are grateful to the National Cancer Institute of the National Institutes of Health for financial support (CA-34303).

(17) We are grateful to Dr. T. Munakata, Yoshitomi Pharmaceutical Industries, Ltd., for a generous sample of natural bactobolin.

(18) All compounds were characterized spectrally and by elemental analysis and/or high-resolution mass spectrometry.

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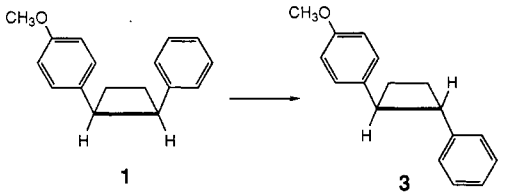
Dioxygen-Promoted Cation Radical Reactions in Brønsted Acids

Summary: Contrary to previous reports, the trifluoroacetic acid promoted cis → trans isomerizations of 1-*p*-anisyl-2-phenylcyclobutane and 1,2-di-*p*-anisylcyclopropane are *not* proton catalyzed; results are presented suggesting that cation radical reactions can be initiated in Brønsted acids when dioxygen is present.

Sir: The difficulties in distinguishing cation radical catalysis from Brønsted acid catalysis *under aminium ion initiation* have been the subject of recent discussion in the literature.[1] For example, Gassman and Singleton have suggested that several aminium ion initiated Diels–Alder reactions are, in fact, catalyzed by adventitious acid which is produced in the reaction mixture.[1a,b] We demonstrate here the inverse of this experiment, namely, that cation radical reactions can apparently be initiated in Brønsted acids *when dioxygen is present.*

The trifluoroacetic acid promoted stereomutations of *cis*-1-*p*-anisyl-2-phenylcyclobutane (1) and *cis*-1,2-di-*p*-anisylcyclopropane (2) have both been claimed to be proton-catalyzed reactions.[2] We were naturally concerned with these reports because of our work[3] on the cis → trans isomerization of 1-*p*-anisyl-2-vinylcyclopropane catalyzed by one-electron oxidants, including the aminium ion salt p-$BrPh_3N^{\bullet+}$ SbF_6^-. We excluded an acid-catalyzed mechanism for this reaction by showing that the addition of 2,6-di-*tert*-butylpyridine did *not* prevent the isomerization. Our work, coupled with the long-known propensity for cation radical formation in Brønsted acids,[4] prompted us to reinvestigate the reaction mechanisms for the trifluoroacetic acid promoted isomerizations of 1 and 2. Especially relevant was the report by Shine and Piette that dioxygen was necessary for the one-electron oxidation of thianthrene in trifluoroacetic acid.[5,7] A similar observation has been made for one-electron oxidations in trifluoromethanesulfonic acid.[6,7] Thus our initial goal was to determine if the presence of dioxygen affected the isomerizations of 1 and 2.

We first verified that 1[8] is indeed isomerized to 3 in distilled trifluoroacetic acid when no special precautions are made to exclude dioxygen. Our isomerization half-life in trifluoroacetic acid-*d* (3.25 h at 25 °C) was noticeably different, however, from that reported earlier (5.25 h at 25 °C).[2a] This discrepancy was easily rationalized by the



following series of experiments. *When degassed*[9] CF_3CO_2D *was vacuum transferred into an NMR tube containing 1 and sealed, the isomerization was dramatically slower.* For example, after 12 days no trans isomer was detected by ^1H NMR.[10] Only after much longer reaction times was a small amount of isomerization observed (5.2% after 32 days). The deuteriation of the *p*-anisyl ring,[2a] however, was not affected by degassing. The rate of deuterium incorporation into the *p*-anisyl ring of trans cyclobutane

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(8) 1 was prepared as follows. Condensation (Lawson, J. E.; Dennis, R. D.; Majewski, R. F.; Gallo, D. G. *J. Med. Chem.* **1974**, *17*, 383) of *p*-methoxyphenacyl bromide with ethyl benzoylacetate provided 1-*p*-anisoyl-2-benzoylethane. This substance was reductively coupled (Baumstark, A. L.; Bechara, E. J. H.; Semigran, M. J. *Tetrahedron Lett.* **1976**, 3265) to give 1-*p*-anisyl-2-phenylcyclobutene which was, in turn, hydrogenated (Dodson, R. M.; Zielske, A. G. *J. Org. Chem.* **1967**, *32*, 28.) to give 1.

(9) The degassing procedure consisted of four to six successive freeze–pump (2×10^{-6} Torr)–thaw cycles.

(10) Our ^1H NMR detection limits are ca. 2%.

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