Total Synthesis of Balanol

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The recent isolation and structural elucidation of balanol (**1**, Figure 1),[1] an unusual metabolite produced by the fungus *Verticillium balanoides*, represents a significant new development in the quest for effective inhibitors of protein kinase C (PKC).[2] PKC-mediated signal transduction is known to lead to a variety of cellular responses, including gene expression and cell proliferation,[2,3] and activated PKC has been implicated in conditions as diverse as cancer, cardiovascular disorders, asthma, inflammation, diabetes, CNS dysfunction, and HIV infection.[3] Consequently, the identification of potent and selective PKC inhibitors not only may serve to further illuminate signal transduction pathways but also may result in the development of novel drugs with considerable therapeutic value.[3] As part of a program directed toward the identification of effective inhibitors of PKC, we have completed, and present herein, the total synthesis of balanol.

A retrosynthetic analysis of balanol (Figure 1) reveals two distinct structural domains coupled through a central ester linkage. The hexahydroazepine-containing fragment can be further simplified by dissection of the amide moiety to reveal the *p*-hydroxybenzoic acid moiety, and the synthetic challenge posed by balanol thus reduces to an asymmetric synthesis of the central hexahydroazepine ring and the generation of the fully-functionalized benzophenone fragment.

Our synthetic approach to the hexahydroazepine fragment is presented in Scheme 1.[4] Treatment of the readily available homochiral amino acid D-serine (**2**) with di-*tert*-butyl dicarbonate (Boc_2O) afforded the *N*-Boc protected amino acid, which was subsequently converted to the corresponding methyl ester and finally silylated to afford the fully protected derivative **3** in quantitative overall yield. Reduction of **3** with excess DIBALH afforded the corresponding amino aldehyde, which was then treated with Brown's diisopinocampheylborane reagent,[5] allyl-$B(^{l}Ipc)_2$, to afford the desired *syn*-amino alcohol **4** as a 12:1 mixture of diastereoisomers. The *syn* configuration of **4** was confirmed by desilylation using TBAF and conversion to the known acetonide **5**.[6]

With the correct stereochemical disposition of the amino and hydroxyl stereogenic centers secured, the stage was now set to develop the hexahydroazepine ring system. Firstly, amino alcohol **4** was protected as the corresponding acetonide (68% yield from **3**), which was then subjected to hydroboration using 9-BBN to furnish the alcohol **6** upon alkaline hydroperoxide workup (97% yield). Introduction of an azide moiety as an amino group surrogate was now achieved by initial mesylation of the hydroxyl moiety within **6** and subsequent sodium azide displacement to furnish **7** in 98% overall yield. Mild catalytic hydrogenolysis of the azide group over Pd/C and protection of the resultant amino moiety as its benzyloxycarbonyl (Z) derivative then provided **8** in quantitative yield overall. In order to facilitate closure to the hexahydroazepine ring, the primary alcohol within **8** was revealed by desilylation using TBAF (96% yield) and then activated toward displacement by formation of the corresponding mesylate. The 7-*Exo*-*Tet* cyclization was then effected by treatment with a slight excess of potassium *tert*-butoxide in THF at ambient temperature under moderately dilute conditions to afford the fully-protected hexahydroazepine fragment **9** in 80% yield. Finally, concomitant removal of the Boc and acetonide protecting groups within **9** by treatment with TFA, followed by *in situ* derivatization of the resultant free amino alcohol with *p*-(benzyloxy)benzoyl chloride, afforded the targeted fragment **10** in 73% overall yield (36% overall from **2**).

With the hexahydroazepine fragment of balanol successfully secured, we anticipated that the remaining benzophenone domain could be prepared by utilization of a Stille-type coupling[7] of the appropriately functionalized acid chloride and arylstannane

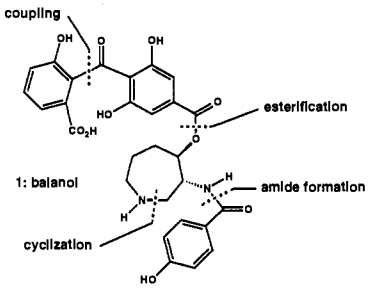
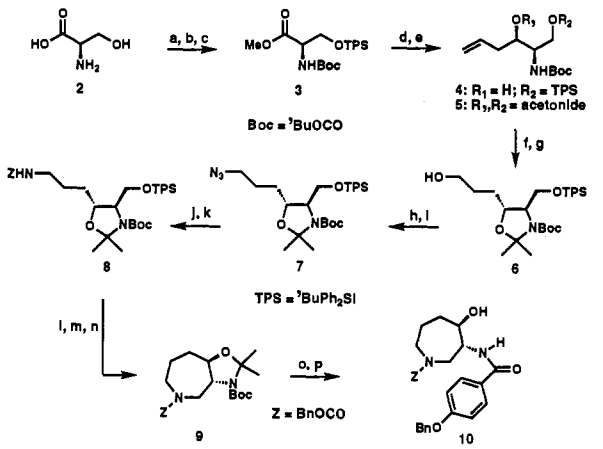


Figure 1.

Scheme 1[a]



[a] Reagents and conditions: (a) 1.2 equiv of $(Boc)_2O$, 2.1 equiv of NaOH, 1,4-dioxane, H_2O, 0 → 25 °C, 2 h, 100%; (b) 1.1 equiv of K_2CO_3, 2.0 equiv of MeI, DMF, 0 → 25 °C, 100%; (c) 1.2 equiv of TPSCl, 1.4 equiv of imidazole, DMF, 25 °C, 14 h, 100%; (d) 2.5 equiv of DIBALH, toluene, −78 °C, 1.5 h; (e) 1.8 equiv of allyl-$B(^{l}Ipc)_2$, Et_2O, −78 °C, 3.5 h; ethanolamine; (f) 5.0 equiv of 2,2-dimethoxypropane, CSA (1 mol %), CH_2Cl_2, 25 °C, 3 h, 68% (three steps); (g) 2.2 equiv of 9-BBN, THF, 20 h; NaOH, H_2O_2, 12 h, 97%; (h) 1.2 equiv of MsCl, 1.5 equiv of Et_3N, CH_2Cl_2, 0 °C, 10 min; (i) 8.0 equiv of NaN_3, DMF, 25 °C, 24 h, 98% (two steps); (j) H_2, Pd/C, THF, 19 h; (k) 1.1 equiv of benzyl chlorocarbonate, 3.0 equiv of NaOH, 1,4-dioxane, H_2O, 0 °C, 15 min, 100% (two steps); (l) 1.2 equiv of TBAF, THF, 25 °C, 16 h, 96%; (m) 1.2 equiv of MsCl, 1.5 equiv of Et_3N, CH_2Cl_2, 0 °C, 20 min; (n) 1.2 equiv of $KO^{t}Bu$ added over 2 h, moderate dilution (0.02 M), THF, 25 °C, 80% (two steps); (o) excess TFA, CH_2Cl_2, 25 °C, 1 h; (p) 1.5 equiv of *p*-(benzyloxy)benzoyl chloride, 5.0 equiv of Et_3N, CH_2Cl_2, 0 → 25 °C, 1.5 h, 73% (two steps).

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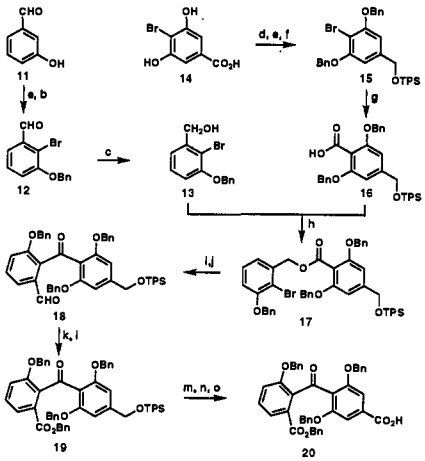
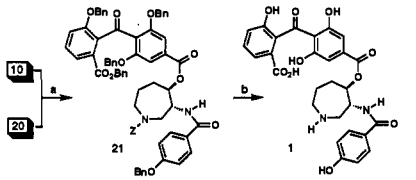
Scheme 2[a]



[a] Reagents and conditions: (a) 1.0 equiv of BnBr, 1.5 equiv of K_2CO_3, DMF, 25 °C, 12 h, 100%; (b) 1.03 equiv of ^nBuLi, 1.07 equiv of $MeNHCH_2CH_2NMe_2$, PhH, 0 → 25 °C, 0.5 h; aldehyde, 0 → 25 °C, 0.5 h; 3.0 equiv of PhLi, 0 → 25 °C, 7.5 h; 4.0 equiv of CF_3BrCF_3Br, THF, −78 → 25 °C, 12 h; 10% aqueous HCl, 0 °C, 77%; (c) 1.2 equiv of DIBALH, CH_2Cl_2, −78 → 25 °C, 1 h, 93%; (d) 3.3 equiv of BnBr, 5.0 equiv of K_2CO_3, DMF, 25 °C, 4 h, 96%; (e) 2.4 equiv of DIBALH, CH_2Cl_2, −78 → 0 °C, 1 h, 100%; (f) 1.2 equiv of TPSCl, 1.5 equiv of imidazole, DMF, 25 °C, 1 h, 82%; (g) 1.3 equiv of ^nBuLi, THF, −78 °C, 0.5 h; excess CO_2, −78 → 25 °C, 0.5 h; 10% aqueous HCl, 60%; (h) 1.1 equiv of DEAD, 1.1 equiv of Ph_3P, THF, 0 → 25 °C, 40 min; 93%; (i) 1.0 equiv of ^nBuLi, THF, −97 → -78 °C, 50 min; NH_4Cl (aqueous); (j) 1.5 equiv of NMO, cat TPAP, CH_3CN, 25 °C, 0.5 h, 74% (two steps); (k) 3.0 equiv of $NaClO_2$, 3.0 equiv of NaH_2PO_4, excess 2-methyl-2-butene, THF, ^tBuOH, H_2O, 25 °C, 8 h; (l) 2.0 equiv of BnBr, 3.0 equiv of K_2CO_3, DMF, 25 °C, 1 h, 98% (two steps); (m) 1.5 equiv of TBAF, THF, 25 °C, 10 min, 95%; (n) 1.5 equiv of NMO, cat TPAP, CH_3CN, 25 °C, 0.5 h, 70%; (o) as in k, 1 h, 95%.

Scheme 3[a]



[a] Reagents and conditions: (a) 1.0 equiv of **10**, 1.0 equiv of **20**, 1.3 equiv of 2-chloro-1-methylpyridinium iodide, 0.5 equiv of DMAP, 20 equiv of Et_3N, CH_2Cl_2, 25 °C, 5 h, 79%; (b) 1 atm of H_2, Pd black, $THF/H_2O/AcOH$ (16:4:1), 25 °C, 8 h, 100%.

components suggested by the disconnection in Figure 1. Unfortunately, such an approach was not rewarded with success and alternative procedures for the generation of this fragment were consequently sought. In particular, model studies[8] demonstrated that lithium–halogen exchange of esters analogous to **17** (*vide infra*) was followed by intramolecular attack of the corresponding aryllithium species at the ester moiety,[9] thereby generating a ketone linkage between the two aromatic components. The successful utilization of this approach in the synthesis of the benzophenone domain of balanol is outlined in Scheme 2.

The alcohol component of ester **17** was prepared from *m*-hydroxybenzaldehyde (**11**) by a three-step sequence commencing with the benzylation of the hydroxyl moiety using benzyl bromide/potassium carbonate in DMF (100% yield). Regiospecific lithiation of the resultant aldehyde,[10] followed by electrophilic bromination of the corresponding aryllithium,[11] then afforded **12** as a single regioisomer in 77% yield, and DIBALH reduction of this aldehyde furnished the desired benzyl alcohol **13** (93% yield). Commercially-available acid **14** was selected as a convenient precursor for the acid component of ester **17**. Thus, tribenzylation of **14** using benzyl bromide/potassium carbonate in DMF occurred smoothly (96% yield), and the resultant benzyl ester was reduced using an excess of DIBALH to the corresponding primary alcohol (100% yield), which was then silylated to afford **15** in 81% yield. With **15** in hand, we successfully secured the desired acid **16** in good yield (60%) *via* lithium–halogen exchange and trapping of the resulting aryllithium with carbon dioxide.

The coupling of **16** and **13** was most efficiently achieved using the Mitsunobu protocol,[12] which furnished the target ester **17** in 93% yield. The aryllithium species resulting from the low temperature (−100 °C) treatment of **17** with butyllithium successfully underwent the desired rearrangement to afford, upon protic workup, the corresponding alcohol, which could be isolated but was more conveniently oxidized directly to the aldehyde **18** (74% yield from **17**) using TPAP–NMO.[13] With this material in hand, sodium chlorite oxidation[14] afforded the carboxylic acid, which was readily converted to the benzyl ester **19** in the normal manner (98% yield from **18**). Subsequent TBAF-mediated desilylation of **19** revealed the corresponding alcohol (95% yield), which was in turn subjected to TPAP–NMO oxidation to afford the aldehyde (70% yield). Finally, oxidation of this aldehyde using sodium chlorite proceeded in excellent yield to furnish the fully-benzylated balanol benzophenone component **20**.

The union of the two protected components **10** and **20** was successfully accomplished *via* esterification using the Mukaiyama procedure[15] to afford the fully-protected balanol progenitor **21** in 79% yield (Scheme 3). The adoption of benzyl-derived protecting groups for the latent funtionalities in this coupling procedure was now rewarded since mild palladium-catalyzed hydrogenolysis of **21** resulted in the liberation of balanol (**1**) as a yellow solid in quantitative yield (>90% purity). Final purification by reverse-phase HPLC afforded a sample of balanol which exhibited characterization data consistent with the proposed structure and a ^1H NMR spectrum which correlated precisely with that of an authentic sample.[16]

It is noteworthy that the aforementioned synthetic strategies for the hexahydroazepine and the benzophenone fragments are particularly suitable for analog generation, and in order to elucidate the structural requirements for PKC inhibition, both the synthesis and biological evaluation of a variety of new balanoids are currently under investigation.

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Supplementary Material Available: Characterization data for compounds **10**, **20**, **21**, and **1** (5 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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