is set in the Diels-Alder reaction used to produce **7**.

For the purposes of this synthesis, direct alkylation of the tosylate **6** with a cyclopentadienyl anion was the most efficient route (Scheme I). Because alkylations with the cyclopentadienyl anions of lithium and sodium resulted in base-catalyzed intramolecular conjugate addition of the functionalized cyclopentadiene,[11] the reagent of choice was the cyclopentadienyl Grignard reagent.[12]

The preparation of the tosylate **6** was achieved starting from lactone **4**.[13] Reduction of **4**, followed by treatment of the corresponding lactol with the anion of $(EtO)_2POCH_2CO_2C(CH_3)_3$, resulted in condensation with the aldehyde and subsequent intramolecular conjugate addition to produce ester **5** in 89% isolated yield. Deprotonation of **5** by LDA, followed by the addition of *p*-TsCl, resulted in formation of **6** in 83% isolated yield.

Alkylation of **6** proceeded smoothly in THF, using CpMgCl to produce the corresponding functionalized cyclopentadiene. Intramolecular cycloaddition was complete within 2 h at 75 °C in benzene to produce **7** (81% isolated yield). Through this single cycloaddition reaction, the relative stereochemistry of all four asymmetric centers of **14** was established.

The generation of **1**, by the addition of a solution of Tebbe reagent to a solution of 4-(dimethylamino)pyridine, in the presence of **7**, resulted in the formation of the metallacycle **8**. Heating of this mixture to 90 °C initiated ring opening to the alkylidene **9**. Subsequent intramolecular trapping of **10** resulted in the complete conversion of **7** to **9**. Due to the sensitivity of the cyclobutene enol ether to hydrolysis and upcoming reaction conditions, the cyclobutanone functionality was protected and isolated as the 1,3-dioxolane **11**. The ketal was isolated in 81% yield based on **7**. This rearrangement established the skeletal framework of capnellene without affecting the asymmetric centers established during the cycloaddition. Completion of the synthesis required only the manipulation of existing functionality.

Transformation of the vinyl substituent to a methyl group was achieved through the use of standard techniques. Cleavage of the olefin using ozonolysis removed the excess carbon and workup with $NaBH_4$[14] reduced the angular substituent to a hydroxyl methyl group. Further reduction to the methyl group was achieved by using a reported procedure involving lithium reduction of the tetramethylphosphorodiamidate ester of the alcohol.[15] Unfortunately, even at −50 °C, reduction of the protected cyclobutanone functionality occurred to a small extent producing the corresponding cyclobutanol of **12**. After removal of the protecting group from the desired product, the mixture was treated with pyridinium dichromate (0.15 equiv) to produce a single organic product, **12**, isolated in 68% yield based on **11**.

Ring expansion of the cyclobutanone to the cyclopentanone resulted in the known capnellene ketone precursor. Although this system appeared similar in nature to that reported to exhibit 100% regiochemical ring expansion,[16] we were able to obtain only a 83:17 ratio of **13** to that of its regiochemical isomer. The use of ethyl diazoacetate, catalyzed by boron trifluoride etherate,[17] produced optimal results. Following decarbonylation,[18] **13** was isolated by flash chromatography in 73% overall yield from **12**. Methylenation of **13** using the Tebbe reagent produced a 93% yield of capnellene.[19] The Tebbe reagent, which can be isolated as a solid[4] or prepared in situ,[20] provides an attractive alternative to Ph_3PCH_2 in the final step. Previous use of this tempermental reagent for the transformation of **13**, formed by hydrogenation of α,β-unsaturated **13**, to **14** has led to inconsistent product yields of 36-80% for these two combined steps.[8] This efficient synthesis (20% overall from **4**) demonstrates the utility of the multifunctional reactivity of titanaethylene in synthetic transformations.

Acknowledgment. Financial support for this work was provided by the National Institues of Health (Grant GM-31332). High-resolution mass spectral determination on **14** was performed by the Mass Spectroscopy Center at the University of California, Riverside. We thank Professor John K. Stille (Colorado State University) for providing spectral data of both **13** and **14**.

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Cobalt-Catalyzed One-Step Assembly of B-Ring Aromatic Steroids from Acyclic Precursors

Stewart H. Lecker, Nhan H. Nguyen, and K. Peter C. Vollhardt*

Department of Chemistry
University of California, Berkeley
Materials and Molecular Research Division
Lawrence Berkeley Laboratory
Berkeley, California 94720
Received September 23, 1985

Because of their varied physiological activity, steroids are important testing grounds on which to explore the utility of novel synthetic methodology.[1] We have used cobalt, in the form of $CpCo(CO)_2$, as a matrix around which to assemble natural and unnatural polycyclic products, including the steroid nucleus.[2] In this way, the total synthesis of A-ring aromatic systems of the estrone type was achieved via the D → ABCD[3] and A → ABCD strategies.[4] We now report an approach in which all four rings are assembled (0 → ABCD) in one step to give B-ring aromatic derivatives with complete control of the crucial stereochemistry of the C,D-ring juncture. To our knowledge, this strategy has been accomplished previously only by employing biomimetic cyclizations[5] and not en route to the rare[6] target class of compounds which has never been constructed by total synthesis.

Our retrosynthetic analysis is shown in Scheme I and relies in the first step on a previously unexplored[2] intramolecular alkyne cyclization to form a cyclobutahydronaphthalene **2**, in turn to be converted to product by an intramolecular Diels-Alder cycloaddition via **3**. On the basis of a model study,[7] the C,D-ring junction was hoped to emerge trans. The convergent and efficient

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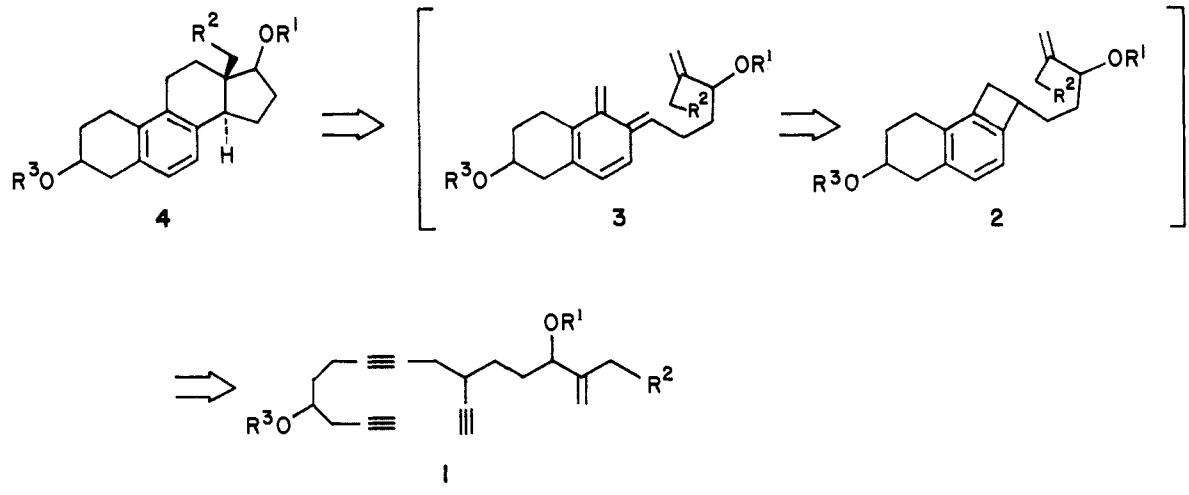
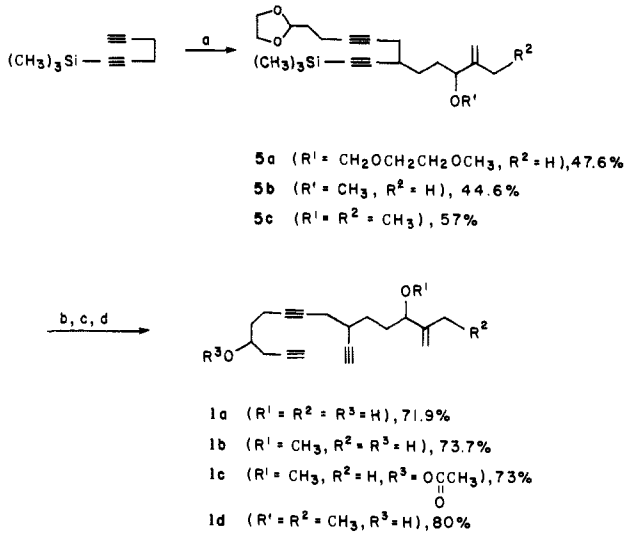
Scheme I



Scheme II[a]



[a] (a) 1. $CH_3CH_2CH_2CH_2Li$ (2 equiv), $(CH_3)_2NCH_2CH_2N(CH_3)_2$ (1 equiv), THF, −78 °C; 2. $BrCH_2CH_2C(OR^1)HC(=CH_2)CH_2R^2$, **6a** ($R^1 = CH_2OCH_2CH_2OCH_3$, $R^2 = H$), **6b** ($R^1 = R^2 = CH_3$), 23 °C; 3. 3-iodopropanal ethylene acetal; (b) HCOOH, petroleum ether, 23 °C; (c) $HC{\equiv}CCH_2MgBr$, ether, −78 → 23 °C; (d) K_2CO_3, CH_3OH, 23 °C (for **1c** this was followed by $CH_3C(=O)OC(=O)CH_3$-pyridine).

synthesis of various cyclization precursors **1** is shown in Scheme II.[8] 3,6-Dilithio-1-(trimethylsilyl)-1,5-hexadiyne[7] was converted to **5** by the sequential addition of various protected bromoalkenols **6**[7,9] and 3-iodopropanal ethylene acetal[10] with complete regioselectivity. Deprotection (including R^1 for **5a**), 3-propynylmagnesium bromide addition, and desilylation then furnished enetriynes **1**.

The results of the cobalt-catalyzed cyclizations are listed in Table I. The complete transformation could be performed in one step as in the cases of **1b–d** or interrupted at the benzocyclobutene stage **2a,b**. Yields in all cases were good to excellent.[2] The stereochemistry at the C,D-ring junction was 100% trans.[7,11] Although the cyclizations proceeded in a stereorandom manner at C-3 and C-17, this result is of no consequence to their ultimate utility, since these centers are controllable after oxidation to the diketones. Thus, treament of **1a** with pyridinium chlorochromate (CH_2Cl_2) gave cleanly the corresponding known 5,7,9(10)-estratriene-3,17-dione **7a** (91.7%)[6e,8,12] providing a chemical proof for the authenticity of the framework of the precursor. Similarly, **4d** was 3-acetylated ($CH_3C(=O)OC(=O)CH_3$, pyridine, 98%), deprotected at C-17 [CH_3CN, NaI, $(CH_3)_3SiCl$, 63%], turned into the 3,17-diol (K_2CO_3, CH_3OH, not isolated), and oxidized (PCC, CH_2Cl_2, 88%) to the single 18-methyl-5,7,9(10)-estratriene-3,17-dione **7d**.[8,12] Since **4a** and related compounds can be reduced selectively by electrochemical means[6b] to the 6,9α-dihydroderivatives, their facile synthesis reported in this paper opens up access to many other known and, more importantly, novel steroids. Finally, correlation of **7a** with a readily available natural product, equilenin, was achieved by A-ring oxidation ($CuBr_2$, LiBr, CH_3CN),[13] identical in its spectral data with authentic material.

Table I. Cyclization of Enetriyne **1** in the Presence of $CpCo(CO)_2$

1, enetriyne	a →	2, % yield	b →	4, % yield[d]
1a		86		93[c]
1b		90		95 (87)
1c				(79)
1d				(92)

[a] $CpCo(CO)_2$, *o*-xylene, Δ, *hν* (GE-ENH 250-W slide projector lamp), 1 h. [b] Decane, Δ, 20 h. [c] Compound **2** in a mixture of decane and *o*-xylene was heated at reflux for 4 days. [d] Yields in parentheses refer to direct conversion of **1** to **4**. The reaction was carried out in boiling decane for 20 h; the light source was turned off after 1 h.

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(8) All isolated new compounds gave satisfactory analytical and/or spectral data (see ref 12 and supplementary material).

(9) Compound **6b** was obtained from 2-methylpropenal (55% overall yield) and **6c** from 2-ethylpropenal (44%) as described in ref 7.

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(12) **7a**: colorless crystals (ether) mp 93–94 °C (lit.[11] mp 94.5–96.5 °C); MS, *m/e* (relative intensity) 268.1452 (calcd 268.1463, M^+, 100%), 253 (7.4), 240 (7.0), 226 (26.2), 212 (68.6); IR ($CDCl_3$) 1734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 7.24 ppm) δ 6.99 (d, *J* = 8.0 Hz, 1 H), 6.95 (d, *J* = 8.0 Hz, 1 H), 3.56 (br s, 2 H), 2.99 (m, 2 H), 2.99 (m, 1 H), 2.89 (dt, *J* = 2.8, 8.7 Hz, 2 H), 2.65 (dd, *J* = 2.8, 8.8 Hz, 1 H), 2.52 (t, *J* = 6.7 Hz, 2 H), 2.37 (m, 2 H), 2.08 (ddd, *J* = 3.4, 5.9, 10.8 Hz, 1 H), 1.92 (m, 2 H), 0.75 (s, 3 H); ^{13}C NMR ($CDCl_3$, 77.0 ppm) δ 219.80, 210.68, 136.35, 134.80, 133.28, 131.63, 126.04, 123.80, 47.04, 46.72, 45.22, 37.82, 36.49, 29.05, 24.46, 24.43, 21.64, 13.38. **7d**: colorless crystals (ether), mp 146–148 °C; MS, *m/e* (relative intensity) 282 (100%), 253 (27.2), 238 (16.9), 225 (85.7), 211 (58.3), 197 (34.1), 167 (34.8), 155 (46.5), 141 (37.1); ^1H NMR (300 MHz, $CDCl_3$) δ 6.99 (d, *J* = 8.1 Hz, 1 H), 6.94 (d, *J* = 8.1 Hz, 1 H), 3.55 (br s, 2 H), 3.09 (dd, *J* = 6.1, 13.3 Hz, 1 H), 2.98 (dt, *J* = 2.5, 7.1 Hz, 2 H), 2.90 (t, *J* = 8.1 Hz, 1 H), 2.77 (dd, *J* = 8.0, 10.4 Hz, 1 H), 2.55–2.73 (m, 2 H), 2.53 (t, *J* = 6.7 Hz, 2 H), 2.21–2.46 (m, 2 H), 1.94–2.13 (m, 1 H), 1.52–1.72 (m, 1 H), 1.22 (m, 2 H), 0.81 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 218.66, 210.76, 136.38, 134.76, 133.65, 131.53, 126.04, 123.82, 47.56, 45.22, 37.86, 36.55, 31.38, 25.11, 24.49, 24.35, 21.15, 17.82, 7.72.

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Supplementary Material Available: Complete yield, melting point, and spectral and/or analytical data of all new compounds reported (11 pages). Ordering information is given on any current masthead page.

Identification and Structure Assignment of Components of Leucinostatin and CC-1014 by Directly Coupled Liquid Chromatography/Fast Atom Bombardment Mass Spectrometry[1]

Justin G. Stroh,[2a] Kenneth L. Rinehart, Jr.,*[2a]
J. Carter Cook,[2a] Tsuyoshi Kihara,[2a] Makoto Suzuki,[2b] and Tadashi Arai[2c]

School of Chemical Sciences, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801
Faculty of Pharmacy, Meijo University Nagoya 468, Japan
Research Institute for Chemobiodynamics Chiba University, Chiba 280, Japan

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We recently described the coupling of liquid chromatography (LC) with fast atom bombardment mass spectrometry (FABMS) via a moving belt interface.[3] While successful in dealing with peptides to molecular weight 1900, the interface showed considerable breakup in the total ion current (TIC) trace, so that separations were difficult to follow and the limit of the spectrometer's sensitivity was nearly reached. In that version of the LC/FAB interface, the sample was deposited from a column onto the moving belt via a jet spray.[4] We have now modified our interface to include a frit in place of the jet at the end of the liquid chromatograph, and we now use microbore (1-mm i.d.) columns at flow rates up to 100 μL/min. With these modifications, component peak shapes resemble much more closely those from the LC/UV detector and sensitivity is no longer a problem. Additional improvement in the peak shape can be effected by measuring the TIC only above a preset mass, which eliminates most of the background ions arising from the belt. One advantage of coupled LC/FAB over isolation of components from the liquid chromatograph and subsequent analysis by FABMS is that no matrix need be included with the effluent (since the moving belt presents the atom beam with a continuously changing surface) and no matrix peaks are observed. We describe here the use of LC/FAB in the identification of a number of new components of the peptide antibiotics leucinostatin and CC-1014.

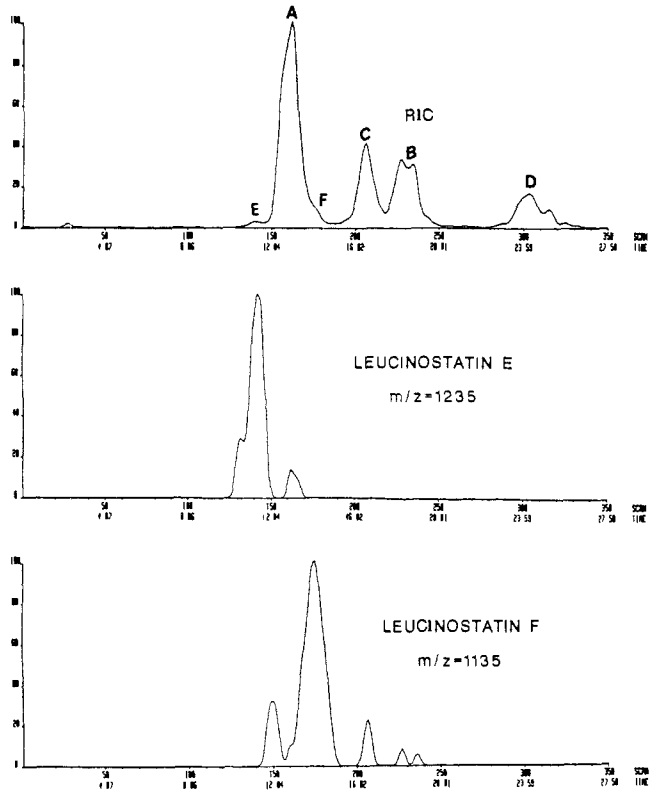
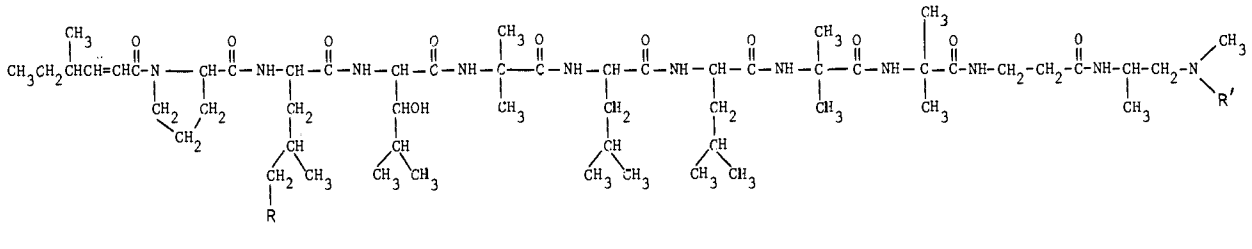


Figure 1. Top trace: limited reconstructed ion chromatogram of leucinostatin mixture. Solvent conditions: methanol:2-propanol:water: acetonitrile:carbon dioxide/diethylamine, 40:30:20:10:0.1. Flow rate: 100 μL/min, 1-mm i.d. C_{18} column, 5 μg injected. Middle trace: single-ion trace of m/z 1235 (leucinostatin E). Bottom trace: single-ion trace of m/z 1135 (leucinostatin F).

The structures of leucinostatins A and B were recently assigned by Fukushima et al.,[5] as shown in Scheme I. Our studies carried out on very limited samples of CC-1014[6,7] suggested that CC-1014 might be very closely related to or perhaps identical with leucinostatin A, and the latter appears to be identical with P168[8] and 1907.[9] Consequently, the two antibiotics were reinvestigated by LC/FABMS and the TIC trace of leucinostatin is shown in Figure 1. Components A and B were identified as leucinostatins A and B, respectively, from their FAB spectra, that of leucinostatin A from the LC/FAB experiment being shown in Figure 2. The remaining components of the leucinostatin mixture, however, had not been previously reported. They were identified as the new leucinostatins C and D and assigned the structures shown in Scheme I on the basis of their FAB spectra. Two more components, leucinostatins E and F, were observed in such low abundance that only molecular weight information was obtained and the

Scheme I



Leucinostatin A:[5] R = $CHOHCH_2COCH_2CH_3$; R' = CH_3
B:[5] R = $CHOHCH_2COCH_2CH_3$; R' = H
C: R = H; R' = CH_3
D: R = H; R' = H

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