initiated by a cycloaminopalladation of **1a** with $PdCl_2$ to form vinylpalladium(II) chloride intermediate **6**, which adds to the double bond of crotyl chloride in such a way as to give β-chloroethylpalladium(II) chloride intermediate **7**.[14] Reductive elimination of a Pd(0) species from **5** or dechloropalladation from **7** provides the final product.

Of these possibilities, pathway b may be safely excluded because it predicts the wrong regiochemistry for the methyl substituent in the product of the reaction of **1** and crotyl chloride (run 4, Table II). Pathway b would be acceptable if crotyl chloride isomerizes to α-methallyl chloride under the reaction conditions and **6** reacted only with α-methallyl chloride. However, no such isomerization was detected when the reaction was monitored by VPC. Pathway a seems to be flawed by the slow reactions and the low yields of **2** observed for the reactions of **1** with stoichiometric amounts of chloro-π-allylpalladium(II) dimers (runs 1 and 2, Table II). In these reactions, to our surprise, nonallylated product **4**, a formal dimerization product of **1g**, was obtained as a major product.[15]

Thus, neither of the mechanisms shown in Scheme I seems to be satisfactory. Nevertheless, we believe that the π-allylpalladium route (pathway a) is the most probable. The side reactions caused by some π-allylpalladium species, which furnish either **3** (run 9, Table I) or **4** (runs 1 and 2, Table II), could be attributed to subtle differences in the ligands on palladium or to the form in which the palladium species exist in solution.

Work is in progress to optimize the yield, to clarify the mechanism, and to apply our route to the synthesis of physiologically important natural and synthetic products.

Acknowledgment. This work was supported by Grants from the Ministry of Education, Science and Culture, Japanese Government (No. 04453089 and No. 04217228) and the CIBA-GEIGY Foundation.

Supplementary Material Available: Characterization data and ^1H NMR spectra for **2–4** (31 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(14) Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5816.

(15) Satisfactory spectral (IR, ^1H NMR) and analytical data (HRMS) were obtained for **2–4**.

A Convenient Procedure for the Synthesis of Bis-steroidal Pyrazines: Models for the Cephalostatins

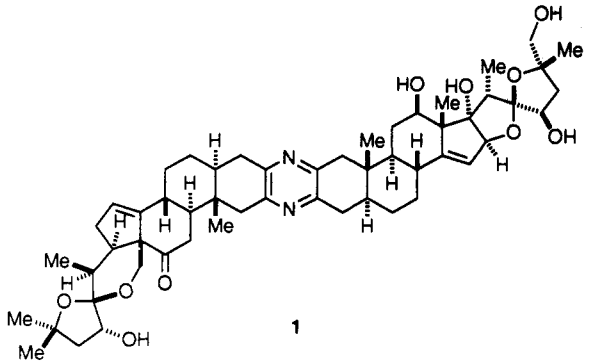
Stephen C. Smith and Clayton H. Heathcock*

Department of Chemistry, University of California, Berkeley, California 94720

Received September 10, 1992

Summary: Efficient routes have been developed for both symmetrical and unsymmetrical bis-steroidal pyrazines from readily available precursors.

The cephalostatins are a group of complex steroidal pyrazine alkaloids that were isolated from the marine worm *Cephalodiscus gilchristi*.[1] They are powerful cytotoxins against the PS cell line (ED_{50} 10^{-7}–10^{-9} μg/mL) and therefore have potential applications as antitumor agents. However, they are rare marine natural products and are available in only small amounts. For example, 166 kg of *C. gilchiristi* (5-mm long tube worms), provided only 139 mg of cephalostatin 1 (**1**) and a total of 272 mg of other cephalostatins. Although the cephalostatins are among the most potent cytotoxins ever screened by National Cancer Institute in the PS system, the limited availability of the natural materials has limited in vivo tests.[2] Because of this limited availability, we have embarked on a program of total synthesis of the cephalostatins. In this paper, we report three new procedures for the formation of bis-steroidal pyrazines. Two of these procedures are applicable to the high-yield preparation of symmetrical bis-steroidal pyrazines, and the other is useful for the synthesis of unsymmetrical analogs, which were hitherto unknown except as embodied in the cephalostatins themselves.



1

A convenient method for the preparation of symmetrical bis-steroidal pyrazines is summarized in Scheme I. Bromination of 3-cholestanone (**2**) at the 2-position,[3] followed by displacement of bromide with sodium azide,[4] provided azido ketone **3** in about 50% overall yield. Treatment of **3** with triphenylphosphine in aqueous THF gave a crude product which was treated with *p*-toluenesulfonic acid in ethanol to obtain pyrazine **4** in 87% yield. We believe that compound **4** results from dimerization of the α-amino ketone that is formed by the Ph_3P-mediated reduction of the azido group. Previously, symmetrical bis-steroidal

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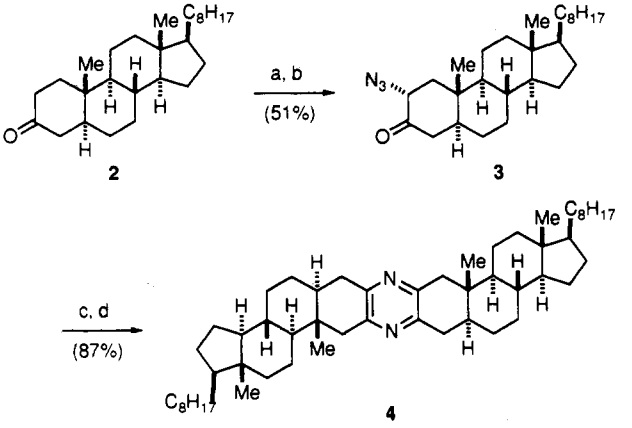
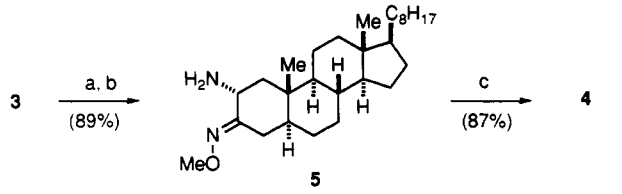
Scheme I[a]



[a] Key: (a) $C_5H_5NH^+Br_3^-$, AcOH; (b) NaN_3, *N*-methylpyrrolidone; (c) Ph_3P, H_2O, THF; (d) *p*-TsOH, ethanol.

Scheme II[a]



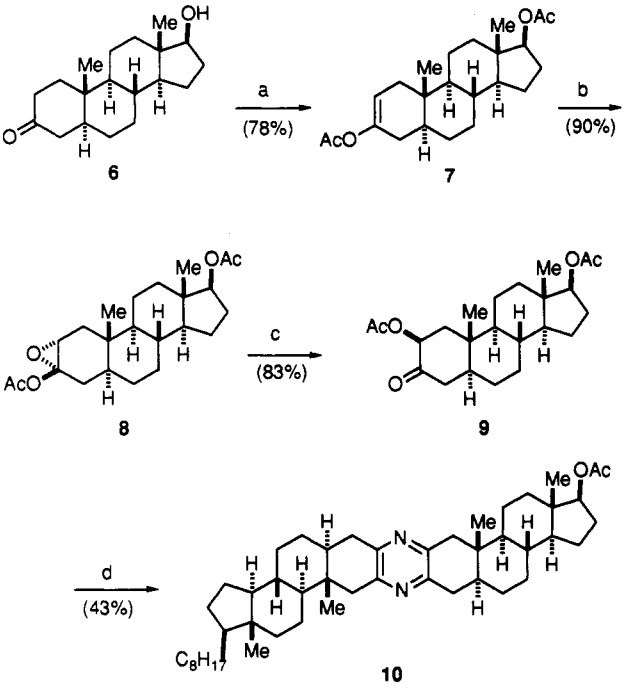
[a] Key: (a) $MeONH_3^+Cl^-$, pyridine; (b) Ph_3P, H_2O, THF; (c) toluene, 140 °C, 24 h.

pyrazines have been prepared from 2-oximino ketones in lower yield (35–54%).[5]

The symmetrical bis-cholestanyl pyrazine was also prepared as shown in Scheme II. Thus, treatment of azido ketone **3** with *O*-methylhydroxylamine provided the *O*-methyloxime, which was reduced with triphenylphosphine in aqueous THF to obtain the 2-amino-3-oxime derivative of cholestane **5**. This material was heated in toluene at 140 °C to obtain pyrazine **4** in about 77% overall yield from **3**.

For the preparation of unsymmetrical bis-steroidal pyrazines, the protocol illustrated in Scheme III was developed. Androstanone **6** was converted to the Δ^2 enol acetate **7**,[6] which was oxidized with dimethyldioxirane[7] to obtain epoxide **8** which crystallized as a single isomer. This material was rearranged to the 2β-acetoxy 3-ketone **9** by refluxing in toluene containing 10% pyridine. When a mixture of **9** and amino oxime **5** were heated in toluene at 90 °C for 24 h and then at 145 °C for a further 24 h, the unsymmetrical pyrazine **10** was formed in 43% yield.

Scheme III[a]



[a] Key: (a) Ac_2O, $HClO_4$, EtOAc; (b) dimethyldioxirane, acetone; (c) toluene, reflux; (d) compound **5**, toluene, 90 °C, 24 h; 145 °C, 24 h.

Control experiments show that amino oxime **5** reacts preferentially with the acetoxy ketone **9** at 90 °C to give a mixture of isolable, but inseparable, intermediates which subsequently form pyrazine **10** upon prolonged heating. The optimum temperature for pyrazine formation was found to be 145 °C. Initial heating at the lower temperature of 90 °C avoids the dimerization of amino oxime **5** which occurs at elevated temperatures (Scheme II).

Acknowledgment. This research was supported by a research grant from the United States Public Health Service (GM 46057) and by an SERC Postdoctoral Fellowship to S.C.S.

Supplementary Material Available: Experimental procedures and analytical data for all new compounds reported in this paper (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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A New Approach to the Synthesis of the CC-1065/Duocarmycin Pharmacophore

Jeffrey H. Tidwell and Stephen L. Buchwald*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received August 20, 1992

Summary: The spirocyclic 1,2,7,7a-tetrahydrocycloprop-[1,2-*c*]indol-4-one subunit of CC-1065 and duocarmycin A, which comprises the common pharmacophore of the two antibiotics, has been efficiently synthesized in six steps from readily available starting materials. The key step of the synthesis utilizes a zirconocene-stabilized benzyne complex.

CC-1065 and duocarmycin A (Figure 1), potent antitumor antibiotics, have received much recent attention.[1]

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