unfavorable interaction, conformational adjustments occur in the "flap" region where the main-chain torsional angles ψ_{48} and φ_{49} rotate by as much as 40° relative to their angles in the HIVP-APS complex.[11] This contact with the indan ring is replaced by a hydrogen bond to an amide group in more peptidyl inhibitors,[11-13,28,29] and affinity might be improved by incorporating a substituent capable of donating a hydrogen bond to the carbonyl of Gly 48. In another adjustment, which is only partially successful in optimizing interactions, ψ_{A27} rotates so as to move the carbonyl oxygen of Gly A27 away from the catalytic Asp residues and toward the indanol hydrogen-bond donors. Because the inhibitor appears unable to form good hydrogen bonds with both ends of the active site simultaneously (Figure 1), decreasing the number of bonds separating inhibitor amides might improve inhibitory potency.

The design of **2** was successful in that it produced an inhibitor with high affinity (0.7 nM) which interacts with the protease in a nearly symmetric manner. The indanol ring system is a novel substituent that simultaneously provides good hydrophobic interactions and is involved in as many as three hydrogen bonds with the protein. However, the presence of unsolvated carbonyl groups, unoptimized hydrogen bonding, and several water-mediated interactions between the protein and inhibitor indicate that inhibitors can be improved.

Acknowledgment. We acknowledge Drs. Paul L. Darke, Emilio A. Emini, and William Schleif for providing us with the results of the HIV protease and cell spread assays. We extend thanks to Drs. P. M. D. Fitzgerald and J. P. Springer for their review of this manuscript.

Stereocontrolled Total Synthesis of (±)-Pentalenolactone P Methyl Ester

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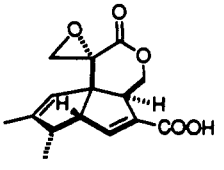
Received July 15, 1991

The isolation in 1957[1,2] of pentalenolactone (**1**) has proven to be a harbinger of many exciting discoveries involving *Streptomyces*-derived triquinane sesquiterpenes.[3] Of these, the identification and characterization by Seto et al.[4] of pentalenolactone P (**2a**) could provide the key to our detailed understanding of the biosynthetic origin of this class of antibiotics. Cane et al. have



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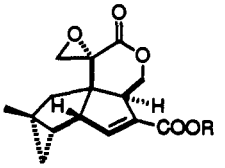
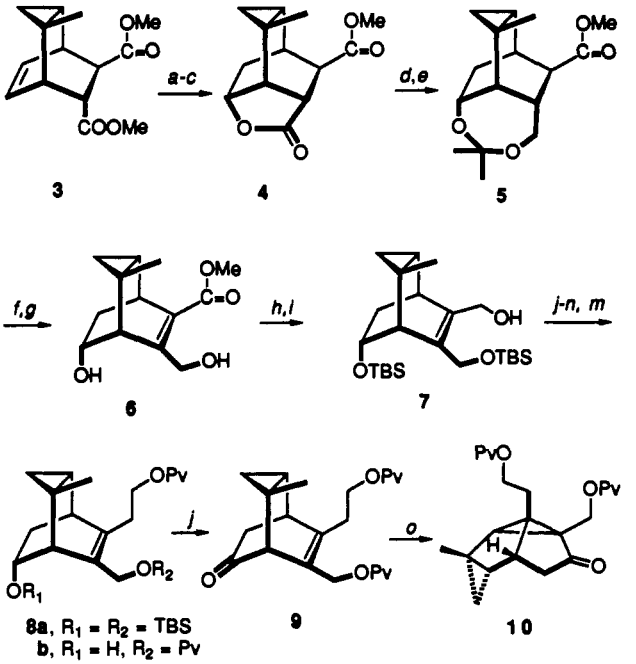


2a, R = H
b, R = CH_3

suggested two possible pathways for the formation of **2a**.[3] From the catabolic perspective, its protonation with rupture of the cyclopropane ring could be the source of a centrally important tertiary carbocation intermediate. Strikingly, pentalenolactone P is the first member of this class to contain a fused three-membered ring, *which is seen to reside on the highly congested concave surface of the molecule.* As a consequence of the latent reactivity

Scheme I



3 **4** **5** **6** **7** **8a**, R_1 = R_2 = TBS; **b**, R_1 = H, R_2 = Pv **9** **10**

[a] NaOH, CH_3OH, H_2O, room temperature. [b] $Hg(OAc)_2$, MeOH, room temperature, $NaBH_4$, -78 °C. [c] CH_2N_2. [d] $NaBH_4$, MeOH, room temperature. [e] $CH_3C(OMe)_2CH_3$, (TsOH), THF. [f] LDA, THF, -78 °C; PhSeCl. [g] MCPBA, $NaHCO_3$, CH_2Cl_2, room temperature. [h] TBSCl, imid, DMF, room temperature. [i] Dibal-H, CH_2Cl_2, -78 °C. [j] $(n\text{-Pr})_4NRuO_4$ (TPAP), 4-methylmorpholine *N*-oxide (NMO), 4-Å sieves, CH_2Cl_2, room temperature. [k] $Ph_3P{=}CH_2$, THF, 0 °C → room temperature. [l] 9-BBN, THF, room temperature; $NaBO_3$. [m] PvCl, Et_3N, DMAP, CH_2Cl_2, room temperature. [n] HF (48%), CH_3CN, 0 °C. [o] *hν*, 3000 Å, acetone, room temperature.

of **2a** and its unusual structural features, we have undertaken a stereocontrolled synthesis of this highly functionalized pentacyclic lactone as its stable methyl ester **2b**.

The requisite trans relationship of the cyclopropane and lactone components was immediately secured by Diels-Alder addition of fumaroyl chloride to 1-methylcycloheptatriene[5] followed directly by methanolysis to give **3** (80%, Scheme I).[6] Once lactone **4** had been produced (75%),[7] chemoselective distinction between the pair of carbonyl groups was made feasible (87%), leading ultimately to **5** (76%). Despite considerable steric shielding about the carbomethoxy group in **5**, phenylselenenylation of the enolate could be satisfactorily accomplished. Direct oxidation of this intermediate with buffered MCPBA gave dihydroxy ester **6** in an overall yield of 72%. Evidently, the substantial strain introduced upon installation of the conjugated double bond accelerates acetal cleavage and hydrolysis. Silylation of the hydroxyl groups in **6** and ester reduction provided **7** (80%) and set the stage for regioselective chain extension.

Toward this end, perruthenate oxidation[8] of **7** delivered the aldehyde, which was directly subjected to Wittig olefination. This two-step sequence gave rise efficiently (93%) to the conjugated diene. As anticipated, its hydroboration-oxidation[9] afforded **8a** after pivaloylation (87%). Desilylation with HF in acetonitrile at 0 °C[10] and subsequent selective acylation with pivaloyl chloride

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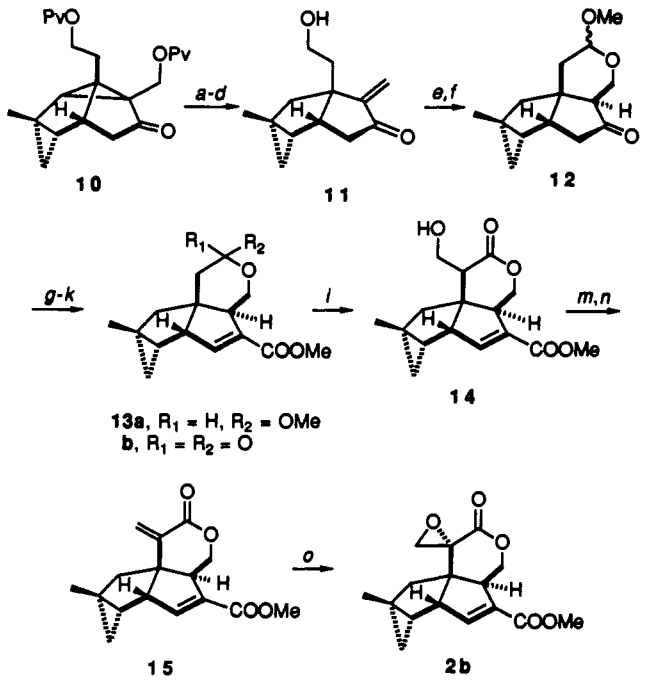
Scheme II



[a] NaOH, EtOH, H_2O, room temperature. [b] Li, NH_3. [c] Ac_2O, Et_3N, DMAP, CH_2Cl_2, −20 °C. [d] Na_2CO_3, MeOH, H_2O, room temperature. [e] Swern oxidation. [f] NaOMe, MeOH, room temperature. [g] LDA, THF, −78 °C; $PhNTf_2$, −78 °C → 0 °C. [h] $Pd(OAc)_2$, Ph_3P, Et_3N, MeOH, DMF, CO atmosphere, room temperature. [i] CH_2N_2. [j] HCl, THF, room temperature. [k] $(n\text{-}Pr)_4NRuO_4$ (TPAP), NMO, 4-Å sieves, CH_2Cl_2, room temperature. [l] LDA, THF, −78 °C; CH_2O. [m] CH_3SO_2Cl, Et_3N, CH_2Cl_2. [n] DBU, C_6H_6, room temperature. [o] MCPBA, CH_2Cl_2, reflux.

made available alcohol **8b** (70%).

Perruthenate oxidation[8] of **8b** delivered the pivotal tricyclic β,γ-unsaturated ketone **9** (97%). At this point, reliance was placed on the oxadi-π-methane rearrangement[11] for establishing a large segment of the structural network of **2**. Indeed, irradiation of **9** in acetone with 3000-Å light proceeded without event to introduce a second three-membered ring as in **10** (91%). Any ambiguity in structure was removed by X-ray analysis[12] of the highly crystalline diol produced by saponification of **10**.

Stereoelectronic factors present in **10** allowed for fully regiocontrolled cleavage of a single cyclopropane bond under dissolving metal conditions (Scheme II). The resultant dihydro diol and **11** (1:2) were separated; the diol was acetylated and treated with Na_2CO_3 in aqueous MeOH to give additional **11** (62% overall). The latter was oxidized to the keto aldehyde and exposed directly to methoxide ion. Intramolecular Michael addition of the hemiacetal anion[13] delivered **12** in 62% yield.

Proper attachment of the carbomethoxy group was realized by conversion of **12** to its enol triflate,[14] $Pd(OAc)_2$-catalyzed carbonylation,[15] and esterification with CH_2N_2 (66% of **13a**). Once **13b** was in hand (88%), several probe experiments indicated that introduction of the remaining carbon atom would be difficult. Recourse to monomeric formaldehyde dissolved in THF[16] as electrophile did, however, result in efficient conversion to **14** (86%, 10:1 α/β). The synthesis of **2b** was completed by formation of methylene lactone **15** (93%)[17] and peracid oxidation (18%). Modest improvement in yield was seen when the three-step sequence[17] involving Dibal-H/*t*-BuOOH, $VO(acac)_2$/TPAP, and NMO was utilized instead. The synthetic product proved identical in all respects with an authentic sample.[18]

Acknowledgment. We gratefully acknowledge the National Institutes of Health (Grant GM-28468) for support of this work.

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Chlorination and Bromination of Fullerenes. Nucleophilic Methoxylation of Polychlorofullerenes and Their Aluminum Trichloride Catalyzed Friedel–Crafts Reaction with Aromatics to Polyarylfullerenes[1a]

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Received September 11, 1991

Since the development of a practical synthesis of buckminsterfullerene, C_{60}, and related fullerene C_{70}, by resistive evaporation of graphite in early 1990,[2] their chemistry has seen an explosive growth. The majority of the work pertains to their redox behavior.[3-10] Recently, we were able to quench fullerene diamagnetic polyanions (probably hexaanions) with methyl iodide to polymethylated fullerenes.[7a] Poly(trimethyl)silylation was also achieved, albeit in poor yield.[7a] Wudl has achieved alkylation and arylation of fullerene,[7b] and Wood et al. reported sequential

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