Total Synthesis of (−)-Balanol[1,2]

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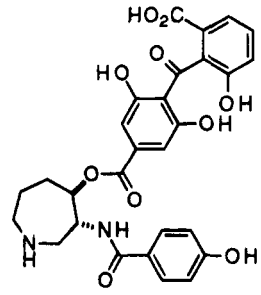
Summary: (−)-Balanol, a fungal metabolite with potent protein kinase C inhibitory properties, has been prepared in a total synthesis which makes use of an anionic homo-Fries rearrangement approach to the benzophenone subunit and in which the azepane subunit is obtained from (2*S*,3*R*)-3-hydroxylysine.

Protein kinase C (PKC) is a family of phospholipid-dependent serine/threonine-specific protein kinases which play an important role in cellular growth control, regulation, and differentiation.[3] Activation of PKC is a key step in processes such as cellular proliferation and gene expression,[4] and the enzyme has been implicated in the progression of a number of diseases, facts which have rendered PKC inhibitors attractive therapeutic targets.[5] Recently, the isolation and structural elucidation of (−)-balanol, **1**, a metabolite produced by the fungus *Verticillium balanoides* which has been found to inhibit PKC at low nanomolar concentrations, was reported from our laboratories.[6] As part of an ongoing program directed toward the discovery of novel therapeutic agents for the treatment of PKC-mediated disorders, we required a synthesis of (−)-balanol which would allow the preparation of larger quantities of the compound for pharmacological characterization and would be sufficiently flexible to provide ready access to synthetic analogs. In this paper we describe a total synthesis of (−)-balanol which meets these goals.



(-)-Balanol, **1**

Retrosynthetic analysis led to the obvious disconnection of balanol at its ester and amide linkages to give benzophenone acid **2**, azepane **3**, and 4-hydroxybenzoic acid. Benzophenone **2** could arise by way of directed metalation of benzyl alcohol **4** followed by coupling to a suitably activated form of benzoic acid **5**. It was anticipated that azepane **3** could be derived from 3-hydroxylysine (**6**)[7] via lactam formation followed by reduction. An efficient nonracemic synthesis of (2*S*,3*R*)-3-hydroxylysine has recently been completed in our laboratories.[8]

The synthesis of the benzophenone subunit began with the preparation of benzoic acid **5** as shown in Scheme 1. The differentially protected aryl bromide **8** was readily prepared from acid **7** in 71% overall yield by a three-step sequence in which **7** was perbenzylated, the benzyl ester was hydrolyzed, and the acid was reesterified after activation with 1,1′-carbonyldiimidazole (CDI). Bromide **8** undergoes rapid transmetalation with *n*-butyllithium at −78 °C followed by trapping of the aryllithium with carbon dioxide to afforded the desired benzoic acid **5** in 48% yield. Acid **5** was then converted in quantitative yield to the acid chloride **9** using oxalyl chloride.

Several attempts to couple **9** directly with aryl nucleophiles bearing substitution appropriate for the construction of the fully substituted benzophenone proved unsuccessful. The difficulty in these couplings is presumably due to the severely crowded nature of the transition states encountered in the assembly of the tetraortho-substituted benzophenone. In order to surmount these steric limitations, an intramolecular approach to the formation of the final benzophenone carbon−carbon bond was adopted (Scheme 2). Thus, benzyl alcohol **4** was metalated by reaction with *n*-butyllithium in analogy to the work of Trost,[9] and the resulting aryllithium was allowed to react with 1,2-dibromo-1,1,2,2-tetrafluoroethane[10] to give aryl bromide **10** in 51% yield. Acylation of **10** with acid chloride **9** gave an 81% yield of ester **11**, the substrate for the planned anionic homo-Fries[11] rearrangement. As anticipated, exposure of **11** to *n*-butyllithium at −78 °C led to rapid metalation and rearrangement to give benzophenone **12** in 51% yield. Oxidation of alcohol **12** with pyridinium dichromate in DMF[12] afforded the corresponding benzaldehyde **13**, which was curiously resistant to further oxidation. However, treatment of aldehyde **13** with tetrabutylammonium permanganate[13] in pyridine gave the desired acid **14** in 97% yield from **12**. Benzylation of the acid afforded the benzyl ester **15** in 73% yield. Diester **15** was unusually sensitive to the acid conditions normally used for the cleavage of *tert*-butyl esters, affording a substantial quantity of a debenzylated side product. In contrast, thermolysis of **15** in

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(1) Presented in part at the 24th Medicinal Chemistry Symposium, The University of Utah, June 21–26, 1994.

(2) Dedicated to the memory of our late colleague, Jeffrey B. Nichols.

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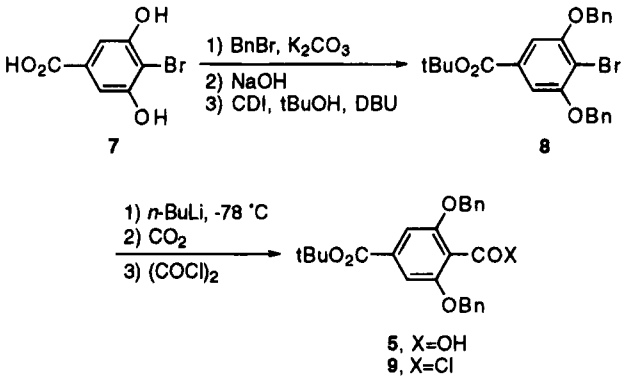
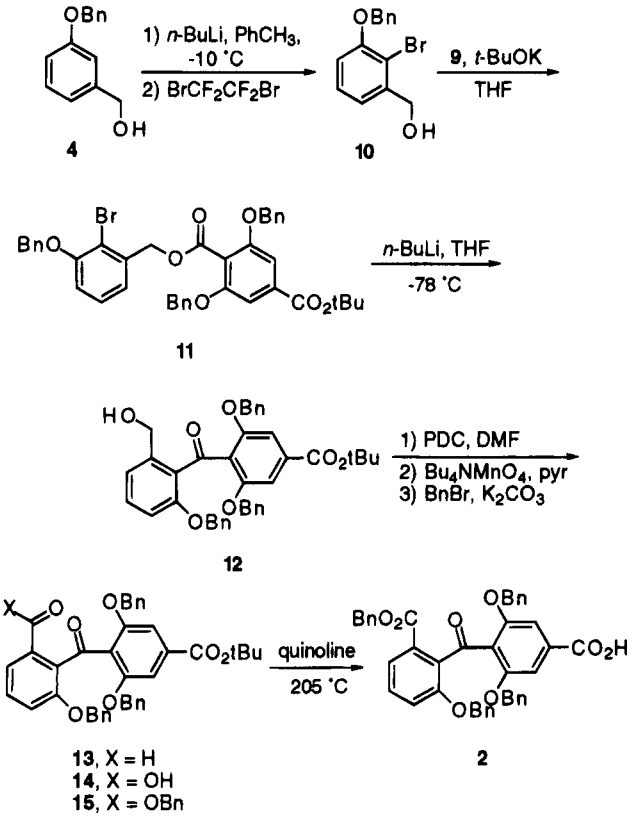
Scheme 1



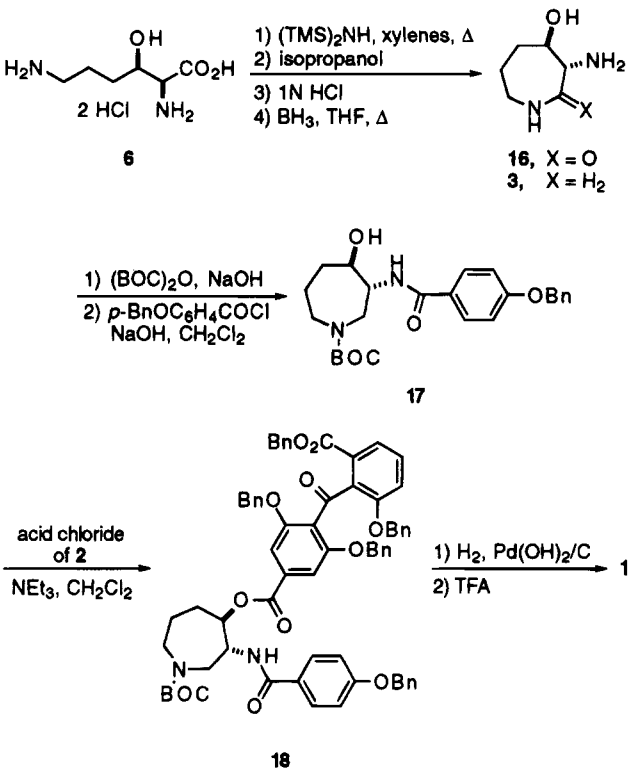
Scheme 2



quinoline at 205 °C led cleanly to the carboxylic acid **2**, which was isolated in 68% yield as a crystalline solid.

Synthesis of azepane **3** from hydroxylysine (**6**) is shown in Scheme 3. As an initial attempt, the methyl ester of **6** was formed (HCl, MeOH) and cyclized with base (K_2CO_3) in refluxing methanol. Unfortunately, complete epimerization of the 3-amino stereocenter was seen. However, drawing from a recent Soviet patent,[14] addition of powdered hydroxylysine (**6**) to hexamethyldisilazane in refluxing xylenes gave a homogeneous solution. Slow addition of 2-propanol[15] then led to the desired lactam and only 7% of the epimeric byproduct. Caprolactam **16** was obtained as a crystalline solid (79%) after ion exchange chromatography (AG-50, H^+-form, 1 N HCl) to remove the epimeric byproduct. Borane reduction followed by decomposition of the resulting borane complex

Scheme 3



by sequential additions of methanol, alkali, and acid afforded the desired azepane **3**, which was isolated as a crystalline solid (67% yield) after ion exchange chromatography (AG-50, H^+-form, 3 N HCl).

The synthesis of balanol was completed as shown in Scheme 3. Selective protection of the azepane nitrogen was accomplished by reaction of **3** with di-*tert*-butyl dicarbonate. Acylation of this monoprotected compound with 4-(benzyloxy)benzoyl chloride provided amide **17** in 66% yield from **3**. Further acylation of **17** with the acid chloride derived from benzophenone acid **2** led to ester **18**. Deprotection by hydrogenolysis followed by treatment with trifluoroacetic acid afforded (−)-balanol (**1**) in 63% yield from **17** after isolation by reversed phase HPLC. This synthetic material was found to be identical with naturally occurring balanol by ^1H NMR, TLC, HPLC, and optical rotation. The natural and synthetic materials were also found to be indistinguishable in their inhibitory potencies as determined in protein kinase C enzyme assays.

In summary, we have described the first total synthesis of (−)-balanol (**1**). The convergent synthesis was accomplished in 18 total operations and proceeds in 22% yield for six linear steps from **6** and 4.3% yield for 14 linear steps from **7**. This synthetic route has allowed the preparation of gram quantities of synthetic (−)-balanol as well as a diverse set of synthetic analogs.

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Supplementary Material Available: A listing of the complete experimental details for the synthesis of **1** (11 pages). This material is contained in 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) Belyaev, A. A.; Konyukhova, E. V.; Radina, L. B. SU Patent no. 1708812-A1, Jan 30, 1994.

(15) Although some product often formed without 2-propanol addition, progress of the reaction was highly variable from run to run and possibly depended on adventitious introduction of moisture. We believe the 2-propanol served to partially desilylate the initially formed and unreactive persilylated compound.