Total Synthesis of (−)- and (+)-Balanol[1]

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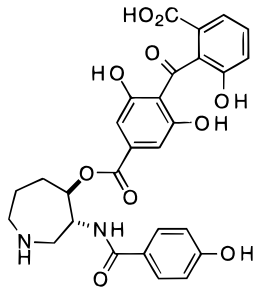
Two total syntheses of the potent protein kinase C inhibitory fungal metabolite balanol are described. In the first approach, the core aminohydroxyazepane subunit was prepared in racemic form by stereospecific functionalization of *N*-benzyl-ϵ-caprolactam. Resolution prior to coupling to the benzophenone subunit provided access to both enantiomers of balanol. In the second approach, an efficient silicon-mediated cyclization of (2*S*,3*R*)-3-hydroxylysine followed by reduction provided the azepane subunit in enantiomerically pure form. The sterically congested benzophenone subunit was assembled from two highly substituted aromatic precursors by way of an anionic homo-Fries rearrangement.

Introduction

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.[2] Activation of PKC is a critical step in the signal transduction pathways controlling processes such as cellular proliferation and gene expression,[3] and the enzyme has been implicated in the progression of a wide variety of diseases, facts which have rendered PKC inhibitors attractive therapeutic targets.[4] Recently, the isolation and structural elucidation of (−)-balanol, (−)-**1**, a metabolite which is produced in trace



(-)-Balanol, (-)-**1**

amounts by the fungus *Verticillium balanoides* and which has been shown to inhibit PKC at low nanomolar concentrations, was reported from our laboratories.[5] The discovery of balanol has provided a new structural motif to the PKC inhibitor area,[6] and the combined structural novelty and low availability of the compound has generated substantial interest in the development of synthetic approaches to the natural material[7−9] and related structures.[10,11] 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 provide access to large quantities of the compound for detailed pharmacological characterization and which would be sufficiently flexible to provide ready access to synthetic analogs with increased enzyme selectivity and improved pharmacokinetic properties. In this paper we present the full account of two synthetic approaches to either enantiomer of balanol.

Results and Discussion

Benzophenone Synthesis. Our synthetic approach began with the obvious disconnection of balanol at its ester linkage to yield the hydroxyazepane and the benzophenone carboxylic acid subunits. We anticipated assembling the sterically congested benzophenone subunit by forming one of the two bonds to the benzophenone

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(1) Dedicated to Clayton H. Heathcock on the occasion of his 60th birthday.

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(11) Koide, K.; Bunnage, M. E.; Paloma, L. G.; Kanter, J. R.; Taylor, S. S.; Brunton, L. L.; Nicolaou, K. C. *Chem. Biol.* **1995**, *2*, 601−608.

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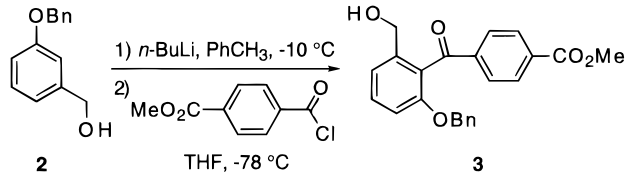
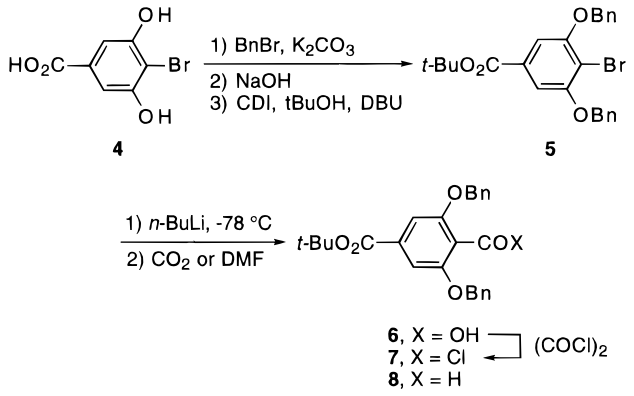
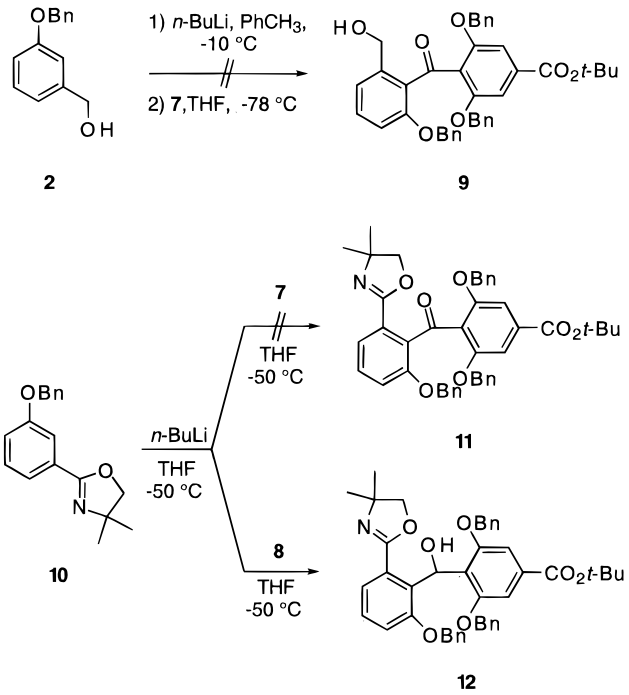
Scheme 1



Scheme 2



Scheme 3



carbonyl carbon by addition of a metalated precursor for one of the two aromatic rings to a suitably activated benzoic acid precursor for the second ring. A model for such a transformation is shown in Scheme 1. Regiospecific metalation of benzyl alcohol **2** in analogy to the method of Trost[12] followed by trapping of the resulting aryllithium with 4-carbomethoxybenzoyl chloride yields the benzophenone **3**, albeit in modest yield. Compound **3** contains the necessary functionality for elaboration into an analog of the balanol benzophenone in which two of the hydroxy substituents have been deleted.

Scheme 2 details the preparation of the acid chloride component for a coupling reaction which would provide a fully functionalized benzophenone. Differentially protected aryl bromide **5** was prepared in 71% overall yield from acid **4** by way of a three-step sequence in which **4** was perbenzylated, the benzyl ester was hydrolyzed, and the acid was reesterified after activation with 1,1′-carbonyldiimidazole. Bromide **5** undergoes rapid transmetalation with *n*-butyllithium at −78 °C to yield the aryllithium, which on trapping with carbon dioxide gives carboxylic acid **6** in 48% yield. Treatment of **6** with oxalyl chloride gives the acid chloride in quantitative yield. Alternatively, the aryllithium may be reacted with DMF to give in 53% yield aldehyde **8**, another potential intermediate for benzophenone synthesis.

Unfortunately, as shown in Scheme 3, acid chloride **7** proved to be inadequate as a substrate for coupling reactions aimed at providing the required benzophenone. Metalation of alcohol **2** and attempted coupling with **7** under the same conditions which yielded **3** provided in this case none of the desired benzophenone **9**. The poor reactivity of this acid chloride extended to a variety of other aryl nucleophiles. For example, oxazoline **10**, prepared from the corresponding carboxylic acid by the method of Meyers and co-workers,[13] afforded none of the benzophenone **11** after metalation and subsequent reaction with **7**. Similar behavior of **10** toward other acid chloride electrophiles has recently been reported by Nicolaou and co-workers,[8b] although the reaction of aryloxazolines related to **10** with acid chlorides to give benzophenones is precedented.[14] In contrast, metalation of **10** and addition to aldehyde **8** was successful, affording a 50% yield of diarylmethanol **12**. This result showed that **10** was metalated successfully and suggested that it might serve as a suitable precursor to highly substituted benzophenones; however, we were unable to elaborate **12** into the benzophenone needed for balanol, as numerous attempts at oxidation of **12** to give a benzophenone led only to decomposition of the starting material.

Thus, **7** proved to be poorly suited to the direct coupling with aryl nucleophiles to provide highly substituted benzophenones. A number of related approaches involving metalation of bromide **5** and addition to activated benzoic acid precursors to the carboxylic acid bearing ring of the benzophenone were similarly unsuccessful. We attributed the failure of these carbonyl additions to the severely crowded transition states encountered along the addition reaction pathways. The chlorocarbonyl substituent of **7** is presumably forced by the two neighboring benzyloxy substituents to lie out of the plane of the aromatic ring. As a result, the benzyloxy substituents effectively block access to either face of the carbonyl by large incoming nucleophiles. Consistent with this view, a related system in which the benzyloxy substituents have been replaced by smaller but less labile methoxy groups has recently been reported to couple successfully to give a benzophenone.[9] In contrast to the behavior exhibited by **7**, the comparatively small aldehyde unit of **8** can assume an orientation coplanar with the aromatic ring of the molecule, such that large nucleophiles can approach the carbonyl relatively unimpeded by the adjacent substituents. This observation regarding the superior accessibility of 2,6-disubstituted aldehydes such as **8** was ultimately exploited in the development of two highly efficient syntheses of differentially protected ben-

(12) (a) Trost, B. M.; Rivers, G. T.; Gold, J. M. *J. Org. Chem.* **1980**, *45*, 1835−1838. (b) Uemura, M.; Tokuyama, S.; Sakan, T. *Chem. Lett.* **1975**, 1195−1198.

(13) Meyers, A. I.; Temple, D. L.; Haidukewych, D.; Mihelich, E. D. *J. Org. Chem.* **1974**, *39*, 2787−2793.

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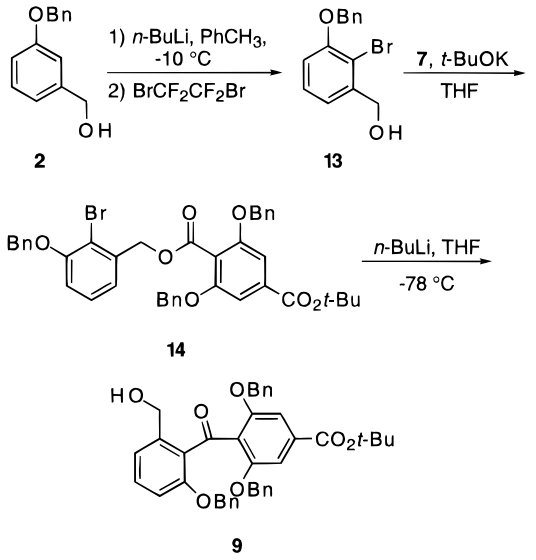
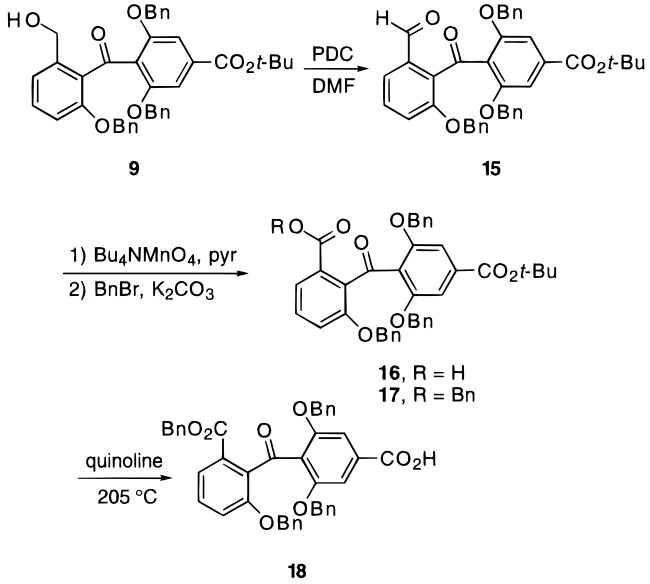
Scheme 4



Scheme 5



zophenones suited for use for the synthesis of balanol and analogs, which has been detailed in a separate communication.[7c]

The initial difficulties which we encountered in the oxidation of diarylmethanol **12** and our desire to avoid as much as possible the protecting group manipulations involved in the use of such an intermediate led us to consider other approaches in which the benzophenone unit could be generated directly. We reasoned that the steric obstacles encountered in the use of electrophiles such as **7** might be overcome if the addition to the carbonyl could be accomplished in an intramolecular fashion.[15] One approach suited to such an intramolecular generation of a benzophenone is the Fries rearrangement.[16] The anionic homologous variant of the Fries rearrangement[17] appeared to be particularly well suited to our needs, although it had not previously been applied to such a hindered and complex system.

The preparation and use of the required precursor for the homo-Fries rearrangement is detailed in Scheme 4. Metalation of **2** as described above followed by trapping of the aryllithium with 1,2-dibromo-1,1,2,2-tetrafluoroethane[18] regiospecifically afforded bromide **13** in 51% yield. Acid chloride **7** smoothly acylates the benzyl alcohol of **13**, a relatively sterically undemanding nucleophile, to give an 81% yield of ester **14**. We were gratified to find that treatment of **14** with *n*-butyllithium at −78 °C led to a rapid transmetalation and rearrangement of the intermediate aryllithium to afford the desired tetra-ortho-substituted benzophenone **9** in 51% yield.[19]

The final elaboration of **9** into the fully-protected balanol benzophenone is shown in Scheme 5. Oxidation of **9** with pyridinium dichromate in DMF[20] afforded aldehyde **15**, which was curiously resistant to further oxidation. The difficulty in the oxidation of **15** is presumably a result of the crowded environment which the tetrahedral intermediate formed in the course of the oxidation experiences due to the many substituents ortho to the benzophenone carbonyl; in contrast to the behavior of **15**, alcohol **3**, which lacks two of the ortho substituents, is oxidized smoothly by pyridinium dichromate to the corresponding carboxylic acid in 72% yield. Screening of a series of oxidants showed that permanganate reagents were capable of effecting the desired transformation to acid **16**, with tetrabutylammonium permanganate[21] proving to be particularly efficacious; sodium chlorite[22] was also effective in bringing about the oxidation. Standard benzylation afforded benzyl ester **17** in 71% overall yield from alcohol **9**.

Diester **17** proved to be particularly sensitive to the acid conditions normally used for the hydrolysis of *tert*-butyl esters. Treatment of **17** with trifluoroacetic acid or formic acid afforded the desired acid **18** along with substantial quantities of a debenzylated side-product. Thermolysis of **17** either neat or in neutral solvents also led to the formation of unacceptable levels of this debenzylated product, presumably due to acid catalysis by the product carboxylic acid; however, thermolysis in quinoline at 205 °C led cleanly to the desired benzophenone carboxylic acid **18**, which was isolated as a crystalline solid in 68% yield.

Racemic Azepane Synthesis and Resolution. Our approach to the synthesis of the azepane ring proceeded along two lines. Although an enantioselective synthesis of the azepane was ultimately desired for the synthesis of analogs, we felt that it would be prudent to pursue a racemic synthesis as well, since a simple racemic synthesis would allow quicker assembly of balanol and analogs and might be more amenable to scale-up. Reso-

(15) The use of intramolecular approaches in the synthesis of sterically congested compounds is well known; for example, see Overman, L. E. *Pure Appl. Chem.* **1994**, *66*, 1423−1430.

(16) (a) Blatt, A. H. *Org. React.* **1942**, *1*, 343−369. (b) Martin, R. *Org. Prep. Proc. Int.* **1992**, *24*, 369−435.

(17) Horne, S.; Rodrigo, R. *J. Chem. Soc., Chem. Commun.* **1992**, 164−166.

(18) (a) Finkelstein, B. L. *J. Org. Chem.* **1992**, *57*, 5538−5540. (b) Paquette, L. A.; Ross, R. J.; Shi, Y.-J. *J. Org. Chem.* **1990**, *55*, 1589−1598.

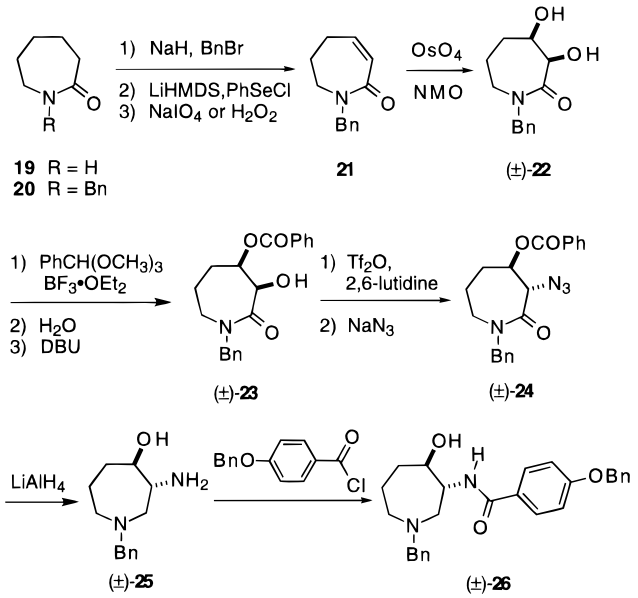
(19) Compound **9** and the related benzophenone **3** proved to be photolabile in solution, although they could be stored for prolonged periods when kept as solids in the dark. Photoreactivity of 2-(alkoxymethyl)benzophenones is well known; for example, see: (a) Oka, M.; Konishi, M.; Oki, T. *Tetrahedron Lett.* **1990**, *31*, 7473−7474. (b) Kraus, G. A.; Wu, Y. *J. Org. Chem.* **1992**, *57*, 2922−2925. (c) Coll, G.; Costa, A.; Deyá, P. M.; Flexas, F.; Rotger, C.; Saá, J. M. *J. Org. Chem.* **1992**, *57*, 6222−6231.

(20) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399−402.

(21) Sala, T.; Sargent, M. V. *J. Chem. Soc., Chem. Commun.* **1978**, 253−254.

(22) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888−890.

Scheme 6



lution of the racemate would also provide access to both enantiomers of the natural product. Our strategy was to assemble the azepane via elaboration of ϵ-caprolactam **19**.[7d] We envisioned that the trans amino alcohol would be introduced via olefin formation, epoxidation of the olefin, and epoxide opening with a suitable nitrogen nucleophile. Hydride reduction would then give the desired differentially protected azepane.

Amide alkylation of ϵ-caprolactam **19** (Scheme 6) gave *N*-benzyl derivative **20** (NaH, benzyl bromide, 96%). Lactam **20** was converted to olefin **21** in 78% yield by selenation (LiHMDS, 2 equiv, C_6H_5SeCl) followed by oxidative elimination of the phenylselenyl group ($NaIO_4$ or H_2O_2). Unfortunately, repeated attempts at carrying out the planned epoxidation of the olefin under a variety of conditions[23] proved unsuccessful, so an alternative approach was taken. Osmium tetraoxide-catalyzed dihydroxylation of the olefin gave diol **22** in 78% yield. Differentiation of the two hydroxyl groups by selective protection of the β-hydroxyl was initially elusive. Acylation with benzoyl chloride gave primarily the α-benzoate, along with some β-benzoate, bisbenzoate, and diol. However, treatment of **22** with trimethyl orthobenzoate in refluxing toluene gave only the β-benzoate, along with some starting diol. On the basis of these findings, it seemed reasonable to suspect that the β-benzoate is the more thermodynamically stable product and that it therefore might be most cleanly prepared by selective monobenzoylation of the diol followed by equilibration of the α,β-benzoate mixture to the β-benzoate. Treatment of the diol **22** with trimethyl orthobenzoate in the presence of boron trifluoride etherate gave the mixed ortho ester which was decomposed with water to a mixture of α and β monobenzoate esters. Extractive workup followed by treatment with DBU gave exclusively the β-benzoate **23** in 72% yield. Nitrogen was then introduced at the α position with inversion of configuration by conversion of the α-hydroxyl to the triflate (Tf_2O, 2,6-lutidine) followed by displacement with sodium azide to give the desired *trans*-α-azido-β-(benzoyloxy)caprolactam **24** in 87% yield. Concomitant reduction of the lactam, azide, and benzoate with $LiAlH_4$ gave azepane **25**, which on acylation with 4-(benzyloxy)benzoyl chloride afforded the desired amide alcohol **26** (55% from **24**), the planned intermediate for coupling with the properly functionalized benzophenone.

Scheme 7

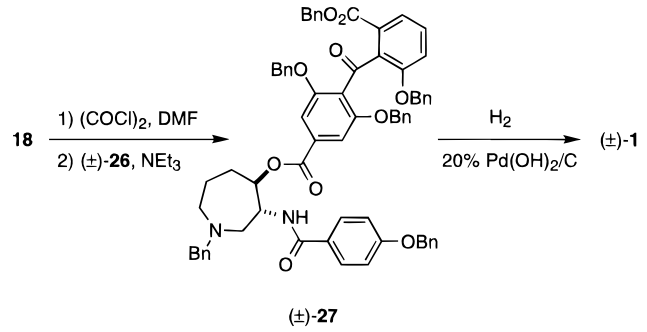


Table 1. PKC Inhibitory Activity of Synthetic Balanol Enantiomers

	IC_{50} values for inhibition of human PKC isozymes, nM[a]				
compd	PKC-α	PKC-βII	PKC-γ	PKC-δ	PKC-ϵ
(±)-**1**	67	30	30	23	38
(−)-**1**	30	10	10	4	10
(+)-**1**	3000	880	400	420	1000

[a] IC_{50} values were calculated from four-point curves of tenfold dilutions; the assays were carried out using partially purified recombinant human PKC isozymes as described previously.[30]

The synthesis of racemic balanol (±)-**1** was completed in two steps as shown in Scheme 7. Conversion of the benzophenone **18** to its acid chloride with oxalyl chloride followed by reaction with alcohol **26** afforded the desired ester **27**. Hexabenzylbalanol **27** was then converted by exhaustive hydrogenolysis (H_2, 20% $Pd(OH)_2/C$) to racemic balanol (±)-**1**. This compound was identical to natural balanol by HPLC and NMR and showed PKC inhibitory potencies remarkably close to half that of natural balanol (Table 1).

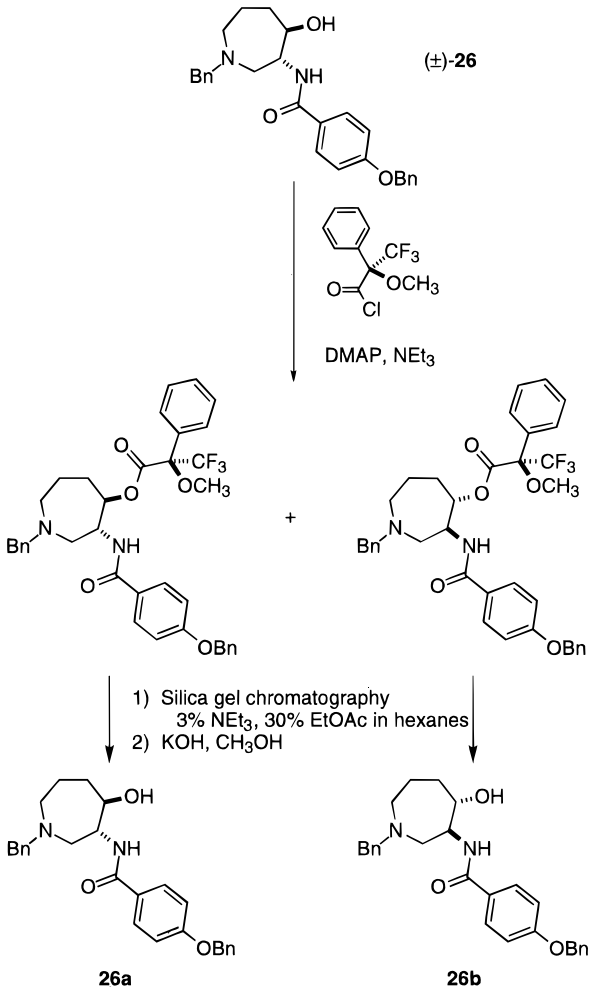
At this point, an enantioselective synthesis of the azepane had not yet been completed, and thus the question of the relative protein kinase inhibitory potencies of the two enantiomers of balanol loomed. This was an important question for two reasons. First, a finding of comparable activity in both enantiomers would suggest that the activity is related to nonspecific interactions or perhaps chemical reactivity, either of which is undesirable for drug development. However, a good separation of activity (>25:1) would suggest a specific interaction amenable to further optimization. Additionally, a good separation of activity would simplify the interpretation of SAR data generated from racemic analogs which are more easily accessible via synthesis.

To obtain both enantiomers of balanol, we chose to resolve the azepane alcohol **26** as shown in Scheme 8. The free alcohol gave a convenient point for attachment and removal of a suitable chiral auxiliary. The diastereomeric Mosher esters[24] were made and separated by repeated silica gel chromatography (3% NEt_3 in 7:3 hexanes:ethyl acetate). The esters were then saponified and the resolved alcohols, **26a** and **26b**, converted to the enantiomers of balanol as described above for racemic balanol. The resolution did not allow for the determination of the absolute stereochemistry of the enantiomers

(23) Li, B.; Smith, M. B. *Synth. Commun.* **1995**, *25*, 1265−1275.

(24) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549.

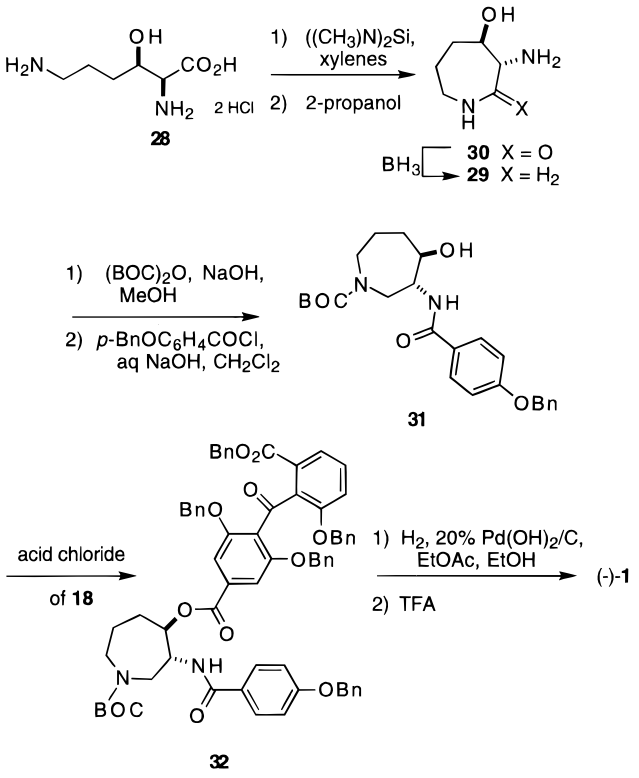
Scheme 8



and the assignment of absolute configuration was based on optical rotation and confirmed by biochemical testing. Evaluation of the two enantiomers as PKC inhibitors (Table 1) indicated that the natural enantiomer was at least 40−100 times as potent as the unnatural enantiomer.[25]

Enantioselective Azepane Synthesis. Development of a balanol synthesis which avoids a resolution required an enantioselective synthesis of the azepane. We envisioned that the chiral balanol azepane could be obtained via cyclization and reduction of (2*S*,3*R*)-3-hydroxylysine **28**. Two complimentary enantioselective syntheses of 3-hydroxylysine were developed in our laboratories and have been previously reported.[7b] Synthesis of azepane **29** from hydroxylysine **28** is shown in Scheme 9. As an initial attempt, the methyl ester of **28** was formed (HCl, MeOH) and cyclized with potassium carbonate in refluxing methanol. Unfortunately, complete epimerization of the 3-amino stereocenter was seen. However, drawing from a recent Soviet patent,[26] addition of powdered hydroxylysine **28** to hexamethyldisilazane in refluxing xylenes gave a homogeneous solution. Slow addition of 2-propanol[27] then led to the desired lactam and only 7% of the epimeric byproduct. Caprolactam **30** was obtained as a crystalline solid in 79% yield after ion

Scheme 9



exchange chromatography (AG-50, H^+-form, 1 N HCl) to remove the epimeric byproduct. Borane reduction followed by decomposition of the resulting borane complex by sequential additions of methanol, alkali (1 N NaOH), and acid (1 N HCl) afforded the desired azepane **29**, which was isolated as a crystalline solid in 67% yield after ion exchange chromatography (AG-50, H^+-form, 3 N HCl). The addition of alkali was an unanticipated requirement to break up the borane-complexed products. If the alkali step was omitted, a substantial amount (20−40%) of a crystalline byproduct was obtained which eluted from the ion-exchange column with 2 N HCl. The ^{1}H-NMR of this material was similar to that of the desired product but showed slight chemical shift differences. Treatment of the ^{1}H-NMR sample with 1 N NaOH led to a rapid release of gas, presumably hydrogen, and ^{1}H-NMR and TLC analysis indicated conversion to the desired azepane. Mass spectral analysis (FAB) gave the base peak at *m*/*z* 143 (M + 1), which together with elemental analysis suggested a molecular formula of $C_6H_{15}N_2OB$ as a hydrochloride salt.[28] Further structural investigation of this interesting and very water stable boron hydride is ongoing.

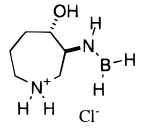
The synthesis of (−)-balanol was completed as shown in Scheme 9. Selective protection of the azepane nitrogen was accomplished by reaction of **29** with di-*tert*-butyl

(25) This figure represents a lower limit on the selectivity, since our limits on determining the enantiomeric purity of **26b** leave open the possibility that (+)-**1** is contaminated by as much as 2% of the potent inhibitor (−)-**1**.

(26) Belyaev, A. A.; Konyukhova, E. V.; Radina, L. B. SU Patent 1708812-A1 January, 30, 1994.

(27) Although 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.

(28) The spectral data are consistent with structure:



though a dimeric or oligomeric structure might be more accurate.

dicarbonate. Acylation of this mono-protected compound with 4-(benzyloxy)benzoyl chloride provided amide **31** in 66% yield from **29**. Further acylation of **31** with the acid chloride derived from benzophenone acid **18** led to ester **32**. Deprotection by hydrogenolysis followed by treatment with trifluoroacetic acid afforded (−)-balanol (−)-**1** in 63% yield from **31** after isolation by reversed phase HPLC. This synthetic material was found to be identical with naturally occurring balanol by ^{1}H 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 two total syntheses of (−)-balanol (−)-**1**. The convergent syntheses have provided ready access to racemic balanol as well as its two enantiomers. The direct synthesis of the enantiomerically pure material was accomplished in eighteen total operations and proceeds in 22% yield for six linear steps from **28** and 4.3% yield for fourteen linear steps from **4**, proving it to be a particularly efficient route to this material. These synthetic routes have allowed the preparation of gram quantities of synthetic (−)-balanol as well as a diverse set of over 400 synthetic analogs.

Experimental Section

General. Melting points are uncorrected. Starting materials were obtained from Aldrich and used without further purification unless otherwise noted. THF was distilled from sodium/benzophenone under nitrogen. Baker silica gel (40 μM) was used for flash chromatography. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively; coupling constants are in Hz. Microanalyses were obtained on crystalline intermediates and were determined either in our laboratories or by Atlantic Microlab, Inc. of Norcross, GA. HPLC chromatography was monitored by UV absorbance at 254 nm.

Methyl 4-[6-(Benzyloxy)-2-(hydroxymethyl)benzoyl]-benzoate (3). To a solution of 1.07 g (5.00 mmol) of 3-(benzyloxy)benzyl alcohol in 15 mL of toluene at −5 °C under nitrogen was added 5.8 mL (12.2 mmol) of a 2.1 M solution of butyllithium in hexanes over 15 min. The solution was stirred at −5 °C for 6 h, after which it was cooled to −78 °C, and a solution of 1.00 g (5.03 mmol) of 4-(methoxycarbonyl)benzoyl chloride in 5 mL of THF was added. The mixture was stirred for 1 h, after which it was poured onto 200 mL of ether and 100 mL of saturated aqueous NH_4Cl, and this mixture was stirred for 10 min. The layers were separated, and the organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated to give the crude product. Flash chromatography on silica gel eluting with 3/1 EtOAc−hexane afforded 0.68 g (36%) of the title compound as a white solid, mp 90−96 °C. The proton NMR for this material showed a 60/40 mixture of ketone and hemiketal forms. For the ketone: ^{1}H NMR ($CDCl_3$) δ 2.66 (t, 1H, J = 6), 3.98 (s, 3H), 4.54 (d, 2H, J = 6), 4.95 (s, 2H), 6.88 (m, 2H), 7.01 (d, 2H, J = 8), 7.16−7.21 (m, 3H), 7.48 (t, 1H, J = 8), 7.86 (d, 2H, J = 8), 8.10 (d, 2H, J = 8). Anal. Calcd for $C_{23}H_{20}O_5$: C, 73.39; H, 5.35. Found: C, 73.35; H, 5.65.

Benzyl 4-Bromo-3,5-bis(benzyloxy)benzoate. Potassium carbonate (8.96 g, 64.4 mmol) and benzyl bromide (8.42 mL, 70.81 mmol) were added to a stirred solution of 4-bromo-3,5-dihydroxybenzoic acid (**4**) (5.00 g, 21.5 mmol) in dry DMF (200 mL) at rt under nitrogen. The resulting solution was stirred for 20 h. The reaction mixture was then filtered and the filtrate partitioned between EtOAc (750 mL) and water (500 mL). The organic portion was washed with water (250 mL), 1 N NaOH (250 mL), and brine (250 mL) and then dried over $MgSO_4$ and concentrated. The resulting residue was recrystallized from CH_2Cl_2−hexanes to afford the title compound (8.10 g, 75%) as a white solid, mp 127−128 °C. ^{1}H NMR ($CDCl_3$) δ 5.20 (s, 4H), 5.34 (s, 2H), 7.33−7.40 (m, 13H), 7.47−7.49 (m, 4H). Anal. Calcd for $C_{28}H_{23}BrO_4$: C, 66.81; H, 4.61. Found: C, 66.68; H, 4.60.

4-Bromo-3,5-bis(benzyloxy)benzoic Acid. A solution of NaOH (216 g, 5.4 mol) in water (2.5 L) was added to benzyl 4-bromo-3,5-bis(benzyloxy)benzoate (503.4 g, 1.1 mol). The resulting suspension was heated to 100 °C and stirred for 12 h. The mixture was poured into ice water (2 L) and adjusted to pH 1−2 by addition of 6 N HCl. The pale yellow solids were filtered, washed with water and dried to give the title compound (422.9 g, 95%), mp 230−232 °C dec. ^{1}H NMR (DMSO-d_6) δ 5.28 (s, 4H), 7.34−7.44 (m, 8H), 7.49−7.51 (m, 4H). Anal. Calcd for $C_{21}H_{17}BrO_4$: C, 61.03; H, 4.15. Found: C, 61.03; H, 4.19.

1,1-Dimethylethyl 3,5-Bis(benzyloxy)-4-bromobenzoate (5). 1,1′-Carbonyldiimidazole (264.14 g, 1.63 mol) was added in portions to a solution of 3,5-bis(benzyloxy)-4-bromobenzoic acid (448.85 g, 1.09 mol) in DMF (1.5 L). The resulting solution was heated to 40 °C and stirred for 1 h. *tert*-Butyl alcohol (204.82 mL, 2.17 mol) was then added dropwise followed by the dropwise addition of DBU (162.41 mL, 1.09 mol). The resulting solution was stirred at 40 °C for 60 h. The reaction was cooled to rt and poured into ice−water (2 L). The mixture was adjusted to pH 5 by addition of concd aqueous HCl and the mixture stirred for 1 h. The tan solids were filtered, washed with water, and dried to give the title compound (499.4 g, 99%), mp 90−92 °C. ^{1}H NMR ($CDCl_3$) δ 1.57 (s, 9H), 5.20 (s, 4H), 7.32−7.42 (m, 8H), 7.49−7.51 (d, 4H, J = 6.8). Anal. Calcd for $C_{25}H_{25}BrO_4$: C, 63.97; H, 5.37. Found: C, 64.19; H, 5.34.

2,6-Bis(benzyloxy)-4-[(1,1-dimethylethoxy)carbonyl]-benzoic Acid (6). To a solution of 10.00 g (21.3 mmol) of 1,1-dimethylethyl 3,5-bis(benzyloxy)-4-bromobenzoate (**5**) in 150 mL of freshly distilled THF at −70 °C under nitrogen was added 10.5 mL (23.4 mmol) of a 2.23 M solution of butyllithium in hexanes over 10 min. The solution was stirred at −70 °C for 10 min, after which CO_2 was bubbled through the mixture for 10 min. The mixture was stirred for an additional 20 min at −78 °C and then was allowed to warm to rt. After 45 min the reaction mixture was poured onto 500 mL of ether and 250 mL of saturated aqueous NH_4Cl, and this mixture was stirred for 15 min. The layers were separated, and the organic phase was washed with 0.2 M HCl and brine, dried over $MgSO_4$, and evaporated to give 9.55 g of the crude product. Recrystallization of the crude material from EtOAc−hexane afforded 4.44 g (48%) of the title compound as a white solid, mp 140−146 °C dec. IR (KBr) 1709, 1589, 1423 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.62 (s, 9H), 5.23 (s, 4H), 7.30 (s, 2H), 7.34−7.43 (m, 6H), 7.46−7.48 (m, 4H). Anal. Calcd for $C_{26}H_{26}O_6$: C, 71.87; H, 6.03. Found: C, 71.76; H, 6.12.

1,1-Dimethylethyl 3,5-Bis(benzyloxy)-4-formylbenzoate (8). To a solution of 0.510 g (1.09 mmol) of 1,1-dimethylethyl 3,5-bis(benzyloxy)-4-bromobenzoate (**5**) in 11 mL of freshly distilled THF at −78 °C under nitrogen was added 478 μL (1.20 mmol) of a 2.5 M solution of butyllithium in hexanes over 3 min. The solution was stirred at −78 °C for 20 min, after which DMF (168 μL, 2.17 mmol) was added dropwise. The mixture was stirred for an additional 20 min at −78 °C and then was allowed to warm to rt. After 3 h the reaction mixture was poured onto 25 mL of EtOAc and 2 mL of 0.1 N HCl, and this mixture was stirred for 10 min. The layers were separated, and the organic phase was washed with brine, dried over $MgSO_4$, and evaporated to give the crude product. Chromatography of the crude material on silica gel eluting with 3−6% EtOAc−hexanes afforded 0.239 g (53%) of the title compound as an off white foam. ^{1}H NMR ($CDCl_3$) δ 1.60 (s, 9H), 5.24 (s, 4H), 7.27−7.28 (d, 1H, J = 2.3), 7.34−7.44 (m, 9H), 7.49−7.50 (d, 2H, J = 6.7), 10.65 (s, 1H). HRMS: calcd for $C_{26}H_{27}O_5$: 419.1858, found 419.1859.

2-[2-[[2,6-Bis(benzyloxy)-4-[(1,1-dimethylethoxy)carbonyl]phenyl]hydroxymethyl]-3-(benzyloxy)phenyl]-4,4-dimethyl-2-oxazoline (12). To a solution of 0.653 g (2.32 mmol) of 2-[3-(benzyloxy)phenyl]-4,4-dimethyl-2-oxazoline (**10**)[29]

(29) This material was prepared in a fashion identical to that used in reference 13 to prepare a closely related compound.

in 22 mL of freshly distilled THF at −50 °C under nitrogen was added 1 mL (2.48 mmol) of a 2.5 M solution of butyllithium in hexanes over 5 min. The solution was stirred at −50 °C for 6 h, after which a solution of 1,1-dimethylethyl 3,5-bis-(benzyloxy)-4-formylbenzoate (**8**) (0.648 g, 1.55 mmol) in 10 mL THF was added dropwise. The mixture was stirred for an additional 1 h at −50 °C and then was allowed to warm to rt. After 16 h the reaction mixture was poured onto 50 mL of EtOAc and 20 mL of water, and this mixture was stirred for 10 min. The layers were separated, and the organic phase was washed with brine, dried over $MgSO_4$, and evaporated to give the crude product. Chromatography of the crude material on silica gel eluting with 15−30% EtOAc−hexanes afforded 0.408 g (38%) of the title compound as a white foam. ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 3H), 1.27 (br s, 3H), 1.63 (s, 9H), 3.26−3.29 (d, 1H, J = 7.9), 3.33−3.37 (d, 1H, J = 12.6), 4.67−5.01 (m, 6H), 6.72−6.75 (d, 2H, J = 8.2), 6.87−6.89 (d, 2H, 8.4), 6.92−6.95 (d, 1H, 7.9), 7.11−7.33 (m, 17H). HRMS: calcd for $C_{44}H_{46}NO_7$: 700.3274, found 700.3273. Anal. Calcd for $C_{44}H_{45}NO_7 \cdot 0.5H_2O$: C, 74.55; H, 6.54; N, 1.98. Found: C, 74.44; H, 6.55; N, 2.27.

3-Benzyloxy-2-bromobenzyl Alcohol (13). To a solution of 10.24 g (47.1 mmol) of 3-(benzyloxy)benzyl alcohol (**2**) in 150 mL of toluene at −10 °C under nitrogen was added 46 mL (115 mmol) of a 2.5 M solution of butyllithium in hexanes over 15 min. The solution was stirred at −5 °C for 6 h, after which it was cooled to −78 °C, and 11.5 mL (25.0 g, 96.3 mmol) of 1,2-dibromo-1,1,2,2-tetrafluoroethane was added. The mixture was allowed to warm to rt. After 16 h the reaction mixture was poured onto 500 mL of ether and 250 mL of saturated aqueous NH_4Cl, and this mixture was stirred for 1 h. The layers were separated, and the organic phase was washed with brine, dried over $MgSO_4$, and evaporated to give the crude product. Recrystallization of the crude material from EtOAc−hexane afforded 7.05 g (51%) of the title compound as a white solid, mp 123−124 °C. IR (KBr) 1699, 1660, 1458 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.06 (t, 1H, J = 7), 4.79 (d, 2H, J = 7), 5.19 (s, 2H), 6.91 (dd, 1H, J = 1.5, 7.5), 7.13 (dd, 1H, J = 1.5, 7.5), 7.27 (t, 1H, J = 7.5), 7.34−7.44 (m, 3H), 7.48−7.51 (m, 2H). Anal. Calcd for $C_{14}H_{13}BrO_2$: C, 57.36; H, 4.47. Found: C, 57.11; H, 4.42.

1,1-Dimethylethyl 2-Bromo-3-(benzyloxy)benzyl 2,5-Bis(benzyloxy)-1,4-dibenzoate (14). To a solution of 10.37 g (23.6 mmol) of 2,6-bis(benzyloxy)-4-[(1,1-dimethylethoxy)-carbonyl]benzoic acid (**6**) in 100 mL of CH_2Cl_2 at 0 °C under nitrogen was added 0.05 mL of DMF and 14.5 mL (29.0 mmol) of a 2.0 M solution of oxalyl chloride in CH_2Cl_2. The solution was stirred at rt for 3 h, after which the solvent was evaporated, and the residue was evaporated twice from 30 mL of CH_2Cl_2 to afford crude acid chloride **7** as a tan solid.

A solution of 6.96 g (23.7 mmol) of 3-(benzyloxy)-2-bromobenzyl alcohol (**13**) in 100 mL of THF at 0 °C under nitrogen was treated with 28.8 mL (28.8 mmol) of a 1.0 M solution of potassium *tert*-butoxide in THF. To this mixture was added a solution of the above acid chloride in 50 mL of THF. After 45 min the reaction mixture was poured onto 500 mL of ether and washed with 250 mL each of saturated aqueous NH_4Cl and brine. The organic phase was dried over $MgSO_4$, stirred with 10 g each of silica gel and alumina, and evaporated to give 13.63 g (81%) of the title compound as a white solid, mp 116−118 °C. IR (KBr) 1744, 1709, 1580, 1423 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.58 (s, 9H), 5.15 (s, 2H), 5.17 (s, 4H), 5.48 (s, 2H), 6.83 (dd, 1H, J = 1.6, 8), 6.93 (t, 1H, J = 8), 7.04 (dd, 1H, J = 1.6, 8), 7.27 (s, 2H), 7.30−7.42 (m, 13H), 7.46−7.48 (m, 2H). Anal. Calcd for $C_{40}H_{37}BrO_7$: C, 67.70; H, 5.26. Found: C, 67.71; H, 5.31.

1,1-Dimethylethyl 3,5-Bis(benzyloxy)-4-[6-(benzyloxy)-2-(hydroxymethyl)benzoyl]benzoate (9). To a solution of 13.53 g (19.1 mmol) of 1,1-dimethylethyl 2-bromo-3-(benzyloxy)benzyl 2,5-bis(benzyloxy)-1,4-dibenzoate (**14**) in 150 mL of freshly distilled THF at −72 °C under nitrogen was added 9.2 mL (23 mmol) of a 2.5 M solution of *n*-butyllithium in hexanes over 10 min. The solution was stirred at −72 °C for 15 min, after which TLC analysis still showed the presence of some starting material. An additional 0.45 mL of *n*-butyllithium was added, and the mixture was stirred at −72 °C for 45 min. The reaction was quenched at low temperature by the addition of 50 mL of saturated NH_4Cl, and the mixture was allowed to warm to rt. The reaction mixture was poured onto 500 mL of ether and washed with water and brine, dried over $MgSO_4$, and evaporated to give 15.28 g of the crude product. Chromatography of the crude material on silica gel eluting with 3/1 hexane−EtOAc afforded 6.32 g (51%) of the title compound as a white solid. An analytical sample was obtained by recrystallization from EtOAc−hexane, mp 113−116 °C. IR (KBr) 1709, 1644, 1583, 1421 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.66 (s, 9H), 3.30 (t, 1H, J = 8), 4.26 (d, 2H, J = 8), 4.73 (s, 6H), 6.82 (d, 2H, J = 7), 6.93 (d, 1H, J = 8), 6.97 (d, 1H, J = 8), 7.06−7.09 (m, 6H), 7.17 (t, 2H, J = 7), 7.27−7.29 (m, 7H), 7.40 (t, 1H, J = 8). Anal. Calcd for $C_{40}H_{38}O_7$: C, 76.17; H, 6.07. Found: C, 75.97; H, 6.26.

1,1-Dimethylethyl 3,5-Bis(benzyloxy)-4-[6-(benzyloxy)-2-formylbenzoyl]benzoate (15). To a solution of 6.21 g (9.85 mmol) of 1,1-dimethylethyl 3,5-bis(benzyloxy)-4-[6-(benzyloxy)-2-(hydroxymethyl)benzoyl]benzoate (**9**) in 100 mL of DMF was added 11.11 g (29.5 mmol) of PDC. The solution was stirred at rt under a nitrogen atmosphere for 8 h, after which it was poured onto 1 L of ether and washed with 500 mL each of water, 0.2 M HCl, and brine and dried over $MgSO_4$. Evaporation of the solvent afforded 6.03 g (97%) of the crude product. This material was sufficiently pure for further use. An analytical sample was obtained by recrystallization from EtOAc−hexane to give the title compound as a white solid, mp 138−139 °C. IR (KBr) 1700, 1652, 1581 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.65 (s, 9H), 4.77 (s, 2H), 4.80 (s, 4H), 6.85 (d, 2H, J = 7.5), 7.07−7.13 (m, 7H), 7.17 (t, 2H, J = 7.5), 7.25−7.28 (m, 7H), 7.41−7.48 (m, 2H), 9.89 (s, 1H). Anal. Calcd for $C_{40}H_{36}O_7$: C, 76.42; H, 5.77. Found: C, 76.42; H, 5.70.

Methyl 4-[6-(Benzyloxy)-2-carboxybenzoyl]benzoate. To a solution of 0.63 g (1.7 mmol) of methyl 4-[6-(benzyloxy)-2-(hydroxymethyl)benzoyl]benzoate (**3**) in 20 mL of DMF was added 4.41 g (11.7 mmol) of PDC. The solution was stirred at rt under a nitrogen atmosphere for 4 days, after which it was poured onto 300 mL of ether, washed with 200 mL of water, 150 mL of 2 M HCl, and 150 mL of brine, and dried over $MgSO_4$. Evaporation of the solvent afforded 0.47 g (72%) of the title compound as a glass. ^{1}H NMR ($CDCl_3$) δ 3.96 (s, 3H), 5.04 (s, 2H), 7.02−7.06 (m, 2H), 7.21−7.27 (m, 4H), 7.47 (t, 1H, J = 8), 7.72 (d, 1H, J = 8), 7.83 (d, 2H, J = 8), 8.08 (d, 2H, J = 8). HRMS: calcd for $C_{23}H_{19}O_6$: 391.1182, found 391.1184.

3-(Benzyloxy)-2-[2,6-bis(benzyloxy)-4-[(1,1-dimethylethoxy)carbonyl]benzoyl]benzoic Acid (16). To a solution of 5.98 g (9.51 mmol) of 1,1-dimethylethyl 3,5-bis(benzyloxy)-4-[6-(benzyloxy)-2-formylbenzoyl]benzoate (**15**) in 75 mL of dry pyridine was added 5.17 g (14.3 mmol) of tetrabutylammonium permanganate. The solution was stirred at rt under a nitrogen atmosphere for 24 h. An additional 2.60 g of tetrabutylammonium permanganate was added, and the mixture was stirred for 20 h more. The mixture was then poured onto 1 L of ether, washed with 500 mL of cold half-saturated $NaHSO_3$, two 500 mL portions of cold 2 M HCl, and brine, and dried over $MgSO_4$. Evaporation of the solvent afforded 6.11 g (100%) of the crude product. This material was sufficiently pure for further use. An analytical sample was obtained by recrystallization from 2-propanol to give the title compound as a tan solid, mp 165−167 °C. IR (KBr) 3470, 1709, 1664, 1578 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.62 (s, 9H), 4.46−5.23 (m, 6H), 6.79 (m, 1H), 6.93−7.03 (m, 4H), 7.11−7.32 (m, 10H), 7.33−7.41 (m, 5H), 8.42 (s, 1H). Anal. Calcd for $C_{40}H_{36}O_8$: C, 74.52; H, 5.63. Found: C, 74.74; H, 5.64.

1,1-Dimethylethyl 4-[6-(Benzyloxy)-2-[(benzyloxy)carbonyl]benzoyl]-3,5-bis(benzyloxy)benzoate (17). To a solution of 5.98 g (9.28 mmol) of 3-(benzyloxy)-2-[2,6-bis-(benzyloxy)-4-[(1,1-dimethylethoxy)carbonyl]benzoyl]benzoic acid (**16**) in 75 mL of dry DMF were added 3.85 g (27.9 mmol) of K_2CO_3 and 1.21 mL (1.74 g, 10.2 mmol) of benzyl bromide. The solution was stirred at rt under a nitrogen atmosphere

(30) (a) Kulanthaivel, P.; Janzen, W. P.; Ballas, L. M.; Jiang, J.; Hu, C.; Darges, J. W.; Seldin, J.; Cofield, D.; Adams, L. *Planta Medica* **1995**, *61*, 41−44. (b) Kashiwada, Y.; Huang, L.; Ballas, L. M.; Jiang, J. B.; Janzen, W. P.; Lee, K.-H. *J. Med. Chem.* **1994**, *37*, 195−200.

for 13 h. The mixture was then poured onto 800 mL of water and extracted with three 400 mL portions of ether. The organic extracts were washed twice with water and then with brine and dried over $MgSO_4$. Evaporation of the solvent afforded 6.76 g of the crude product, which was chromatographed on silica gel, eluting with 4/1 hexane−EtOAc to give 4.98 g (73%) of the title compound as a colorless oil. IR (KBr) 1716, 1668, 1580, 1456 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.64 (s, 9H), 4.74 (s, 2H), 4.80 (s, 4H), 5.15 (s, 2H), 6.89 (d, 2H, $J = 7$), 6.96 (dd, 1H, $J = 1.7, 7.6$), 7.07−7.16 (m, 8H), 7.20−7.32 (m, 14H). Anal. Calcd for $C_{47}H_{42}O_8 \cdot 0.5H_2O$: C, 75.89; H, 5.83. Found: C, 75.97; H, 5.76.

4-[6-(Benzyloxy)-2-[(benzyloxy)carbonyl]benzoyl]-3,5-bis(benzyloxy)benzoic Acid (18). A solution of 0.428 g (0.582 mmol) of 1,1-dimethylethyl 4-[6-(benzyloxy)-2-[(benzyloxy)carbonyl]benzoyl]-3,5-bis(benzyloxy)benzoate (**17**) in 5 mL of distilled quinoline was heated at 200 °C under nitrogen for 3 h. The mixture was then cooled, poured onto 75 mL of ether, and washed three times with 2 N HCl and once with brine. The organic extracts were dried over $MgSO_4$ and evaporated to give 0.42 g of the crude product, which was recrystallized from 2-propanol to give 0.270 g (68%) of the title compound as a tan solid, mp 151−156 °C. IR (KBr) 3433, 1718, 1654, 1582, 1425 cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.72 (s, 2H), 4.80 (s, 4H), 5.14 (s, 2H), 6.85 (d, 2H, $J = 7$), 6.97 (d, 1H, $J = 8$), 7.05−7.08 (m, 4H), 7.13 (t, 2H, $J = 8$), 7.18−7.34 (m, 16H). Anal. Calcd for $C_{43}H_{34}O_8 \cdot H_2O$: C, 74.12; H, 5.21. Found: C, 73.74; H, 5.24.

***N*-Benzyl-2-oxoazepane (20).** To a 0 °C suspension of NaH (80% in mineral oil, 10.1 g, 0.34 mol, prewashed with hexane (30 mL × 2)) in THF (100 mL) was added a solution of 2-oxoazepane (34.7 g, 0.3 mol) in THF (450 mL) through an addition funnel at such a rate that H_2 generation remained gentle. The reaction mixture was allowed to warm up to rt for 2 h prior to the addition of benzyl bromide (55 g, 35 mL, 0.32 mol). The resulting mixture was stirred at rt for additional 2 h. The sodium bromide was filtered and rinsed with EtOAc. The combined filtrate was concentrated and crystallized in EtOAc/hexane to afford a white solid (60 g, 96%), mp 54−56 °C. IR (KBr) 1625, 1493, 1453 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.46 (m, 2H), 1.68 (m, 4H), 2.59 (dd, $J = 4.3, 6.3$, 2H), 3.28 (t, $J = 5$, 2H), 4.57 (s, 2H), 7.27 (m, 5H). Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.88. Found: C, 76.78; H, 8.45; N, 6.86.

***N*-Benzyl-2-oxoazep-3-ene (21).** To a cooled solution (−45 °C) of *N*-benzyl-2-oxoazepane (**20**, 101.6 g, 0.5 mol) in THF (350 mL) was added LHMDS (1.0 M solution in THF, 1 L, 1.0 mol). The mixture was allowed to warm up to 0 °C for 30 min and cooled to −45 °C while a solution of PhSeCl (96 g, 0.501 mol) in THF (150 mL) was added. The resulting mixture was warmed up to rt over 5 h and then poured into 1 N HCl (400 mL). The THF layer was separated. The aqueous was extracted with EtOAc (200 mL × 2). The combined organic layer was washed with brine, dried ($MgSO_4$), concentrated, and diluted with hexane to precipitate *N*-benzyl-2-oxo-3-(phenylselenyl)azepane as a while solid (142.7 g, 80%), mp 97−98 °C. IR (KBr) 1634, 1476 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.48−1.62 (m, 2H), 1.80 (m, 1H), 1.99−2.19 (m, 3H), 3.33 and 3.48 (m and m, 1H and 1H), 4.35 (m, 1H), 4.60 (m, 2H), 7.29 (m, 8H), 7.59 (m, 2H). Anal. Calcd for $C_{19}H_{21}NOSe$: C, 63.37; H, 5.91; N, 3.91. Found: C, 63.40; H, 5.90; N, 3.87.

Method A: To a solution of *N*-benzyl-2-oxo-3-(phenylselenyl)azepane (142.7 g, 0.398 mol) in CH_2Cl_2 (500 mL) was added pyridine (65 mL, 0.804 mol), followed by H_2O_2 (10%, 50 mL) dropwise. The mixture was heated to reflux at which time additional H_2O_2 (10%, 100 mL) was added dropwise. After cooling to rt, the CH_2Cl_2 layer was separated, washed with saturated $NaHCO_3$ (300 mL × 3), 1 N HCl (300 mL × 3), and brine, dried ($MgSO_4$), and concentrated. The crude material was flash chromatographed (silica gel, 80% hexane/EtOAc) to afford the product as a light brown oil (78.4 g, 98%). IR (neat) 1650, 1602 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.79 (m, 2H), 2.29 (m, 2H), 3.31 (m, 2H), 4.67 (s, 2H), 6.05 (d, 1H, $J = 13.6$), 6.21 (m, 1H), 7.31 (m, 5H). Anal. Calcd for $C_{13}H_{15}NO \cdot 0.1H_2O$: C, 76.89; H, 7.54; N, 6.89. Found: C, 76.76; H, 7.56; N, 6.96.

Method B: To a solution of *N*-benzyl-2-oxo-3-(phenylselenyl)azepane (6.0 g, 16.74 mmol) in THF (100 mL) was added a solution of $NaIO_4$ (13.6 g, 63.62 mmol) in MeOH:H_2O (7:3, 350 mL). The resulting mixture was stirred at rt for 72 h. Upon removal of volatiles, the crude material was flash chromatographed (silica gel, 80% hexane/EtOAc) to afford the product as a light brown oil (3.25 g, 97%).

***N*-Benzyl-*cis*-3,4-dihydroxy-2-oxoazepane (22).** *N*-Benzyl-2-oxoazep-3-ene (**21**) (6.9 g, 34.3 mmol) was added in acetone (10 mL) to a mixture of osmium tetraoxide (95 mg, 0.38 mmol) and *N*-methylmorpholine *N*-oxide (6.02 g, 51.4 mmol, 8.9 mL of 60% aqueous solution) in *tert*-butyl alcohol (20 mL) and acetone (20 mL). After 4 h, TLC showed almost complete reaction (starting material $R_f = 0.57$, product $R_f =$ 0.47 in 100% EtOAc). After 1.5 d, more *N*-methylmorpholine *N*-oxide (2 mL of 60% solution) was added but no further reaction appeared to take place by TLC. The reaction mixture was concentrated and the residue chromatographed (7 × 12 cm, 100% EtOAc) to give the product (7.8 g, 97%). The product was recrystallized from EtOAc/hexanes to give white crystals (6.3 g, 78%), mp 87−88 °C. ^1H-NMR ($CDCl_3$) δ 1.45−1.56 (1H, m), 1.6−1.8 (2H, m), 2.03−2.08 (1H, m), 2.63 (1H, br s), 3.17−3.36 (2H, m), 4.14 (1H, br s), 4.46 (1H, d, $J = 4$), 4.63 (1H, d, $J = 15$), 4.72 (1H, d, $J = 15$), 4.76 (1H, d, $J = 4$), 7.21−7.35 (5H, m). IR (KBr) 3438, 3387, 1623 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.37; H, 7.40; N, 5.89.

***N*-Benzyl-*cis*-4-(benzoyloxy)-3-hydroxy-2-oxoazepane (23).** *N*-Benzyl-*cis*-3,4-dihydroxy-2-oxoazepane (**22**, 4.17 g, 17.7 mmol) was dissolved in CH_2Cl_2 (20 mL) and treated with trimethyl orthobenzoate (4.84 g, 26.6 mmol) followed by BF_3 etherate (110 μL, 886 μmol). The mixture was stirred at rt for 2 h and then treated with water (20 mL) and stirred for 30 min. The mixture was partitioned between EtOAc and brine (50 mL each). The organic layer was removed, dried ($MgSO_4$), and concentrated to an oil. The oil was dissolved in CH_2Cl_2 (10 mL) and treated with DBU (132 μL, 886 μmol). The mixture was then poured onto a silica gel column (7 × 14 cm, packed in and eluted with 40% EtOAc in hexanes) and chromatographed to give, after concentration, the product as a white solid. The product was recrystallized from EtOAc/hexanes to give white crystals (4.32 g, 72%), mp 113−114 °C. ^1H-NMR ($CDCl_3$) δ 1.4−1.65 (2H, m), 1.8−1.95 (1H, m), 2.36−2.42 (1H, m), 3.36−3.51 (2H, m), 4.58−4.65 (3H, m), 4.93 (1H, d, $J = 15$), 5.46 (1H, m), 7.2−7.3 (3H, m), 7.31−7.39 (2H, m), 7.45 (2H, pseudo t, $J = \approx 7$), 7.58 (1H, t, $J = 7$), 8.00 (2H, d, $J = 7$). IR (KBr) 3386, 1707, 1642 cm^{-1}. Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.70; H, 6.27; N, 4.00.

***N*-Benzyl-*trans*-4-(benzoyloxy)-3-azido-2-oxoazepane (24).** *N*-Benzyl-*cis*-4-(benzoyloxy)-3-hydroxy-2-oxoazepane (**23**, 2.0 g, 5.89 mmol) and 2,6-lutidine (757 mg, 840 μL, 7.07 mmol) were dissolved in CH_2Cl_2 (20 mL), cooled in an ice bath, and treated with triflic anhydride (1.83 g, 1.09 mL, 6.48 mmol). TLC analysis (silica gel, 1/4 EtOAc/hexanes-eluted twice) showed instantaneous, though incomplete, formation of the desired triflate (starting material $R_f = 0.06$, triflate $R_f = 0.29$). After stirring for 16 h, with no further reaction, the mixture was recooled and treated with 2,6-lutidine (380 mg, 420 μL, 3.5 mmol) followed by triflic anhydride (0.91 g, 0.54 mL, 3.2 mmol). TLC immediately showed complete reaction. Sodium azide (3.8 g, 58.9 mmol), slurried in methanol (50 mL), was added followed by benzyltrimethylammonium bromide (40 mg). TLC analysis (as above) showed very slow formation of the azide product (azide $R_f = 0.32$), so the mixture was treated with DMF (5 mL), concentrated to ≈20 mL, and stirred for 3 d. TLC analysis showed complete reaction. The mixture was partitioned between ether and water (50 mL each). The aqueous layer was washed with ether (50 mL), and the combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), and concentrated. The residue was chromatographed (silica gel, 7 × 13 cm, 1/4 EtOAc/hexanes) to give clean azide as an oil (1.86 g, 87%). ^1H-NMR ($CDCl_3$) δ 1.4−1.65 (2H, m), 1.45−1.70 (2H, m), 1.91−2.12 (2H, m), 3.29−3.38 (1H, m), 3.61−3.68 (1H, m), 4.49 (1H, d, $J = 14$), 4.65 (1H, d, $J = 8$), 4.82 (1H, d $J = 14$), 5.33 (1H, m), 7.26−7.32 (5H, m), 7.45 (2H,

pseudo t, $J = \approx 7$), 7.59 (1H, t, $J = 7$), 8.02 (2H, d, $J = 7$). IR (KBr) 3063, 2941, 1719, 1655 cm^{-1}. Anal. Calcd for $C_{20}H_{20}N_4O_3$: C, 65.92; H, 5.53; N, 15.37. Found: C, 66.07; H, 5.62; N, 15.51.

***N*-Benzyl-*trans*-4-hydroxy-3-[4-(benzyloxy)benzamido]-azepane (26).** *N*-Benzyl-*trans*-4-(benzoyloxy)-3-azido-2-oxo-azepane (**24**, 1.7 g, 4.6 mmol) was dissolved in THF (20 mL) in a flask equipped with an overhead stirrer. $LiAlH_4$ (14.9 mL of a 1 M solution in THF, 14.9 mmol) was added dropwise and the mixture heated to reflux for 1 h. The mixture was cooled to rt and treated with water (566 μL), 15% NaOH (566 μL), and water (1.7 mL) with stirring for 30 m after the first two additions and for 16 h after the third. The solid was filtered off and the solution treated with 12 N HCl (870 μL) in methanol and concentrated to give azepane **25** as an amber oil. The oil was treated with CH_2Cl_2 (20 mL), 1 N NaOH (5 mL), Na_2CO_3 (1.96 g, 23.3 mmol), water (20 mL), and *p*-(benzyloxy)benzoyl chloride (1.72 g, 7.0 mmol) in CH_2Cl_2 (15 mL) and stirred vigorously for 16 h. The mixture was then extracted with EtOAc (2 × 50 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to an oil. The oil was chromatographed (silica gel, 4.1 × 15 cm, 19/1 CH_2Cl_2/methanol) to give the product as a glass (1.1 g, 55% from **24**). The product was triturated in ether to give white crystals, mp 119−120 °C. ^{1}H NMR (CDCl3) δ 1.60−1.95 (m, 4H), 2.50 (td, $J = 3.8, 9.4$, 1H), 2.73 (dd, $J = 2.0, 14.4$, 1H), 2.93 (dd, $J = 2.6, 14.4$, 1H), 3.02 (m, 1H), 3.41 (d, $J = 12.9$, 1H), 3.74 (d, $J = 12.9$, 1H), 3.78 (dddd, $J = 8.7, 2.9, 2.6$, and 2.0, 1H), 3.87 (m, 1H), 5.13 (s, 2H), 6.54 (d, $J = 8.7$, 1H), 6.94 (d, $J = 6.6$, 2H), 7.30−7.47 (m, 12H); IR (KBr) 3419, 3356, 1623 cm^{-1}. Anal. Calcd for $C_{27}H_{30}N_2O_3$: C, 75.32; H, 7.02; N, 6.50. Found: C, 75.52; H, 7.20; N, 6.43.

(±)-Balanol ((±)-1). A solution of 84 mg (0.12 mmol) of 4-[6-(benzyloxy)-2-[(benzyloxy)carbonyl]benzoyl]-3,5-bis(benzyloxy)benzoic acid (**18**) in 2 mL of CH_2Cl_2 containing a trace (approximately 0.5 μL) of DMF was cooled to 0 °C. Oxalyl chloride (11.9 μL, 0.136 mmol) was added, and the mixture was stirred under a nitrogen atmosphere for 1.5 h. An additional 11.9 μL of oxalyl chloride was added, and the mixture was stirred for an additional 1.5 h. The reaction mixture was evaporated, and the residue was evaporated twice from 15 mL of CH_2Cl_2. The residue was dissolved in 2 mL of CH_2Cl_2, and was added to a solution of 59.1 mg (0.137 mmol) of *trans*-*N*-benzyl-3-[4-(benzyloxy)benzamido]-4-hydroxyazepane (**26**), 19.0 μL (0.136 mmol) of triethylamine, and 3 mg of DMAP in 1.5 mL of CH_2Cl_2 at 0 °C. The mixture was stirred at rt under a nitrogen atmosphere for 22 h, after which it was diluted with 30 mL of CH_2Cl_2, washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated to give 139 mg of the crude product. Chromatography on silica gel eluting with 6/4 hexane−EtOAc gave 89.4 mg (66%) of the ester as a yellow oil, which was used directly in the deprotection step.

A solution of 65 mg (0.060 mmol) of the ester in 30 mL of 1/2/2 methanol−ethanol−CH_2Cl_2 was treated with 17 μL of TFA and evaporated. The residue was dissolved in 12 mL of 3/1 ethanol−methanol, 15.6 mg of moist 10% palladium hydroxide on carbon was added, and the mixture was shaken on a Parr apparatus under 50 psi of hydrogen for 5 h. The mixture was filtered and evaporated, and the residue was chromatographed on a 21 × 250 mm C18 column (solvent A: 95:5 water/acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient: 0−100% B over 60 min, flow: 15 mL/min). The pure fraction was evaporated and then lyophilized from water to give 11.2 mg (33%) of the title compound as a yellow fluffy solid, which was identical with natural balanol by IR, ^{1}H NMR, ^{13}C NMR, FABMS, and HPLC.

Resolution of *N*-Benzyl-*trans*-4-hydroxy-3-[4-(benzyloxy)benzamido]azepane (26a and 26b). *N*-Benzyl-*trans*-4-hydroxy-3-[4-(benzyloxy)benzamido]azepane (**26**, 1.2 g, 2.79 mmol), DMAP (4 mg, 0.3 mmol), and triethylamine (2.25 g, 3.1 mL, 22.3 mmol) were dissolved in CH_2Cl_2 (10 mL) and treated with (*S*)-Mosher's acid chloride (1.8 g, 1.3 mL, 7 mmol). When TLC indicated complete reaction, the mixture was concentrated and chromatographed (7 × 15 cm, 3% triethylamine in 4/1 EtOAc/hexanes). The products were separated into clean upper, mixed, and clean lower fractions. All three fractions were each again chromatographed on a silica column (41.4 mm ID × 30 cm length) using a linear gradient from 20% to 60% B (A = hexanes, B = 10% triethylamine in EtOAc) over 60 m at 25 mL/min. The clean upper HPLC fractions from the upper and mixed runs were combined (490 mg) for hydrolysis. ^{1}H-NMR ($CDCl_3$) δ 1.6−1.8 (2H, m), 1.94 (2H, m), 2.48 (1H, m), 2.77 (1H, m), 2.9−3.0 (2H, m), 3.50 (1H, d, $J = 13$), 3.54 (3H, s), 3.72 (1H, d, $J = 13$), 4.1−4.2 (1H, m), 5.14 (2H, s), 5.28 (1H, m), 6.84−7.65 (14H, m).

The clean lower HPLC fractions from the lower run were combined (260 mg) for hydrolysis. ^{1}H-NMR ($CDCl_3$) δ 1.64−1.8 (2H, m), 1.8−1.94 (2H, m), 2.53 (1H, m), 2.77 (1H, m), 2.9−3.0 (2H, m), 3.50 (1H, d, $J = 13$), 3.52 (3H, s), 3.72 (1H, d, $J = 13$), 4.1 (1H, m), 5.13 (2H, s), 5.28 (1H, m), 6.84−7.54 (14H, m).

The upper ester (490 mg, 0.76 mmol) was dissolved in methanol (5 mL) and treated with 85% KOH (97 mg, 1.52 mmol) dissolved in methanol (5 mL) and stirred for 16 h. The mixture was treated with water (15 mL) and extracted with CH_2Cl_2 (2 × 25 mL). The organic layer was concentrated and chromatographed (2.5 × 10 cm, EtOAc) to give the chiral alcohol **26a** (266 mg) as an oil.

The lower ester (260 mg, 0.40 mmol) was dissolved in methanol (5 mL) and treated with 85% KOH (53 mg, 0.8 mmol) dissolved in methanol (5 mL) and stirred for 48 h. The mixture was treated with water (15 mL) and extracted with CH_2Cl_2 (2 × 25 mL). The organic layer was concentrated and chromatographed (2.5 × 10 cm, EtOAc) to give the chiral alcohol **26b** (154 mg) as an oil.

(−)-Balanol ((−)-1). This material was prepared in 37% overall yield as a pale yellow powder from benzophenone **18** and amido alcohol **26a** in an identical fashion to that described for (±)-**1**, with the exception that the hydrogenolysis was carried out at atmospheric pressure. This compound was identical with natural balanol by IR, ^{1}H NMR, and TLC. $[\alpha]^{25}_D = -104°$ ($c = 0.111$, methanol).

(+)-Balanol ((+)-1). This material was prepared in 22% overall yield as a pale yellow powder from benzophenone **18** and amido alcohol **26b** in an identical fashion to that described for (±)-**1**, with the exception that the hydrogenolysis was carried out at atmospheric pressure. This compound was identical with natural balanol by IR, ^{1}H NMR, and TLC. $[\alpha]^{25}_D = +97.8°$ ($c = 0.319$, methanol).

(−)-(*R*)-3-Amino-(*S*)-4-hydroxy-2-oxoazepane Hydrochloride (30). Hydroxylysine dihydrochloride (**28**) (4 g, 17 mmol) was added as a powder to hexamethyldisilizane (17.9 mL, 13.7 g, 85.1 mmol) in xylenes (200 mL), and the mixture was heated to reflux. After heating for 2 h, the now homogeneous reaction mixture was treated with 2-propanol (5 mL, 4 g, 66 mmol) via syringe pump over 6 h. After 2 days at reflux, TLC analysis (9:1 MeOH:NH_4OH) showed complete reaction (starting material $R_f = 0.13$, product $R_f = 0.43$, epimeric product $R_f = 0.35$). The reaction mixture was allowed to cool and treated with 1 N HCl (50 mL) and stirred for 1 h. The aqueous layer was removed and the organic layer washed again with 1 N HCl (50 mL). The combined aqueous layers were concentrated to a glass. Crude NMR indicated a 13:1 ratio of desired to epimerized product. The glass was added to a cation exchange resin (AG50-X8, 200−400 mesh, H^+ form, 2.5 × 27 cm) and eluted with 1 N HCl. The product eluted in 35 mL fractions 16−26, followed by the epimeric byproduct. The active fractions were combined and concentrated to a glass. The glass was slurried in minimal methanol, triturated with 2-propanol, and stirred overnight. The resulting powder was filtered off under nitrogen, washed with 2-propanol, and dried under nitrogen flow to give the title compound (2.7 g, 79% based on 0.4 molar equiv of NH_4Cl contamination) as a white powder. ^{1}H-NMR (D_2O) δ 1.5−1.65 (1H, m), 1.75−1.95 (2H, m), 2.25−2.35 (1H, m), 3.25−3.35 (2H, m), 3.77 (1H, dt, $J = 3.8, 10.5$), 4.33 (1H, d, $J = 10.5$); ^{13}C-NMR (D_2O) δ 26.0, 37.1, 40.9, 57.5, 66.2, 66.5 (dioxane reference), 170.2; IR (KBr) 3428, 1673, 1490 cm^{-1}; $[\alpha]^{25}_D = -42°$ ($c = 0.61$ in methanol, corrected for NH_4Cl contamination). A sample was obtained from another reaction by first concentrating the xylenes before workup to minimize the NH_4Cl contamination in the product.

Anal. Calcd for $C_6H_{12}N_2O_2$·HCl: C, 39.90; H, 7.25; N, 15.51. Found: C, 39.89; H, 7.11; N, 15.16.

(−)-(*R*)-3-Amino-(*R*)-4-hydroxyazepane Dihydrochloride (29). (−)-(*R*)-3-Amino-(*S*)-4-hydroxy-2-oxoazepane hydrochloride (**30**) (2 g of 89.4% product with NH_4Cl, 9.9 mmol) was slurried in THF (30 mL), treated with borane (1 M in THF, 55 mL, 55 mmol) slowly, and then heated to reflux for 18 h. TLC analysis (9:1 MeOH:NH_4OH) showed complete reaction (starting material $R_f = 0.43$, product $R_f = 0.15$). The reaction mixture was treated with methanol (40 mL) and concentrated to an oil. The oil was dissolved in water (10 mL) and treated with 1 N NaOH until pH = 13 (≈20 mL). The mixture was then treated with 3 N HCl (20 mL). Both additions elicited gas evolution. The aqueous solution was added to a cation exchange resin (AG50-X8, 200−400 mesh, H^+ form, 2.5 × 27 cm) and eluted with water and 1 N HCl (≈200 mL ea.), and the product was eluted with 3 N HCl. The active fractions were concentrated to a glass. The glass was slurried in minimal methanol, triturated with 2-propanol, and stirred overnight. The resulting powder was filtered off under nitrogen, washed with 2-propanol, and dried under nitrogen flow to give the title compound (1.34 g, 67%) as a white powder, mp 175−180 °C. ^{1}H-NMR (D_2O) δ 1.70−1.95 (2H, m), 2.00−2.10 (1H, m), 2.2−2.3 (1H, m), 3.25−3.42 (3H, m), 3.5−3.65 (2H, m), 3.8−3.9 (1H, m); ^{13}C-NMR (D_2O) δ 18.4, 31.8, 42.1, 45.9, 53.3, 66.5 (dioxane reference), 71.1; IR (KBr) 3419, 2953, 1619 cm^{-1}; $[\alpha]^{25}_D = -19.3°$ ($c = 0.171$ in CH_3OH). Anal. Calcd for $C_6H_{14}N_2O$·2HCl: C, 35.48; H, 7.94; N, 13.79. Found: C, 35.27; H, 8.22; N, 13.43.

***N*-(*tert*-Butoxycarbonyl)-(*R*)-3-[4-(benzyloxy)benzamido]-(*R*)-4-hydroxyazepane (31).** (−)-(*R*)-3-Amino-(*R*)-4-hydroxyazepane dihydrochloride (**29**) (150 mg, 738 μmol) was dissolved in methanol (6 mL) and treated with 1 N NaOH (2.2 mL) and cooled in an ice bath. Di-*tert*-butyl dicarbonate (187 μL, 177 mg, 812 μmol) was added and the reaction mixture stirred for 18 h. The mixture was concentrated, partitioned between 1 N NaOH (5 mL) and CH_2Cl_2 (5 mL), treated with *p*-(benzyloxy)benzoyl chloride (482 mg, 1.9 mmol) in CH_2Cl_2 (1 mL) and stirred vigorously for 16 h. The organic layer was removed and chromatographed (2.5 × 15 cm, 1:1 EtOAc:hexanes) and concentrated to give the product (217 mg, 66%) as a glass. ^{1}H-NMR ($CDCl_3$) δ 1.47 (9H, s), 1.6−2.0 (4H, m), 2.70 (1H, dt, J = 3.5, 15.5), 3.25 (1H, dd, J = 5.2, 15.5), 3.76 (1H, m), 4.1 (3H, m), 5.09 (2H, s), 5.41 (1H, br s), 6.99 (2H, d J = 8.8), 7.3−7.42 (5H, m), 7.84 (2H, d, J = 8.8), 8.91 (1H, d, J = 5.4); ^{13}C-NMR ($CDCl_3$) δ 27.9, 29.0, 33.4, 50.5, 51.1, 61.3, 70.6, (77.2, 77.6, 78.1 - $CDCl_3$), 80.4, 81.4, 115.2, 126.4, 128.1, 128.7, 129.2, 129.7, 137.0, 157.9, 162.1, 169.0; IR (KBr) 3374, 2933, 1692, 1624, 1505 cm^{-1}; mass spectrum (FAB) *m*/*z* 441 (100%, $M^+ + 1$), 385 (68%, $M^+ + 1 - C_4H_8$), 341 (35%, $M^+ + 1 - CO_2 - C_4H_8$). Anal. Calcd for $C_{25}H_{32}N_2O_5$: C, 68.16; H, 7.32; N, 6.36. Found: C, 68.45; H, 7.36; N, 6.42.

Protected Balanol 32. Balanol benzophenone **18** (367 mg, 542 mmol) was slurried in CH_2Cl_2 (2 mL) and treated with DMF (1 drop) and oxalyl chloride (542 μL of 2 M CH_2Cl_2 solution, 137 mg, 1.08 mmol). After stirring for 1 h, the homogeneous solution was concentrated under full vacuum to give the acid chloride. *N*-(*tert*-Butoxycarbonyl)-(*R*)-3-[4-(benzyloxy)benzamido]-(*R*)-4-hydroxyazepane (**31**) (217 mg, 492 μmol) was dissolved in CH_2Cl_2 (5 mL) and treated with triethylamine (271 μL, 199 mg, 1.97 mmol) and DMAP (6 mg, 49 μmol) followed by the acid chloride in CH_2Cl_2 (2 mL). The mixture was stirred 3 days and then directly chromatographed (4.1 × 10 cm, 3:2 hexanes:EtOAc) to give the product (283 mg, 52%) as a glass. ^{1}H-NMR ($CDCl_3$) δ occurs as a ≈3:1 rotameric mixture 1.4−2.1 (4H, m's), 1.54 and 1.57 (≈1:3 9H, s), 2.8 (1H, m), 3.31 (1H, m), 3.9−4.1 (2H, m's), 4.65 (2H, s), 4.8−4.9 (1H, m), 4.81 (2H, s), 5.03, (2H, s), 5.08 (2H, s), 4.95−5.05 (1H, m), 6.8−7.4 (32H, m's), 7.7 and 8.0 (2H, d's).

(−)-Balanol ((−)-1). Protected balanol **32** (280 mg, 254 μmol) was dissolved in EtOAc and ethanol (10 mL each), treated with 20% palladium hydroxide on carbon (30 mg), and put under hydrogen (balloon) for 16 h. The balloon was recharged with hydrogen, additional catalyst (30 mg) was added, and stirring was continued for 16 h. The reaction mixture was flushed with nitrogen, filtered, and concentrated to a solid. The solid was dissolved in TFA (1.5 mL) and stirred at rt for 1 h. The mixture was concentrated, and the residue was chromatographed on a C_{18} column (41 × 300 mm) using a linear gradient from 100% A (0.1% TFA and 5% acetonitrile in water) to 50% B (pure acetonitrile) over 60 m at 25 mL/min. The clean product, which eluted in 37 min, was concentrated to remove acetonitrile and freeze-dried to give synthetic (−)-balanol as a light yellow powder (132 mg, 76%). This sample was identical to balanol by TLC, HPLC, and ^{1}H-NMR. mp ≈ 200 °C dec. Anal. Calcd for $C_{28}H_{26}N_2O_{10}$·$2H_2O$·$1.25CF_3CO_2H$: C, 50.25; H, 4.32; N, 3.84. Found: C, 50.03; H, 4.42; N, 3.87. $[\alpha]^{25}_D = -107°$ (c = 0.252 in CH_3OH).

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