Total Synthesis of (−)-Balanol

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The efficient total synthesis of (−)-balanol, a potent inhibitor of the protein kinase C, is described. (−)-Balanol consists of a chiral hexahydroazepine-containing fragment and a benzophenone fragment, both of which were prepared via novel synthetic routes. The hexahydroazepine fragment was prepared in racemic form through either Bu_3SnH- or SmI_2-promoted radical cyclization of oxime ethers **2ab** intramolecularly connected with the formyl group. SmI_2-promoted radical cyclization of **2b** was found to be particularly successful in the selective synthesis of the seven-membered *trans*-amino alcohol **8b**. Preparation of the enantiomerically pure hexahydroazepine-containing fragment was achieved through the enantioselective enzymatic acetylation of racemic alcohol **9**, employing the immobilized lipase from *Pseudomonas* sp. The benzophenone fragment was prepared in short steps through a biomimetic oxidative anthraquinone ring cleavage starting from commercially available natural chrysophanic acid **15c**. This reaction proceeded via [4 + 2]-cycloaddition of singlet oxygen to anthracene derivative **17c**, followed by Baeyer−Villiger-type rearrangement of the resulting hydroperoxide to afford the benzophenone derivatives **22** and **23**.

Introduction

Protein kinase C (PKC) is a family of phospholipid-dependent serine/threonine specific protein kinases that mediate a wide range of signal transduction processes in cells.[1] Human PKC enzyme consists of at least eight isoforms α, β-I, β-II, δ, ϵ, γ, η, and ζ, which play important roles in cellular growth control, regulation, and differentiation. Since activation of PKC enzymes has been implicated in a number of diseases such as cancer, cardiovascular disorders, central nervous system dysfunction, HIV infection, and so on, a selective inhibitor against PKC isozyme may have wide-ranging therapeutic potential.[2]

Balanol (**1**), initially isolated from the fungus *Verticillium balanoides* by Kulanthaivel and co-workers at Sphinx Pharmaceuticals, has been shown to inhibit human PKC isozymes at low nanomolar concentrations (IC_{50} ranges 4−9 nM).[3] It was also more recently isolated from a species of *Fusarium* by researchers at Nippon Roche Research, who called it azepinostatin instead of balanol.[4] Its remarkable inhibitory activity and its structural novelty have attracted significant attention as a new lead compound of potent drugs against diseases associated with PKC activation. Thus, balanol and its analogues have been the recent new subject of synthetic studies, and independently, three total syntheses of balanol were achieved by Nicolaou's group and by researchers at Sphinx and at Rhone-Poulenc Rorer.[5−9] We have also started synthetic studies involving sufficiently flexible synthetic routes to allow ready access to a variety of balanol analogues for the improvement of enzyme selectivity and pharmacokinetic properties.[10] In this paper, we describe full details of our total synthesis of (−)-balanol via novel synthetic routes.

Balanol consists of two distinct structural domains, a chiral hexahydroazepine-containing fragment and a ben-

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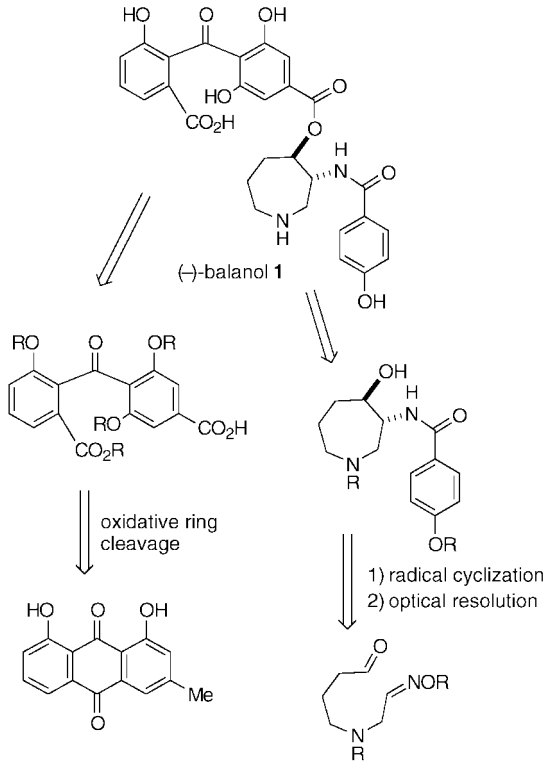

Figure 1. Retrosynthesis of (−)-balanol.

zophenone fragment. Our synthetic approach includes the preparation of the enantiomerically pure hexahydroazepine-containing fragment through either the Bu_3-SnH- or SmI_2-promoted radical cyclization of the oxime ether intramolecularly connected with the formyl group, followed by the lipase-catalyzed optical resolution of the resulting racemic alcohols. Preparation of a benzophenone fragment was achieved through a biomimetic oxidative anthraquinone ring cleavage starting from natural chrysophanic acid (Figure 1).

Results and Discussion

Radical Cyclization and Racemic Hydroazepine Synthesis. Strategies involving radical reactions have become useful tools in organic synthesis.[11] Particularly, free radical-mediated cyclization has been an important method for the construction of various types of cyclic compounds. While there have been extensive investigations into radical-mediated five- or six-membered ring formation,[12] the difficulty in achieving radical-mediated construction of the seven-membered ring has remained unresolved.[13] Thus, the radical-promoted intramolecular construction of seven-membered compounds and its stereocontrol are subjects of considerable interest. Previously, we reported the first example of the synthesis of cyclic amino alcohols via a route involving the tributyltin hydride-induced radical cyclization of oxime ethers, which were intramolecularly connected with an aldehyde or a ketocarbonyl group.[13] This approach was particularly successful for the synthesis of not only five- and six-membered compounds but also seven-membered cyclic amino alcohols. Thus, this procedure would provide a convenient method for preparing natural balanol and its analogues with readily accessible replacement of the hexahydroazepine moiety.

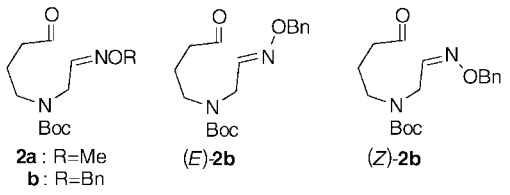

Figure 2. Substrates **2ab**, (*E*)-**2b**, and (*Z*)-**2b**.

Since trans relative stereochemistry of the two aromatic side chains of balanol are indispensable for optimal potency,[9a] we explored the selective synthesis of trans cyclic amino alcohols. To investigate the substituent effects of the *O*-alkyl groups R and the geometry of the oxime ether group on the trans/cis selectivity of radical cyclizations, we selected the substrates **2ab**, (*E*)-**2b**, and (*Z*)-**2b** (Figure 2), which were prepared as shown in Scheme 1. α-Chloroacetaldoxime ethers **4ab** were readily prepared from chloroacetaldehyde and the corresponding *O*-alkylhydroxyamine hydrochloride.[14] Alkylation of commercially available 4-aminobutanol **3** with **4ab** gave the secondary amines **5ab** in 69 and 82% yields, respectively, as an *E*/*Z* mixture in a 3:2 ratio. The *E*/*Z* ratios were

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Scheme 1

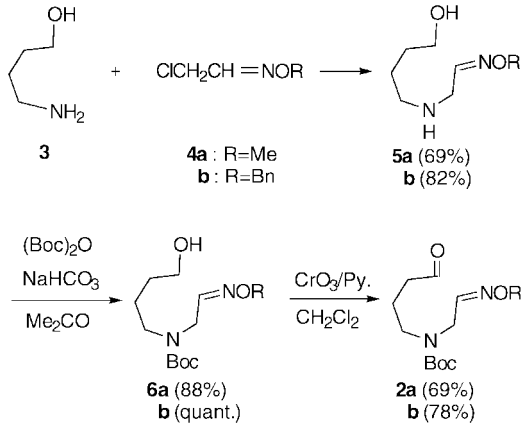
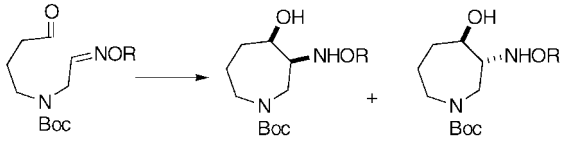


Table 1. Radical Cyclization of Oxime Ether 2ab



entry	substrate	ratio *E*:*Z*	conditions: reagent	conditions: *T* (°C)	yield[c] (%)	ratio[d] **7ab**:**8ab**
1	**2a**	3:2	Bu_3SnH[a]	reflux	48	1:2.0
2	**2b**	3:2	Bu_3SnH[a]	reflux	50	1:2.6
3	(*E*)-**2b**	1:0	Bu_3SnH[a]	reflux	51	1:2.9
4	(*Z*)-**2b**	0:1	Bu_3SnH[a]	reflux	43	1:2.6
5	**2b**	3:2	SmI_2[b]	rt	no reaction	
6	**2b**	3:2	SmI_2, HMPA[b]	−78 to rt	53	1:6.6

[a] Reaction was carried out in the presence of AIBN in boiling benzene. [b] Reaction was carried out in the presence of *t*-BuOH in THF. [c] Combined yield of cis and trans cyclic products. [d] Ratio is based on respective isolated yields of cis and trans cyclic products.

determined by ^{1}H NMR spectroscopy. In general, the signals due to the imino hydrogen of the *E*-oxime ether are shifted downfield by the influence of the alkoxy group of the oxime ether moiety.[15] In the case of **5a**, the triplet signal due to the imino hydrogen of the *E*-isomer (δ 7.42 ppm) was shifted downfield with respect to that of the *Z*-isomer (δ 6.76 ppm). These amines **5ab** were protected as the *N*-Boc derivatives **6ab** in good yields by treatment with di-*tert*-butyl dicarbonate under the Schotten−Baumann-type conditions. Mild oxidation of **6ab** with chromium(VI) oxide−pyridine afforded the unstable aldehydes **2ab** in 69 and 78% yields, respectively, in favor of the *E* isomer in a 3:2 ratio. After careful separation of (*E*)-**2b** and (*Z*)-**2b** by medium-pressure column chromatography, these isomers were subjected to the following radical cyclization.

At first, we examined stannyl radical-promoted cyclization of the *O*-methyl oxime ether **2a** (Table 1). Treatment of an *E*/*Z* mixture of **2a** with tributyltin hydride (2 equiv) in the presence of AIBN (1 equiv) in boiling benzene gave a 1:2 mixture of two cyclized products **7a** and **8a** in 48% combined yield in favor of *trans*-amino alcohol **8a** (Table 1, entry 1). We were able to separate and purify each isomer by either flash or medium-pressure column chromatography. Relative stereochemistry of the major product **8a** was determined to

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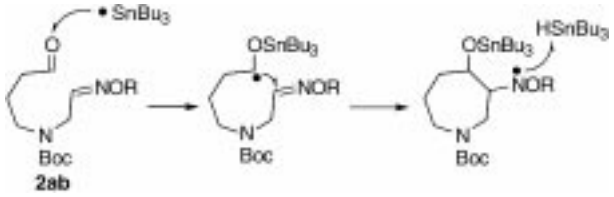
Scheme 2



be trans by converting it into an authentic compound **9**.[5−7] In the case of the radical cyclization employing an *E*/*Z* mixture of *O*-benzyl oxime ether **2b**, similar selectivity and chemical yield were obtained (Table 1, entry 2). The rationale of the reaction pathway of this 7-*exo*-*trig* radical cyclization is that the stannyl radical initially reacted with the oxygen atom of the formyl group to form the ketyl radical, which attacked intramolecularly the oxime ether moiety (Scheme 2). In this reaction, the oxime ether group acts as an excellent radical acceptor because of the extra stabilization of the intermediate aminyl radical provided by the lone pair on the adjacent oxygen atom.[16,17] Interestingly, we have also observed no remarkable effect of the geometry of the starting oxime ether group on either the chemical yield or trans/cis selectivity by employing geometrically pure (*E*)-**2b** and (*Z*)-**2b** (Table 1, entries 3 and 4). A similar trend has been recently reported by Bartlett in a tributyltin hydride-induced reductive coupling of phenyl thionocarbonates with oxime ethers.[18]

In recent years, samarium diiodide (SmI_2) has evolved as a unique single-electron reducing agent that is well suited for highly chemo- and stereoselective radical reactions.[19,20] Next, we examined the intramolecular reductive coupling of *O*-benzyl oxime ether **2b** by SmI_2 for the selective synthesis of the seven-membered *trans*-amino alcohol. Cyclizations were performed in the presence of 2.2 equiv of *t*-BuOH as a proton donor in THF from −78 °C to room temperature by the use of a 0.1 M solution of SmI_2 in THF (4.0 equiv). In the absence of HMPA, the cyclization of an *E*/*Z* mixture of **2b** did not proceed at all and resulted in the recovery of the starting

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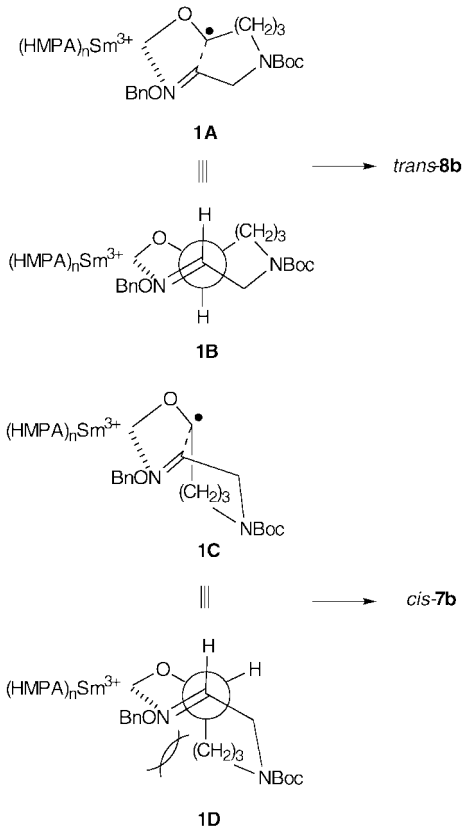
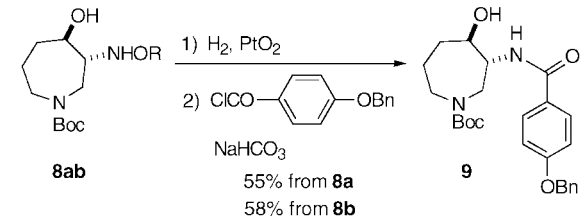


Figure 3. Proposed radical intermediate favoring trans cyclization.

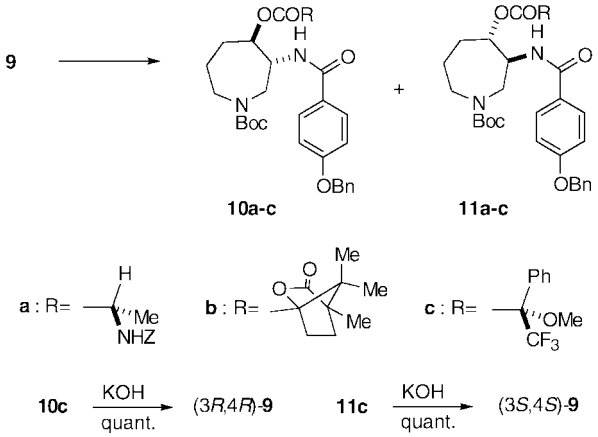
material **2b** (Table 1, entry 5). The addition of HMPA (10 equiv), which was recognized to increase the reaction rate by SmI_2, was found to be essential for successful cyclization of **2b** to afford trans cyclized product **8b** in 46% yield accompanied with a minor amount of cis product **7b** in 7% yield (Table 1, entry 6).[21] This one-electron reducing agent has been recently used for the intramolecular coupling of aldehydes and ketones with oxime ethers for the synthesis of five-membered amino-cyclopentitols.[20a] In these cases, the coupling reaction proceeded even in the absence of HMPA, in contrast to our seven-membered ring formation. Probably, this reductive coupling reaction was initiated by single-electron transfer to the formyl group with generation of a ketyl radical, which then attacked the oxime ether moiety. The preferential formation of the trans isomer **8b** could be explained by chelation of the ketyl radical and the oxime ether group to a Sm(III)$(HMPA)_n$ cation as shown in Figure 3.[22] There are less steric and electronic repulsions in the chelated radical **1A** = **1B** leading to the trans isomer **8b** than in the chelated radical **1C** = **1D** leading to the cis isomer **7b**.

Subsequent hydrogenolysis of the alkoxyamino group of trans product **8ab** in the presence of platinum dioxide

Scheme 3



Scheme 4



in MeOH followed by *N*-acylation of the resulting crude amine with *p*-(benzyloxy)benzoyl chloride afforded the desired racemic hydroazepine **9** in 55 and 58% yields, respectively (Scheme 3). This compound **9** was identical with an authentic sample upon comparison of their spectral data.[6] Thus, we have succeeded in the six-step preparation of a racemic hexahydroazepine-containing fragment.

Optical Resolution. To prepare the enantiomerically pure hexahydroazepine-containing fragment, racemic hydroazepine **9** was then subjected to chemical optical resolution by forming the corresponding diastereomeric esters and enzymatic optical resolution using lipase.

Among the diastereomeric esters **10a**−**c** and **11a**−**c** derived from *N*-Z-L-alanine, (*S*)-camphanic acid chloride, and (*R*)-2-methoxy-2-(trifluoromethyl)phenylacetyl (MTPA) chloride, the esters (3*R*,4*R*)-**10c** and (3*S*,4*S*)-**11c** were found to be readily separable by medium-pressure column chromatography eluting with pentane−ethyl acetate (4:7, v/v) (Scheme 4). Alkaline hydrolysis of esters (3*R*,4*R*)-**10c** and (3*S*,4*S*)-**11c** gave the desired hydroazepine (3*R*,4*R*)-**9** and its isomer (3*S*,4*S*)-**9**, respectively, in 95% overall yield from racemic hydroazepine **9**. The enantiomeric purity of (3*R*,4*R*)-**9** and (3*S*,4*S*)-**9** was found to be not less than 99% ee using chiral chromatography (Chiral Pack AD column) eluting with ethanol−heptane (15:85, v/v). The absolute configuration of (3*R*,4*R*)-**9** was determined by comparison with the literature value of the optical rotation.[6]

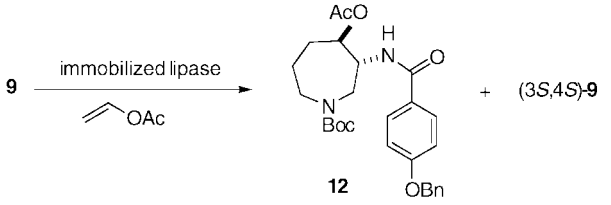
Enzymes have become increasingly popular as a chiral catalyst in organic synthesis.[23] Lipases are especially attractive for this purpose because they are relatively inexpensive, effective in both organic and aqueous solutions, and useful under mild reaction conditions. For the

(21) Although the cleavage of the N−O bond of a hydroxyamine by excess SmI_2 was reported, the N−O bond cleavage of **8b** could not be observed. See: (a) Keck, G. E.; Wager, T. T. *J. Org. Chem.* **1996**, *61*, 8366−8367. (b) Chiara, J. L.; Destabel, C.; Gallego, P.; Marco-Contelles, J. *J. Org. Chem.* **1996**, *61*, 359−360.

(22) In the reactions of the ketyl radical induced by SmI_2, the chelated intermediates were proposed. See: (a) Molander, G. A.; McWilliams, J. C.; Noll, B. C. *J. Am. Chem. Soc.* **1997**, *119*, 1265−1276. (b) Taniguchi, N.; Uemura, M. *Synlett* **1997**, 51−53. (c) Taniguchi, N.; Kaneta, N.; Uemura, M. *J. Org. Chem.* **1996**, *61*, 6088−6089. (d) Kawatsura, M.; Dekura, F.; Shirahama, H.; Matsuda, F. *Synlett* **1996**, 373−376.

(23) Santaniello, E.; Ferraboschi, P.; Paride, G.; Manzocchi, A. *Chem. Rev.* **1992**, *92*, 1071−1140.

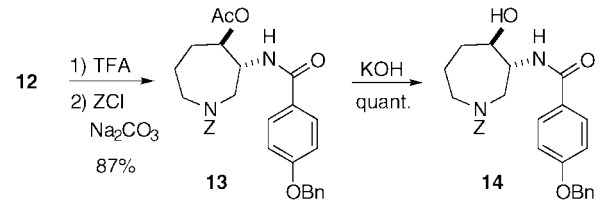
Table 2. Lipase-Catalyzed Optical Resolution of 9



		12		(3S,4S)-9	
entry	immobilized lipase[a]	yield[d] (%)	ee[e] (%)	yield[d] (%)	ee[e] (%)
1	*Pseudomonas* sp.[b] (320 g/mol)	11	97	72	3
2	*Pseudomonas* sp.[b] (1600 g/mol)	42	96	49	82
3	*Pseudomonas fluorescence*[c] (500 g/mol)	no reaction			

[a] Reactions were carried out in *t*-BuOMe at 20 °C for 48 h (run 1), 20−45 °C for 20 h (run 2), and 20 °C for 52 h (run 3), respectively. [b] 0.5 unit/mg. [c] 4.0 unit/mg. [d] Isolated yield. [e] Enantiomeric excess was determined by chiral HPLC analysis.

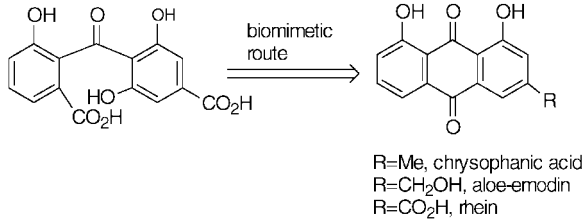
Scheme 5



convenient preparation of enantiomerically pure hexahydroazepine, we next investigated the lipase-catalyzed optical resolution such as the enzymatic esterification of racemic alcohol **9** and the enzymatic hydrolysis of racemic acetate (±)-**12**. The screening of several enzymes showed that the lipase from *Pseudomonas* sp. was the enzyme of choice to perform the esterification of **9** in high yields and enantiomeric purity. These enzymatic esterifications of **9** were carried out by use of vinyl acetate as an acylating agent in *tert*-butyl methyl ether as a solvent. The acetylation of **9** employing the immobilized lipase (1600 g/mol, 0.5 unit/mg) from *Pseudomonas* sp. (Wako Pure Chemical Industries, Ltd.) at 20−45 °C for 20 h was found to be most effective and the optimum reaction conditions. Chromatographic separation of the products afforded the desired acetate **12** in 42% yield (96% ee) with the recovered (3*S*,4*S*)-**9** in 49% yield (82% ee) (Table 2, entry 2). The enantiomeric purity of **12** and (3*S*,4*S*)-**9** was checked by chiral column chromatography (Chiral Pack AD column) eluting with ethanol−heptane (15:85, v/v). The absolute configuration of **12** was determined by converting it into (3*R*,4*R*)-**9** mentioned above. Alternative enantioselective enzymatic hydrolysis of racemic acetate (±)-**12** was unsuccessful, and the starting acetate (±)-**12** was completely recovered when the immobilized lipase from *Pseudomonas* sp. was employed. Treatment of acetate **12** with trifluoroacetic acid in CH_2Cl_2 gave the deprotected product, which without further purification, was reprotected with benzyloxycarbonyl chloride in acetone to afford *N*-Z acetate **13** in 87% from **12** (Scheme 5). Alkaline hydrolysis of *N*-Z acetate **13** gave enantiomerically pure alcohol **14**, which was found to be identical with an authentic sample upon comparison of their spectral data, including optical rotation.[5−7]

Benzophenone Synthesis. From the fact that the conversion of anthraquinones to benzophenones via the Baeyer−Villiger-type reaction has been recognized as a key reaction in biosynthesis of fungal metabolites,[24] we planned to explore the biomimetic route for the synthesis of the benzophenone fragment of balanol (Scheme 6). Although the biosynthetic features of balanol have not been confirmed, the oxidative ring cleavage of natural anthraquinones such as chrysophanic acid, aloe-emodine, and rhein could be one of the possible pathways for the benzophenone fragment. Our synthesis of the benzophenone fragment of balanol started from natural chrysophanic acid as the commercially available natural anthraquinone. In general, chemical Baeyer−Villiger reactions of anthraquinones are known to proceed slowly because they give the unstable seven-membered lactones as an intermediate.[25] The only two successful examples of anthraquinone ring cleavage are the experiments using an enzyme or singlet oxygen.[24,26,27]

Scheme 6

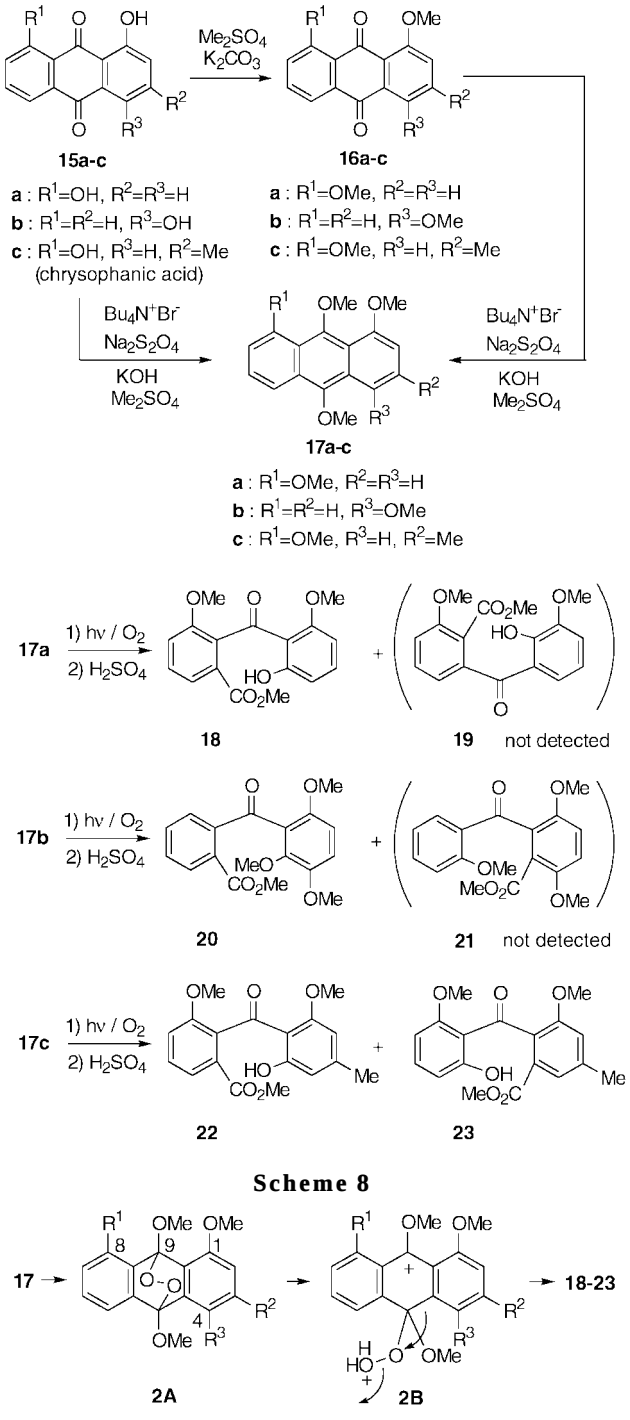


Despite its importance from a synthetic point of view, a detailed survey of the latter method mentioned above has not been reported yet. To learn about the substituent effects of anthraquinone structure on both the regioselectivity of the ketal hydrolysis step and the migratory aptitude of the following rearrangement step, we carried out extensive studies of this process by employing three methoxy-substituted derivatives **17a**−**c**.

Hydroxyanthraquinone **15c** was first protected by methylation using dimethyl sulfate and K_2CO_3 in acetone to give methyl ether **16c** (Scheme 7). Quinone derivative **16c** was then reductively methylated to the corresponding anthracene derivative **17c** by treatment with sodium hydrosulfite in the presence of tetrabutylammonium bromide as a phase-transfer catalyst followed by methylation employing dimethyl sulfate and KOH.[28] According to the literature,[27] an etheral solution of anthracenes **17a**−**c**, which also served as a sensitizer, was irradiated with a halogen lamp through a Pyrex filter under oxygen bubbling. After the solvent was evaporated in vacuo, the resulting oxygen adducts were treated with a catalytic amount of sulfuric acid in acetone to give the benzophenone derivatives **18**−**23**.[29] The reaction pathway from **17** to **18**−**23** can be rationalized by a [4 + 2]-cycloaddition of anthracene **17** to singlet oxygen, regioselective hy-

(24) Frank, B. In *The Biosynthesis of Mycotoxins*, Steyn, P. S., Ed.; Academic Press: New York, 1980; pp 151−191.
(25) Svensson, L.-Å. *Acta Chem. Scand.* **1972**, *26*, 2372−2384.
(26) Fujii, I.; Ebizuka, Y.; Sankawa, U. *J. Biochem.* **1988**, *103*, 878−883.
(27) Frank, B.; Berger-Lohr, B. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 818−819.
(28) (a) Blankespoor, R. L.; Schutt, D. L.; Tubergen, M. B.; De Jong, R. L. *J. Org. Chem.* **1987**, *52*, 2059−2064. (b) Hydroxyanthraquinones **15ab** could be directly converted into the corresponding methylated anthracene derivatives **17ab** by treatment with sodium hydrosulfite in the presence of tetrabutylammonium bromide as a PTC followed by methylation employing dimethyl sulfate and KOH. See: Kraus, G. A.; Man, T. O. *Synth. Commun.* **1986**, *16*, 1037−1042.
(29) The reason trimethoxy-substituted benzophenone **20** was obtained from **17b** even in the absence of methanol and/or other methylating agents is not clear at the moment.

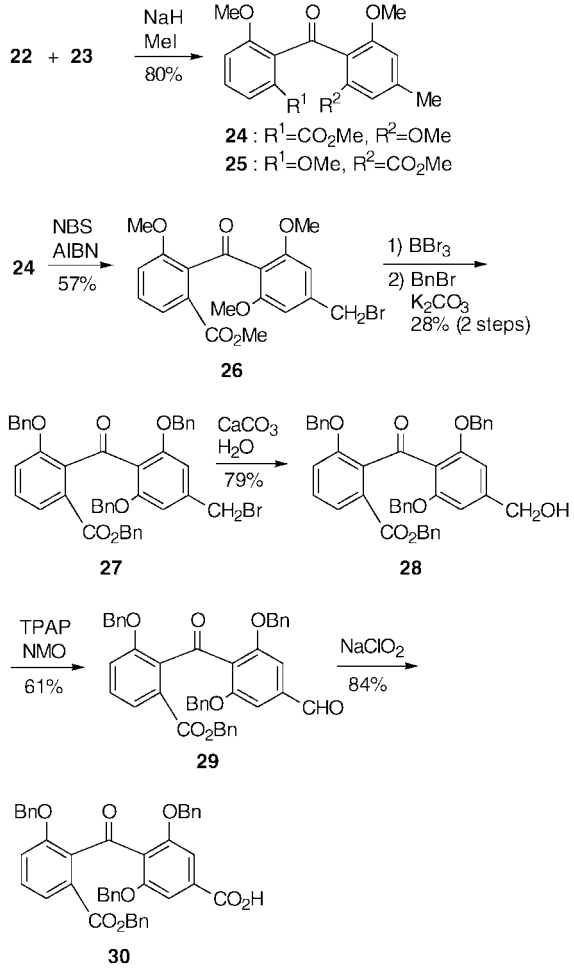
Scheme 7



Scheme 8

drolysis of the resulting ketal moiety at the 9-position of **2A**, and the Baeyer−Villiger type of acid-catalyzed rearrangement of the resulting hydroperoxide **2B**, in which the migrating group can be placed antiperiplanar to the O−O bond (Scheme 8). The reaction of anthracene **17a** having 1,8-dimethoxy groups took place smoothly to afford the benzophenone derivative **18** as a single isomer in 67% yield via a completely regioselective ketal hydrolysis process. In the case of **17b** having 1,4-dimethoxy groups, trimethoxy-substituted benzophenone derivative **20** was obtained in 27% yield with no detection of another product **21** via a regioselective migration process. These results indicate that the electron-donating property of 1,8-dimethoxy groups of **17a** was sufficient for the formation and stabilization of the cation at C-9 of **2B**,

Scheme 9



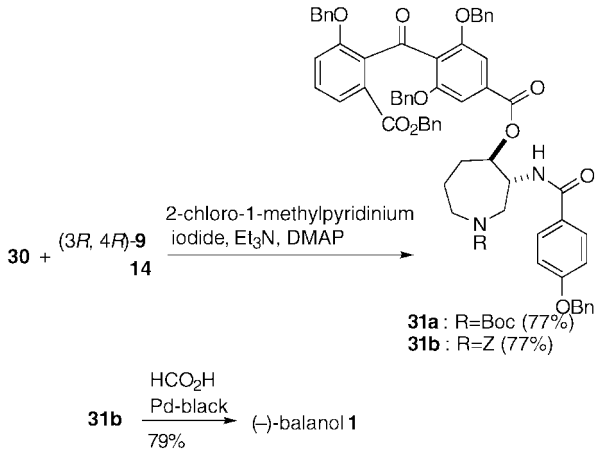
and 1,4-dimethoxy groups of **17b** dramatically affected the migratory aptitude on the Baeyer−Villiger-type rearrangement of **2B**. Therefore, in the case of **17c** possessing 1,8-dimethoxy groups and a 3-methyl group, an inseparable mixture of two regioisomeric benzophenones **22** and **23** was obtained in 57% combined yield in a 1:1 ratio among four possible regioisomers via the regioselective ketal hydrolysis process and a nonselective migration process in addition to 30% yield of the starting anthraquinone **16c**, which could be recycled.[30]

A mixture of benzophenones **22** and **23** was converted into a mixture of the corresponding methyl ethers **24** and **25** that was separated by medium-pressure column chromatography (Scheme 9). Fortunately, benzophenones **24** and **25** were fully characterized by their spectral data including NOESY spectral analysis. Bromination of **24** with NBS in the presence of a catalytic amount of AIBN proceeded smoothly to give bromide **26** in 57% (67%)[31] yield. Bromide **26** was treated with boron tribromide in CH_2Cl_2 to give the crude deprotected triphenolic acid, which was then reprotected by benzylation using benzyl bromide and K_2CO_3 to afford the tetrabenzyl derivative **27** in 28% yield. Hydrolysis of **27** under mild conditions using $CaCO_3$ provided the desired alcohol **28**

(30) The formation of this peroxide intermediate was also confirmed by EI and high-resolution mass spectra. A peroxide intermediate: MS (EI) *m*/*z* 330 (M^+); high-resolution MS calcd for $C_{18}H_{18}O_6$ 330.1102, found 330.1115.

(31) Yield in parentheses is based on the consumed starting material.

Scheme 10



in 79% yield, which was found to be identical with an authentic sample upon direct comparison of their spectra.[5] According to Nicolaou's conditions, alcohol **28** was oxidized into acid **30** by use of TPAP−NMO followed by sodium chlorite.[5] Thus, we succeeded in the biomimetic synthesis of the desired benzophenone **30**, which was the known key intermediate for the synthesis of balanol.

The synthesis of (−)-balanol was completed as shown in Scheme 10. The coupling of benzophenone fragment **30** with hydroazepine fragments (3*R*,4*R*)-**9** or **14** was accomplished by the Mukaiyama procedure[32] to afford the protected balanols **31ab** in 77 and 77% yields, respectively. These two products **31ab** were found to be identical with the respective authentic chiral samples upon comparison of their spectral data.[5−7] Finally, palladium black-catalyzed hydrogenolysis of **31b** in formic acid gave (−)-balanol (**1**) under the same conditions as the Nicolaou method.[5] Purification of the resulting crude balanol (**1**) was accomplished by a combination of normal-phase preparative TLC and reversed-phase preparative TLC. The synthetic (−)-balanol (**1**) exhibited characterization data consistent with authentic spectral data.[5,6]

Conclusions

We succeeded in the total synthesis of (−)-balanol by the preparation of the chiral hexahydroazepine fragment through the SmI_2-promoted radical cyclization followed by enzymatic esterification using the immobilized lipase from *Pseudomonas* sp. and by the facile preparation of the benzophenone fragment through a biomimetic oxidative anthraquinone ring cleavage starting from natural chrysophanic acid.

Experimental Section

General Methods. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 200, 300, or 500 MHz and at 50 or 125 MHz, respectively. IR spectra were recorded using FTIR apparatus. Mass spectra were obtained by EI, CI, or SIMS methods. Preparative TLC separations were carried out on precoated silica gel plates (E. Merck 60F_{254} or E. Merck reversed-phase plates RP-18WF_{254S}). Medium-pressure column chromatography was performed using Lobar grösse B (E. Merck 310-25, Lichroprep Si60). Flash column chromatography was performed using E. Merck Kieselgel 60 (230−400 mesh).

(32) Mukaiyama T. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 707−721.

4-[[2-(Methoxyimino)ethyl]amino]-1-butanol (5a). To 4-amino-1-butanol (**3**) (12 g, 135 mmol) was added chloroacetaldehyde *O*-methyloxime (**4a**)[14] (6.0 g, 56 mmol) under a nitrogen atmosphere at 0 °C. After being stirred at room temperature for 48 h, the reaction mixture was added to saturated aqueous $NaHCO_3$ and CH_2Cl_2. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4 and concentrated at reduced pressure. Purification of the residue by flash chromatography (AcOEt to CH_2Cl_2/MeOH 10:1) afforded **5a** (6.2 g, 69%) as a yellow oil and a 3:2 mixture of *E*/*Z*-oxime: IR ($CHCl_3$) 3670−3200 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42 (3/5H, t, J = 5.5 Hz), 6.76 (2/5H, t, J = 4.5 Hz), 3.88 (6/5H, s), 3.84 (9/5H, s), 3.59 (2H, t, J = 6 Hz), 3.50 (4/5H, d, J = 4.5 Hz), 3.37 (6/5H, d, J = 5.5 Hz), 2.67 (2H, m), 1.73−1.48 (4H, m); HRMS calcd for $C_7H_{16}N_2O_2$ (M^+) 160.1211, found 160.1220.

4-[[2-[(Phenylmethoxy)imino]ethyl]amino]-1-butanol (5b). To a solution of chloroacetaldehyde *O*-(phenylmethyl)oxime (**4b**)[14] (7.0 g, 38 mmol) in MeOH (150 mL) was added 4-amino-1-butanol (**3**) (6.8 g, 76 mmol) under a nitrogen atmosphere at 0 °C. The reaction mixture was heated at reflux for 2 h. After the solvent was evaporated at reduced pressure, the resulting residue was added to saturated aqueous $NaHCO_3$ and CH_2Cl_2. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4 and concentrated at reduced pressure. Purification of the residue by flash chromatography (AcOEt/hexane 1:9 to AcOEt/MeOH 5:1) afforded **5b** (7.4 g, 82%) as a yellow oil and a 3:2 mixture of *E*/*Z*-oxime: IR ($CHCl_3$) 3600−3200 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.49 (3/5H, t, J = 5.5 Hz), 7.42−7.22 (5H, m), 6.80 (2/5H, t, J = 4.5 Hz), 5.10 (4/5H, s), 5.06 (6/5H, s), 3.62−3.49 (14/5H, m), 3.35 (6/5H, d, J = 5.5 Hz), 2.63 (2H, t, J = 6 Hz), 1.71−1.48 (4H, m); HRMS calcd for $C_{13}H_{20}N_2O_2$ (M^+) 236.1524, found 236.1541.

1,1-Dimethylethyl (4-Hydroxybutyl)[2-(methoxyimino)ethyl]carbamate (6a). To a solution of **5a** (6.2 g, 38.8 mmol) in acetone (93 mL) was added a solution of Na_2CO_3 (3.4 g, 32.0 mmol) in H_2O (15.5 mL) under a nitrogen atmosphere at room temperature. After di-*tert*-butyl dicarbonate (12.7 g, 58.3 mmol) was added dropwise at 0 °C, the reaction mixture was heated at reflux for 5 h. After the reaction mixture was filtered through a pad of Celite, the filtrate was concentrated at reduced pressure. The resulting residue was quenched with 5% HCl at 0 °C and then extracted with $CHCl_3$. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (AcOEt/hexane 2:1) afforded **6a** (8.92 g, 88%) as a colorless oil and a 3:2 mixture of *E*/*Z*-oxime. The presence of rotamers precluded a comprehensive assignment of all proton resonances: IR ($CHCl_3$) 3600−3400 (OH), 1685 (NCOO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32 (3/5H, br m), 6.64 (2/5H, br m), 4.03 (4/5H, br m), 3.90 (6/5H, br m), 3.88 (6/5H, s), 3.84 (9/5H, s), 3.67 (2H, td, J = 6, 2 Hz), 3.25 (2H, br m), 1.77−1.48 (4H, m), 1.46 (9H, s); HRMS calcd for $C_{12}H_{24}N_2O_4$ (M^+) 260.1735, found 260.1717.

1,1-Dimethylethyl (4-Hydroxybutyl)[2-[(phenylmethoxy)imino]ethyl]carbamate (6b). Following the same procedure as for **6a**, compound **6b** was obtained from **5b** in almost quantitative yield as a colorless oil and a 3:2 mixture of *E*/*Z*-oxime. The presence of rotamers precluded a comprehensive assignment of all proton resonances: IR ($CHCl_3$) 3600−3400 (OH), 1686 (NCOO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40 (3/5H, t, J = 5.5 Hz), 7.39−7.25 (5H, m), 6.70 (2/5H, br t, J = 4 Hz), 5.11 (4/5H, s), 5.07 (6/5H, s), 4.15−4.00 (4/5H, br m), 3.89 (6/5H, br d, J = 4 Hz), 3.69−3.55 (2H, m), 3.30−3.10 (2H, m), 1.64−1.40 (4H, m), 1.44 (9H, s); HRMS calcd for $C_{18}H_{28}N_2O_4$ (M^+) 336.2047, found 336.2049.

1,1-Dimethylethyl [2-(Methoxyimino)ethyl](4-oxobutyl)carbamate (2a). To a solution of pyridine (14.6 g, 185 mmol) in CH_2Cl_2 (240 mL) was portionwise added CrO_3 (9.23 g, 92.3 mmol) under a nitrogen atmosphere at room temperature. After the solution was stirred at room temperature for 15 min, a solution of **6a** (4.0 g, 15.4 mmol) in CH_2Cl_2 (54 mL) was added to the reaction mixture. The reaction mixture was

stirred at the same temperature for 2 h, and then the solvent was evaporated at reduced pressure. The resulting residue was diluted with Et_2O and filtered through a pad of Celite, and the filtrate was concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (AcOEt/hexane 1:2) afforded **2a** (2.76 g, 69%) as a colorless oil and a 3:2 mixture of *E*/*Z*-oxime. The presence of rotamers precluded a comprehensive assignment of all proton resonances. After characterization by IR and NMR spectra, unstable **2a** was immediately subjected to radical cyclization: IR ($CHCl_3$) 1723 (CHO), 1688 (NCOO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.78 (1H, br s), 7.32 (3/5H, br m), 6.64 (2/5H, br m), 4.03 (4/5H, br m), 3.89 (6/5H, br m), 3.88 (6/5H, s), 3.84 (9/5H, s), 3.27 (2H, t, J = 7 Hz), 2.47 (2H, br t, J = 7 Hz), 1.84 (2H, quint, J = 7 Hz), 1.46 (9H, s).

1,1-Dimethylethyl [2-[(Phenylmethoxy)imino]ethyl](4-oxobutyl)carbamate (2b). Following the same procedure as for **2a**, compound **2b** was obtained from **6b** in 78% yield as a colorless oil and a 3:2 mixture of *E*/*Z*-oxime. Subsequent separation of *E*/*Z*-isomers by medium-pressure column chromatography (AcOEt/hexane 1:4) afforded (*E*)-**2b** and (*Z*)-**2b**. The presence of rotamers precluded a comprehensive assignment of all proton resonances. After characterization by IR, NMR, and MS spectra, unstable (*E*)-**2b** and (*Z*)-**2b** were immediately subjected to the following radical cyclization: IR ($CHCl_3$) 1723 (CHO), 1688 (NCOO) cm^{-1}. (*E*)-**2b**: ^1H NMR ($CDCl_3$) δ 9.71 (1H, t, J = 1 Hz), 7.41−7.20 (5H, m), 7.39 (1H, t, J = 5.5 Hz), 5.06 (2H, s), 3.98−3.82 (2H, m), 3.31−3.08 (2H, m), 2.45−2.30 (2H, br t, J = 7 Hz), 1.90−1.70 (2H, quint, J = 7 Hz), 1.44 (9H, s). (*Z*)-**2b**: ^1H NMR ($CDCl_3$) δ 9.74 (1H, t, J = 1 Hz), 7.41−7.20 (5H, m), 6.69 (1H, t, J = 4.5 Hz), 5.11 (2H, s), 4.15−4.00 (2H, m), 3.33−3.12 (2H, m), 2.47−2.35 (2H, br t, J = 7 Hz), 1.90−1.70 (2H, quint, J = 7 Hz), 1.44 (9H, s). (*E*)-**2b** + (*Z*)-**2b**: HRMS calcd for $C_{18}H_{26}N_2O_4$ (M^+) 334.1891, found 334.1889.

General Procedure for Radical Cyclization Using Bu_3SnH. To a boiling solution of **2** (10 mmol) in benzene (76 mL) was added portionwise (17 mL/h) a solution of Bu_3SnH (20 mmol) and AIBN (10 mmol) in benzene (46 mL) under a nitrogen atmosphere. The reaction mixture was heated at reflux for 6−8 h, and then the solvent was evaporated at reduced pressure. The resulting residue was diluted with acetonitrile, and the acetonitrile phase was washed with hexane and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (AcOEt/hexane 2:1) afforded **7** and **8** as colorless oils. The presence of rotamers precluded a comprehensive assignment of all proton resonances.

1,1-Dimethylethyl *cis*-(±)-hexahydro-4-hydroxy-3-(methoxyamino)-1*H*-azepine-1-carboxylate (7a): IR ($CHCl_3$) 3600−3300 (OH, NH), 1682 (NCOO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.07 (1H, br m), 3.72−3.40 (2H, m), 3.56 (3H, s), 3.30−3.06 (3H, m), 2.05−1.91 (2H, m), 1.71−1.48 (2H, m), 1.46 (9H, s); HRMS calcd for $C_{12}H_{24}N_2O_4$ (M^+) 260.1735, found 260.1735.

1,1-Dimethylethyl *trans*-(±)-hexahydro-4-hydroxy-3-(methoxyamino)-1*H*-azepine-1-carboxylate (8a): IR ($CHCl_3$) 3600−3200 (OH, NH), 1680 (NCOO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.66 (1H, ddd, J = 4, 1.5, 0.5 Hz), 3.54 (3H, s), 3.55−3.03 (4H, m), 2.85 (1H, m), 2.05−1.70 (2H, m), 1.70−1.40 (2H, m), 1.48 (9H, s); HRMS calcd for $C_{12}H_{24}N_2O_4$ (M^+) 260.1735, found 260.1741.

1,1-Dimethylethyl *cis*-(±)-hexahydro-4-hydroxy-3-[(phenylmethoxy)amino]-1*H*-azepine-1-carboxylate (7b): IR ($CHCl_3$) 3600−3300 (OH, NH), 1682 (NCOO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42−7.28 (5H, m), 4.70 (2H, s), 4.05 (1H, m), 3.66−3.07 (5H, m), 2.08−1.55 (4H, m), 1.44 (9H, s); HRMS calcd for $C_{18}H_{28}N_2O_4$ (M^+) 336.2047, found 336.2036.

1,1-Dimethylethyl *trans*-(±)-hexahydro-4-hydroxy-3-[(phenylmethoxy)amino]-1*H*-azepine-1-carboxylate (8b): IR ($CHCl_3$) 3600−3300 (OH, NH), 1681 (NCOO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42−7.25 (5H, m), 4.70 and 4.68 (2H, ABq, J = 14 Hz), 3.71−2.83 (6H, m), 2.00−1.40 (4H, m), 1.44 (9H, s); HRMS calcd for $C_{18}H_{28}N_2O_4$ (M^+) 336.2047, found 336.2032.

Radical Cyclization Using SmI_2. To a solution of HMPA (3.0 mL, 17.2 mmol), *t*-BuOH (0.2 mL, 2.15 mmol), and SmI_2 (0.1 M in THF) (43.1 mL, 4.31 mmol) was added dropwise a solution of **2b** (300 mg, 0.862 mmol) in THF (10 mL) under an argon atmosphere at −78 °C. After being stirred at the same temperature for 2 h, the reaction mixture was slowly allowed to warm to room temperature over 10 h. After the solvent was evaporated at reduced pressure, the resulting residue was diluted with Et_2O and filtered through a pad of Celite. After the filtrate was concentrated at reduced pressure, purification of the residue by medium-pressure column chromatography (AcOEt/hexane 3:2) afforded **7b** (133 mg, 46%) and **8b** (20 mg, 7%) as colorless oils.

1,1-Dimethylethyl *trans*-(±)-Hexahydro-4-hydroxy-3-[[4-(phenylmethoxy)benzoyl]amino]-1*H*-azepine-1-carboxylate (9). From 8a. A suspension of PtO_2 (25 mg, 0.11 mmol) in MeOH (1 mL) was stirred under a hydrogen atmosphere at room temperature for 1 h. To this suspension was added a solution of **8a** (50 mg, 0.19 mmol) in MeOH (6 mL). After being stirred under a hydrogen atmosphere at room temperature for 5 h, the reaction mixture was filtered and the filtrate was concentrated at reduced pressure to afford the crude amine. To a solution of the resulting crude amine in CH_2Cl_2 (3 mL) were added a solution of $NaHCO_3$ (18 mg, 0.21 mmol) in H_2O (0.5 mL) and a solution of *p*-(benzyloxy)-benzoyl chloride (52 mg, 0.21 mmol) in CH_2Cl_2 (1 mL) under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 2.5 h, the reaction mixture was extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (AcOEt/hexane 2:1) afforded **9** (46 mg, 55%) as a white powder. **From 8b.** Following the same procedure as above, compound **9** was obtained from **8b** in 58% yield as a white powder. The presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances: IR ($CHCl_3$) 1666, 1630 (NCOO, NHCO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.95 (1H, br d, J = 5 Hz), 7.86 (2H, br d, J = 9 Hz), 7.46−7.32 (5H, m), 7.02 (2H, br d, J = 9 Hz), 5.12 (2H, s), 4.12−4.02 (3H, m), 3.78 (1H, m), 3.28 (1H, dd, J = 15, 5.5 Hz), 2.73 (1H, td, J = 13, 3.5 Hz), 1.98−1.59 (4H, m), 1.49 (9H, s); ^{13}C NMR ($CDCl_3$) δ 168.5, 161.6, 157.3, 136.4, 129.1, 128.7, 128.1, 127.5, 125.9, 114.7, 80.8, 79.8, 70.1, 60.8, 50.6, 49.9, 32.8, 28.4, 27.3; HRMS calcd for $C_{25}H_{32}N_2O_5$ (M^+) 440.2309, found 440.2298.

1,1-Dimethylethyl [3*R*-[3α,4*β*(*S)])-Hexahydro-3-[[4-(phenyl methoxy)benzoyl]amino]-4-[2-[[(phenylmethoxy)-carbonyl]amino]-1-oxopropoxy]-1*H*-azepine-1-carboxylate (10a) and 1,1-Dimethylethyl [3*S*-[3α,4*β*(*R**)])-Hexahydro-3-[[4-(phenylmethoxy)benzoyl]amino]-4- [2-[[(phenylmethoxy)carbonyl]amino]-1-oxopropoxy]-1*H*-azepine-1- carboxylate (11a).** To a solution of 2-chloro-1-methylpyridinium iodide (12.3 mg, 0.047 mmol), Et_3N (15.3 mg, 0.15 mmol), and a catalytic amount of DMAP in CH_2Cl_2 (0.34 mL) were added **9** (15 mg, 0.034 mmol) and *N*-Z-L-alanine (7.6 mg, 0.034 mmol) under a nitrogen atmosphere at room temperature. After the reaction mixture was heated at reflux for 10 h, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (AcOEt/hexane 2:1) afforded a mixture of **10a** and **11a** (11.2 mg, 51%) as a white powder and **9** (3.4 mg, 23%). The presence of rotamers precluded a comprehensive assignment of all proton resonances: IR ($CHCl_3$) 1720 (COO), 1705 (NCO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.00 (1/2H, d, J = 8 Hz), 7.93 (1/2H, br d, J = 8 Hz) 7.75 (2H, br d, J = 9 Hz), 7.46−7.28 (10H, m), 6.97 (2H, br d, J = 9 Hz), 5.75 (1/2H, br m) 5.45 (1/2H, br m), 5.05 (1H, m), 5.09 (4H, s), 4.52−4.24 (2H, m), 4.04−3.86 (2H, m), 3.29 (1H, br m), 2.82 (1H, br m), 2.00−1.20 (7H, m), 1.52 (9H, s); HRMS calcd for $C_{36}H_{43}N_3O_8$ (M^+) 645.3047, found 645.3029.

1,1-Dimethylethyl [3*R*-[3α,4*β*(*S)])-Hexahydro-3-[[4-(phenylmethoxy)benzoyl]amino]-4-[[(4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]hept-1-yl)carbonyl]oxy]-1*H*-azepine-1-carboxylate (10b) and 1,1-Dimethylethyl [3*S*-[3α,4*β*(*R**)])-Hexahydro-3-[[4-(phenylmethoxy)benzo-**

yl]amino]-4-[[(4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]-hept-1- yl)carbonyl]oxy]-1*H*-azepine-1-carboxylate (11b). To a solution of **9** (9.8 mg, 0.023 mmol), Et_3N (2.4 mg, 0.024 mmol), and a catalytic amount of DMAP in CH_2Cl_2 (2 mL) was added *S*-camphanic acid chloride (26.5 mg, 0.12 mmol) under a nitrogen atmosphere at room temperature. After being stirred at 50 °C for 30 min, the reaction mixture was diluted with 3% HCl and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (AcOEt/hexane 3:2) afforded a mixture of **10b** and **11b** (13.8 mg, quantitative) as a white powder. The presence of rotamers precluded a comprehensive assignment of all proton resonances: IR ($CHCl_3$) 1740 (COO), 1660 (NCO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.88 (1H, br d, J = 5.5 Hz), 7.79, 7.76 (each 1H, br d, J = 9 Hz), 7.45−7.31 (5H, m), 6.99, 6.98 (each 1H, br d, J = 9 Hz), 5.34 (1/2H, br t, J = 7 Hz), 5.23 (1/2H, br t, J = 7 Hz), 5.11 (2H, s), 4.39 (1H, m), 4.04 (1H, br m), 3.90 (1H, m), 3.34 (1H, dd, J = 15, 4 Hz), 2.95 (1H, m), 2.50−0.80 (17H, m), 1.53 (9H, s); HRMS calcd for $C_{35}H_{44}N_2O_8$ (M^+) 620.3095, found 620.3080.

1,1-Dimethylethyl [3*R*-[3α,4*β*(*S)]]-Hexahydro-3-[[4-(phenylmethoxy)benzoyl]amino]-4-(3,3,3-trifluoro-2-methoxy-1-oxo-2-phenylpropoxy)-1*H*-azepine-1-carboxylate (10c) and 1,1-Dimethylethyl [3*S*-[3α,4*β*(*R**)]]-Hexahydro-3-[[4-(phenylmethoxy)benzoyl]amino]-4-(3,3,3-trifluoro-2-methoxy-1-oxo-2-phenylpropoxy)-1*H*-azepine-1-carboxylate (11c).** To a solution of **9** (144 mg, 0.33 mmol), Et_3N (66 mg, 0.65 mmol), and DMAP (37 mg, 0.3 mmol) in CH_2Cl_2 (1.7 mL) was added dropwise a solution of (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (96 mg, 0.38 mmol) in CH_2Cl_2 (1.7 mL) under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 7.5 h, the reaction mixture was concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (AcOEt/hexane 7:4) afforded **10c** (101 mg, 47%) and **11c** (95 mg, 44%) as white powders. The presence of rotamers precluded a comprehensive assignment of all proton resonances. **10c**: $[\alpha]^{20}_D$ −53.3 (*c* 0.77, MeOH); IR ($CHCl_3$) 1750 (COO), 1661 (NCO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.83 (1H, br s), 7.75 (2H, br d, J = 9 Hz), 7.56−7.18 (10H, m), 6.98 (2H, br d, J = 9 Hz), 5.56 (1H, br m), 5.12 (2H, s), 4.27 (1H, br m), 4.10 (1H, br d, J = 15 Hz), 3.72 (1H, br m), 3.50 (3H, s), 3.16 (1H, d, J = 15 Hz), 2.86 (1H, br m), 2.14−1.10 (4H, m), 1.51 (9H, s); HRMS calcd for $C_{35}H_{39}N_2O_7F_3$ (M^+) 656.2706, found 656.2697. **11c**: $[\alpha]^{20}_D$ −2.6 (*c* 2.43, MeOH); IR ($CHCl_3$) 1750 (COO), 1660 (NCO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.91 (1H, br d, J = 4.5 Hz), 7.80 (2H, br d, J = 8.5 Hz), 7.60−7.22 (10H, m), 6.99 (2H, br d, J = 8.5 Hz), 5.50 (1H, br m), 5.11 (2H, s), 4.33 (1H, br m), 4.05 (1H, br d, J = 15 Hz), 3.72 (1H, br m), 3.50 (3H, s), 3.19 (1H, br d, J = 15 Hz), 2.81 (1H, br m), 2.17−1.17 (4H, m), 1.51 (9H, s); HRMS calcd for $C_{35}H_{39}N_2O_7F_3$ (M^+) 656.2706, found 656.2698.

1,1-Dimethylethyl (3*R*-*trans*)-Hexahydro-4-hydroxy-3-[[4-(phenylmethoxy)benzoyl]amino]-1*H*-azepine-1-carboxylate ((3*R*,4*R*)-9). To a solution of **10c** (89 mg, 0.14 mmol) in MeOH (3.7 mL) was added a methanolic solution of KOH (1M, 1.5 mL) at room temperature. After being stirred at the same temperature for 5 h, the reaction mixture was concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (AcOEt/hexane 4:1) afforded (3*R*,4*R*)-**9** (59.3 mg, quantitative) as colorless crystals. This compound was identical with an authentic sample upon comparison of their spectral data.[6] The presence of rotamers precluded a comprehensive assignment of all proton resonances: mp 136−138 °C (Et_2O/petroleum ether) [lit.[6] mp 115−117 °C]; $[\alpha]^{20}_D$ −2.9 (*c* 1.30, MeOH) [lit.[6] $[\alpha]_D$ −8.9 (*c* 1.98, MeOH)]. Anal. Calcd for $C_{25}H_{32}N_2O_5$: C, 68.16; H, 7.32; N, 6.36. Found: C, 67.89; H, 7.34; N, 6.20.

1,1-Dimethylethyl (3*S*-*trans*)-Hexahydro-4-hydroxy-3-[[4-(phenylmethoxy)benzoyl]amino]-1*H*-azepine-1-carboxylate ((3*S*,4*S*)-9). Following the same procedure as for (3*R*,4*R*)-**9**, compound (3*S*,4*S*)-**9** was obtained from **11c** in almost quantitative yield: mp 136−138 °C (Et_2O/petroleum ether); $[\alpha]^{20}_D$ +2.5 (*c* 1.26, MeOH). Anal. Calcd for $C_{25}H_{32}N_2O_5$2/3H_2O: C, 66.35; H, 7.43; N, 6.19. Found: C, 66.38; H, 7.24; N, 6.03.

Enzymatic Optical Resolution Using Lipase. To a solution of **9** (435 mg, 0.99 mmol) and vinyl acetate (2.57 g, 0.030 mol) in *t*-BuOMe (10 mL) was added immobilized lipase from *Pseudomonas* sp. (0.5 unit/mg) (1.58 g) under a nitrogen atmosphere at room temperature. The reaction mixture was stirred at 20 °C for 12 h and then at 45 °C for 8 h. After dilution with CH_2Cl_2, the reaction mixture was filtered and the filtrate was concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (AcOEt/hexane 2:1) afforded **12** (200 mg, 42%) as a white powder and recovered (3*S*,4*S*)-**9** (213 mg, 49%) as a white powder.

1,1-Dimethylethyl (3*S*-*trans*)-4-(Acetyloxy)hexahydro-3-[[4-(phenylmethoxy)benzoyl]amino]-1*H*-azepine-1-carboxylate (12). The presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances: $[\alpha]^{20}_D$ +5.5 (*c* 1.27, MeOH); IR ($CHCl_3$) 1727 (COO), 1660 (NCO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.78 (2H, br d, J = 8.5 Hz), 7.73 (1H, br s), 7.50−7.29 (5H, m), 6.98 (2H, br d, J = 8.5 Hz), 5.10 (2H, s), 5.07 (1H, br m), 4.38 (1H, br m), 3.93 (1H, m), 3.59 (1H, br m), 3.32 (1H, dd, J = 15, 3 Hz), 2.91 (1H, br m), 2.02 (3H, s), 2.13−1.34 (4H, m), 1.52 (9H, s); ^{13}C NMR ($CDCl_3$) δ 172.6, 166.1, 136.3, 128.7, 128.5, 128.0, 127.3, 126.7, 114.4, 80.5, 74.9, 69.9, 53.9, 49.1, 48.7, 28.2, 27.6, 23.5, 21.0; HRMS calcd for $C_{27}H_{34}N_2O_6$ (M^+) 482.2415, found 482.2422.

Phenylmethyl (3*R*-*trans*)-4-(Acetyloxy)hexahydro-3-[[4-(phenylmethoxy)benzoyl]amino]-1*H*-azepine-1-carboxylate (13). To a solution of **12** (174 mg, 0.36 mmol) in CH_2Cl_2 (4.0 mL) was added dropwise TFA (0.5 mL, 6.5 mmol) under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 4 h, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and concentrated at reduced pressure to afford the crude amine. To the resulting crude amine in acetone (4.0 mL) were successively added a solution of Na_2CO_3 (31.7 mg, 0.30 mmol) in H_2O (0.14 mL) and a solution of benzyloxycarbonyl chloride (90 mg, 0.53 mmol) in acetone (1.0 mL) under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 14 h, the reaction mixture was concentrated at reduced pressure. After dilution with H_2O, the mixture was extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (AcOEt/hexane 2:1) afforded **13** (162 mg, 87%) as a white powder. The presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances: mp 129−131 °C (AcOEt/hexane); $[\alpha]^{20}_D$ +9.3 (*c* 1.10, MeOH); IR ($CHCl_3$) 1729 (COO), 1684, 1656 (NCOO, NHCO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.73 (2H, br d, J = 8 Hz), 7.63−6.81 (11H, m), 6.98 (2H, br d, J = 8 Hz), 5.25−4.94 (5H, m), 4.40 (1H, br m), 4.02 (1H, br m), 3.69 (1H, br m), 3.40 (1H, dd, J = 15.5, 4.5 Hz), 2.88 (1H, m), 2.02 (3H, s), 2.06−1.70 (4H, m); ^{13}C NMR ($CDCl_3$) δ 170.1, 166.1, 161.1, 157.6, 136.3, 136.2, 128.7, 128.44, 128.39, 128.0, 127.9, 127.6, 127.2, 126.6, 114.4, 75.0, 69.8, 67.5, 53.7, 49.6, 48.4, 27.9, 23.7, 20.9; HRMS calcd for $C_{30}H_{32}N_2O_6$ (M^+) 516.2258, found 516.2268.

Phenylmethyl (3*R*-*trans*)-Hexahydro-4-hydroxy-3-[[4-(phenylmethoxy)benzoyl]amino]-1*H*-azepine-1-carboxylate (14). To a solution of **13** (130 mg, 0.25 mmol) in MeOH (7.0 mL) was added a methanolic solution of KOH (1 M, 3.0 mL) at room temperature. After being stirred at the same temperature for 2 h, the reaction mixture was concentrated under reduced pressure. Purification of the residue by medium-pressure column chromatography (AcOEt/hexane 4:1) afforded **14** (121 mg, quantitative) as colorless crystals. The presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances. This compound was identical with an authentic sample upon comparison of their spectral data:[5,7] mp 101−103 °C (AcOEt) [lit.[5] mp 123−124.5 °C (lit.[7] mp 132−134 °C)]; $[\alpha]^{20}_D$ −6.5 (*c* 1.09, MeOH); IR ($CHCl_3$) 3500−3200 (OH), 1671, 1630 (NCOO, NHCO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.68 (1H, br d, J = 3.5 Hz), 7.82 (2H, br d, J = 8.5

Hz), 7.53−7.18 (10H, m), 7.00 (2H, br d, J = 8.5 Hz), 5.19, 5.10 (each 2H, s), 4.29−3.93 (3H, m), 3.78 (1H, br m), 3.33 (1H, dd, J = 15, 3 Hz), 2.80 (1H, m), 2.14−1.50 (4H, m); ^{13}C NMR ($CDCl_3$) δ 167.9, 161.2, 157.4, 136.0, 135.9, 128.7, 128.3, 128.2, 127.8, 127.7, 127.3, 127.1, 125.4, 114.3, 78.0, 69.6, 67.3, 59.8, 49.5, 49.4, 31.7, 26.0; HRMS calcd for $C_{28}H_{30}N_2O_5$ (M^+) 474.2153, found 474.2155.

Methyl 2-(2-Hydroxy-6-methoxy-4-methylbenzoyl)-3-methoxybenzoate (22) and Methyl 2-(2-Hydroxy-6-methoxybenzoyl)-3-methoxy-5-methylbenzoate (23). A solution of **17c** (231 mg, 0.74 mmol) in Et_2O (200 mL) was irradiated with a halogen lamp through a Pyrex filter under oxygen bubbling at 30 °C for 1.5 h. The solvent was evaporated at reduced pressure to afford the crude oxygen adduct. To a solution of the crude oxygen adduct in acetone (100 mL) was added a catalytic amount of concentrated H_2SO_4 under a nitrogen atmosphere at room temperature. After the mixture was stirred at the same temperature for 12 h, the solvent was evaporated at reduced pressure. After dilution with H_2O, the mixture was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (AcOEt/hexane 1:6) afforded a mixture of **22** and **23** (138 mg, 57%) as colorless crystals and **16c** (63 mg, 30%) as yellow crystals. **22**: IR ($CHCl_3$) 1721 (ArCOO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 12.95 (1H, s), 7.62 (1H, dd, J = 8, 1 Hz), 7.37 (1H, t, J = 8 Hz), 7.11 (1H, dd, J = 8, 1 Hz), 6.47 (1H, br s), 6.05 (1H, br s), 3.75 (3H, s), 3.72 (3H, s), 3.31 (3H, s), 2.29 (3H, s); ^{13}C NMR ($CDCl_3$) δ 199.5, 166.2, 164.3, 160.9, 155.6, 148.0, 135.1, 128.7, 127.5, 121.8, 115.1, 111.1, 110.2, 102.9, 56.3, 55.6, 52.1, 22.5; HRMS calcd for $C_{18}H_{18}O_6$ (M^+) 330.1102, found 330.1091. **23**: IR ($CHCl_3$) 1720 (ArCOO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 12.92 (1H, s), 7.43 (1H, br s), 7.33 (1H, t, J = 8.5 Hz), 6.93 (1H, br s), 6.63 (1H, dd, J = 8.5, 1 Hz), 6.25 (1H, dd, J = 8.5, 1 Hz), 3.73 (3H, s), 3.70 (3H, s), 3.35 (3H, s), 2.43 (3H, s); ^{13}C NMR ($CDCl_3$) δ 200.5, 166.4, 164.2, 161.1, 155.5, 139.0, 136.1, 132.5, 127.4, 122.2, 116.0, 112.5, 110.7, 101.6, 56.2, 55.7, 52.1, 21.6; HRMS calcd for $C_{18}H_{18}O_6$ (M^+) 330.1102, found 330.1104. **22** + **23**. Anal. Calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.26; H, 5.47.

Methyl 2-(2-Hydroxy-6-methoxybenzoyl)-3-methoxybenzoate (18). Following the same procedure as for **22** and **23**, compounds **18** (67% yield as a colorless solid) and **16a** (23% yield as yellow crystals) were obtained from **17a**: IR ($CHCl_3$) 1721 (ArCOO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 12.90 (1H, s), 7.62 (1H, dd J = 8.1, 0.9 Hz), 7.38 (1H, t, J = 8.1 Hz), 7.33 (1H, t, J = 8.3 Hz), 7.12 (1H, dd, J = 8.1, 0.9 Hz), 6.64 (1H, dd, J = 8.3, 1 Hz), 6.24 (1H, dd, J = 8.3, 1 Hz), 3.74 (3H, s), 3.72 (3H, s), 3.32 (3H, s); ^{13}C NMR ($CDCl_3$) δ 200.3, 166.2, 164.2, 161.0, 155.6, 136.3, 135.1, 128.8, 127.5, 121.8, 115.2, 112.3, 110.7, 101.6, 56.3, 55.6, 52.1; HRMS calcd for $C_{17}H_{16}O_6$ (M^+) 316.0946, found 316.0962.

Methyl 2-(2,3,6-Trimethoxybenzoyl)benzoate (20). Following the same procedure as for **22** and **23**, compounds **20** (27% yield as colorless crystals) and **16b** (31% yield as yellow crystals) were obtained from **17b**: mp 115.5−117 °C (AcOEt/hexane); IR ($CHCl_3$) 1731 (ArCOO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.29 (1H, d, J = 7.8 Hz), 8.19 (2H, m), 7.66 (2H, m), 5.76 (1H, d, J = 7.8 Hz), 4.04 (3H, s), 3.90 (3H, s), 3.88 (3H, s), 3.87 (3H, s); ^{13}C NMR ($CDCl_3$) δ 192.1, 171.6, 166.5, 151.2, 150.9, 129.6, 129.2, 128.2, 123.3, 123.2, 122.7, 120.0, 107.0, 77.1, 63.6, 62.5, 56.7, 52.3; SIMS calcd for $C_{18}H_{18}O_6$ (QM^+) 330.1102, found 330.1126. Anal. Calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.17; H, 5.39.

Methyl 2-(2,6-Dimethoxy-4-methylbenzoyl)-3-methoxybenzoate (24) and Methyl 2-(2,6-Dimethoxybenzoyl)-3-methoxy-5-methylbenzoate (25). To a stirred suspension of NaH (60% oil suspension) (182 mg, 4.55 mmol) in DMF (15 mL) was added a solution of a mixture of **22** and **23** (1.0 g, 3.03 mmol) under a nitrogen atmosphere at room temperature. After the mixture was stirred at the same temperature for 20 min, MeI (0.26 mL, 4.24 mmol) was added to the reaction mixture, which was stirred at the same temperature for 30 min. After dilution with Et_2O, the organic phase was washed with water and brine, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (AcOEt/hexane 1:1) afforded **24** (409 mg, 39%) and **25** (431 mg, 41%) both as colorless crystals. **24**: mp 118−119 °C (AcOEt/hexane); IR ($CHCl_3$) 1721 (ArCOO), 1665 (ArCOAr) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.47 (1H, dd, J = 8, 1 Hz), 7.32 (1H, t, J = 8 Hz), 7.04 (1H, dd, J = 8, 1 Hz), 6.35 (2H, s), 3.71 (3H, s), 3.68 (3H, s), 3.64 (6H, s), 2.33 (3H, s); ^{13}C NMR ($CDCl_3$) δ 192.0, 167.5, 160.1, 156.9, 143.9, 135.3, 129.6, 128.9, 121.7, 116.3, 115.2, 105.7, 56.6, 56.1, 52.0, 22.4; HRMS calcd for $C_{19}H_{20}O_6$ (M^+) 344.1258, found 344.1229. Anal. Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85. Found: C, 66.00; H, 5.84. **25**: mp 161−162 °C (AcOEt/hexane); IR ($CHCl_3$) 1720 (ArCOO), 1667 (ArCOAr) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.29 (1H, t, J = 8.5 Hz), 7.19 (1H, s), 6.83 (1H, s), 6.54 (2H, d, J = 8.5 Hz), 3.70 (3H, s), 3.67 (6H, s), 3.64 (3H, s), 2.37 (3H, s); ^{13}C NMR ($CDCl_3$) δ 192.2, 168.4, 159.4, 157.5, 140.5, 132.1, 131.3, 130.6, 122.0, 119.8, 115.8, 104.7, 56.5, 56.2, 52.1, 21.6; HRMS calcd for $C_{19}H_{20}O_6$ (M^+) 344.1258, found 344.1264. Anal. Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85. Found: C, 66.30; H, 5.87.

Methyl 2-[4-(Bromomethyl)-2,6-dimethoxybenzoyl]-3-methoxybenzoate (26). To a boiling solution of **24** (35 mg, 0.10 mmol) in CCl_4 (1 mL) were added NBS (19 mg, 0.1 mmol) and AIBN (1.7 mg, 0.01 mmol) under a nitrogen atmosphere. The reaction mixture was heated at reflux for 30 min. After dilution with H_2O, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (AcOEt/hexane 1:1) afforded **26** (24 mg, 57%) and **24** (5.3 mg, 15%) both as colorless crystals: mp 129−130 °C (AcOEt/hexane); IR ($CHCl_3$) 1719 (ArCOO), 1666 (ArCOAr) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45 (1H, dd, J = 8, 1 Hz), 7.36 (1H, t, J = 8 Hz), 7.04 (1H, dd, J = 8, 1 Hz), 6.57 (2H, s), 4.42 (2H, s), 3.72 (3H, s), 3.69 (3H, s), 3.69 (6H, s); ^{13}C NMR ($CDCl_3$) δ 191.7, 167.6, 159.9, 157.1, 142.2, 134.0, 130.4, 129.6, 121.7, 118.9, 115.1, 105.5, 56.5, 56.3, 52.2, 33.2; HRMS calcd for $C_{19}H_{19}O_6{}^{79}Br$ (M^+) 422.0363, found 422.0374; calcd for $C_{19}H_{19}O_6{}^{81}Br$ (M^+) 424.0343, found 424.0358. Anal. Calcd for $C_{19}H_{19}O_6Br$: C, 53.92; H, 4.52. Found: C, 53.72; H, 4.40.

Phenylmethyl 2-[4-(Bromomethyl)-2,6-bis(phenylmethoxy)benzoyl]-3-(phenylmethoxy)benzoate (27). To a solution of **26** (120 mg, 0.28 mmol) in CH_2Cl_2 (5 mL) was added BBr_3 (70 mg, 0.28 mmol) under a nitrogen atmosphere at room temperature. The reaction mixture was stirred at the same temperature for 5 days. After the mixture was quenched with 10% HCl saturated with NaCl, the layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was dried over $MgSO_4$ and concentrated at reduced pressure to afford the crude triphenolic acid. To a solution of the crude triphenolic acid in DMF (5.7 mL) were added K_2CO_3 (554 mg, 4.0 mmol) and benzyl bromide (0.33 mL, 2.8 mmol) under a nitrogen atmosphere at room temperature. The reaction mixture was stirred at the same temperature for 4.5 h. After dilution with Et_2O, the organic phase was washed with water and brine, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (AcOEt/hexane 1:3) afforded **27** (57 mg, 28%) as colorless crystals: mp 119−120 °C (AcOEt/hexane); IR ($CHCl_3$) 1720 (ArCOO), 1665 (ArCOAr) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.25−7.11 (16H, m), 7.08−6.98 (4H, m), 6.96−6.86 (3H, m), 6.52 (2H, s), 5.09, 4.73 (each 2H, s), 4.70 (4H, s), 3.89 (2H, s); ^{13}C NMR ($CDCl_3$) δ 191.6, 166.9, 158.8, 155.8, 141.7, 136.2, 136.1, 135.8, 134.4, 131.8, 129.7, 128.3, 128.2, 127.9, 127.6, 127.5, 127.4, 127.2, 122.3, 115.6, 106.5, 70.4, 66.9, 33.3; SIMS calcd for $C_{43}H_{35}O_6{}^{79}Br$ + H (QM^+) 727.1693, found 727.1699; calcd for $C_{43}H_{35}O_6{}^{81}Br$ + H (QM^+) 729.1673, found 729.1700. Anal. Calcd for $C_{43}H_{35}O_6Br$: C, 70.98; H, 4.85. Found: C, 71.59; H, 4.83.

Phenylmethyl 2-[4-(Hydroxymethyl)-2,6-bis(phenylmethoxy)benzoyl]-3-(phenylmethoxy)benzoate (28). A mixture of **27** (129 mg, 0.177 mmol) and $CaCO_3$ (86 mg, 0.86 mmol) in dioxane (5.8 mL) and water (3 mL) was heated at reflux under a nitrogen atmosphere for 15 h. The reaction mixture was concentrated at reduced pressure. After dilution

with H_2O, the aqueous phase was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (AcOEt/hexane 1:1) afforded **28** (93 mg, 79%) as colorless crystals. This compound was identical with an authentic sample upon comparison of their spectral data:[5] mp 142−143 °C (AcOEt/hexane) (lit.[5] mp 138.5−139.5 °C); IR ($CHCl_3$) 1722 (ArCOO), 1661 (ArCOAr) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28−7.16 (14H, m), 7.16−6.86 (8H, m), 6.90 (1H, dd, J = 8, 1 Hz), 6.50 (2H, s), 5.13 (2H, s), 4.77 (6H, s), 4.60 (2H, s); ^{13}C NMR ($CDCl_3$) δ 192.2, 166.9, 159.1, 155.8, 146.0, 136.5, 136.3, 135.9, 134.3, 131.7, 129.6, 128.22, 128.16, 127.8, 127.6, 127.5, 127.1, 122.2, 118.7, 115.7, 103.6, 70.4, 66.8, 65.0; HRMS calcd for $C_{43}H_{36}O_7$ (M^+) 664.2459, found 664.2437.

Phenylmethyl 2-[4-Formyl-2,6-bis(phenylmethoxy)-benzoyl]-3-(phenylmethoxy)benzoate (29). To a solution of **28** (51 mg, 0.077 mmol) in acetonitrile (0.4 mL) were added NMO (13.5 mg, 0.115 mmol) and TPAP (1.4 mg, 0.004 mmol) in the presence of 4 Å molecular sieves under a nitrogen atmosphere at room temperature. The reaction mixture was stirred at the same temperature for 30 min. After dilution with AcOEt, the reaction mixture was filtered, and the filtrate was concentrated at reduced pressure. Purification of the residue by flash column chromatography (AcOEt/hexane 1:1) afforded **29** (31 mg, 61%) as colorless crystals. This compound was identical with an authentic sample upon comparison of their spectral data:[5] ^1H NMR ($CDCl_3$) δ 9.80 (1H, s), 7.33 (1H, t, J = 8 Hz), 7.26−7.15 (13H, m), 7.12−7.04 (6H, m), 6.97 (1H, dd, J = 8, 1 Hz), 6.90 (2H, s), 6.83 (1H, dd, J = 8, 1 Hz), 5.14 (2H, s), 4.81 (4H, s), 4.70 (2H, s); ^{13}C NMR ($CDCl_3$) δ 191.4, 191.3, 167.6, 158.2, 156.6, 138.1, 135.9, 135.7, 135.5, 133.4, 131.3, 131.0, 128.31, 128.26, 128.2, 127.9, 127.7, 127.1, 125.4, 122.0, 115.1, 106.5, 70.6, 70.4, 67.2; HRMS calcd for $C_{43}H_{34}O_7$ (M^+) 662.2302, found 662.2287.

3,5-Bis(phenylmethoxy)-4-[2-(phenylmethoxy)-6-[(phenylmethoxy)carbonyl]benzoyl]benzoic Acid (30). To a solution of **29** (31 mg, 0.0467 mmol) in THF (0.2 mL), *t*-BuOH (0.2 mL), and H_2O (0.07 mL) were added 2-methyl-2-butene (2.0 M in THF, 0.19 mL), NaH_2PO_4 (1.0 M in H_2O, 0.14 mL) and 80% $NaClO_2$ (16 mg, 0.14 mmol) under a nitrogen atmosphere at room temperature. The reaction mixture was stirred at the same temperature for 3 h. The reaction mixture was concentrated at reduced pressure. After dilution with aqueous $KHSO_4$ (0.5 M), the aqueous phase was extracted with AcOEt. The organic phase was washed with H_2O, saturated aqueous Na_2SO_3, and brine, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by flash column chromatography (MeOH/CH_2Cl_2 1:20) afforded **30** (26.6 mg, 84%) as colorless crystals. This compound was identical with an authentic sample upon comparison of their spectral data:[5−7] mp 155−157 °C (AcOEt/hexane) (lit.[5] mp 158−160.5 °C; lit.[6] mp 151−156 °C; lit.[7] mp 132−134 °C); IR ($CHCl_3$) 1720 (ArCOO), 1671 (ArCOAr) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35−7.00 (22H, m), 6.95 (1H, dd, J = 8, 1.5 Hz), 6.85 (2H, br m), 5.13 (2H, s), 4.77 (4H, s), 4.69 (2H, s); ^{13}C NMR ($CDCl_3$) δ 191.6, 171.0, 167.5, 157.9, 156.5, 136.1, 135.8, 135.6, 133.0, 131.9, 131.6, 130.7, 128.3, 128.2, 127.9, 127.6, 127.2, 124.6, 122.0, 115.3, 114.4, 107.2, 70.6, 70.4, 67.1; HRMS calcd for $C_{43}H_{34}O_8$ (M^+) 678.2251, found 678.2246.

1,1-Dimethylethyl (3*R*-*trans*)-4-[[3,5-Bis(phenylmethoxy)-4-[2-(phenylmethoxy)-6-[(phenylmethoxy)carbonyl]-benzoyl]benzoyl]oxy]hexahydro-3-[[4-(phenylmethoxy)-benzoyl]amino]-1*H*-azepine-1-carboxylate (31a). To a solution of (3*R*,4*R*)-**9** (8.8 mg, 0.02 mmol) and **30** (13.3 mg, 0.02 mmol) in CH_2Cl_2 (0.2 mL) were added 2-chloro-1-methylpyridinium iodide (6.64 mg, 0.026 mmol) and triethylamine (0.0056 mL, 0.04 mmol) under a nitrogen atmosphere at room temperature. After the mixture was stirred at the same temperature for 30 min, DMAP (1.2 mg, 0.01 mmol) was added to the reaction mixture. After being stirred at the same temperature for 24 h, the reaction mixture was concentrated at reduced pressure. Purification of the residue by preparative TLC (AcOEt/hexane 2:3) afforded **31a** (17 mg, 77%) as colorless crystals. The presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances. This compound was identical with an authentic sample upon comparison of their spectral data:[6] $[\alpha]^{27}_D$ −63.9 (*c* 0.85, MeOH); IR ($CHCl_3$) 1713 (ArCOO), 1661 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.03 (1/2H, br d, J = 8.5 Hz), 7.76 (3/2H, br d, J = 8.5 Hz), 7.42−6.79 (33H, m), 5.10, 5.05, 4.84, 4.83, 4.67 (each 2H, s), 5.03, 4.81 (each 1H, m), 4.08 (1H, d, J = 15 Hz), 4.00 (1H, d, J = 12 Hz), 3.34 (1H, dd, J = 15, 4 Hz), 2.83 (1H, br m), 2.12−1.23 (4H, m), 1.56 (9H, s); ^{13}C NMR ($CDCl_3$) δ 191.6, 167.4, 166.0, 165.6, 161.3, 158.0, 157.5, 156.3, 136.4, 135.8, 132.7, 132.3, 130.4, 128.8, 128.6, 128.3, 128.2, 127.9, 127.8, 127.5, 127.43, 127.38, 127.2, 123.7, 122.0, 115.3, 114.6, 107.0, 93.4, 80.8, 77.8, 70.5, 70.0, 67.0, 53.6, 50.2, 49.6, 31.6, 29.7, 28.8, 28.4, 24.7, 22.6; SIMS calcd for $C_{68}H_{64}N_2O_{12}$ + H (QM^+) 1101.4533, found 1101.4563.

Phenylmethyl (3*R*-*trans*)-4-[[3,5-Bis(phenylmethoxy)-4-[2-(phenylmethoxy)-6-[(phenylmethoxy)carbonyl]benzoyl]oxy]hexahydro-3-[[4-(phenylmethoxy)benzoyl]amino]-1*H*-azepine-1-carboxylate (31b). Following the same procedure as for **31a**, compound **31b** was obtained from **14** and **30** in 77% yield as colorless crystals. This compound was identical with an authentic sample upon comparison of their spectral data.[5,7] The presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances: $[\alpha]^{23}_D$ −71.0 (*c* 1.08, MeOH); IR ($CHCl_3$) 1717 (ArCOO), 1660 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.78 (1/2H, br d, J = 8 Hz), 7.72 (3/2H, br d, J = 8 Hz), 7.55−6.78 (38H, m), 5.30−4.58 (2H, m), 5.25, 5.04, 4.83, 4.67 (each 2H, s), 5.10 (4H, s), 4.12 (2H, m), 3.42 (1H, br d, J = 14 Hz), 2.90 (1H, br m), 2.14−1.50 (4H, m); ^{13}C NMR ($CDCl_3$) δ 191.6, 167.3, 166.0, 165.6, 161.3, 158.0, 156.3, 136.4, 136.3, 135.8, 132.7, 132.4, 130.4, 128.9, 128.6, 128.24, 128.16, 127.9, 127.7, 127.5, 127.4, 127.3, 127.2, 122.0, 115.3, 114.6, 107.0, 77.9, 70.48, 70.46, 70.0, 67.9, 67.0, 53.5, 50.7, 49.3, 28.8, 24.9; SIMS calcd for $C_{71}H_{62}N_2O_{12}$ + H (QM^+) 1135.4377, found 1135.4372.

(−)-Balanol (1). According to Nicolaou's conditions,[5] palladium black (8 mg) was added to a solution of **31b** (30 mg, 0.0265 mmol) in formic acid (1.3 mL) at room temperature. After the mixture was stirred at the same temperature for 12 h, palladium black (16 mg) was added. After being stirred at the same temperature for 4.5 h, the reaction mixture was filtered and the filtrate was concentrated at reduced pressure. Purification of the residue by preparative TLC on silica gel (*t*-BuOH/AcOH/H_2O 4:1:1) followed by preparative TLC on C_{18} reversed-phase silica gel (acetonitrile/H_2O 2:3) afforded **1** (11.5 mg, 79%) as a yellow solid. This compound was identical with an authentic sample upon comparison of their spectral data:[3,5−7] $[\alpha]^{22}_D$ −106.7 (*c* 0.042, MeOH); IR (film) 1633 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.61 (2H, d, J = 8.5 Hz), 7.31 (1H, dd, J = 8, 1 Hz), 7.19 (1H, t, J = 8 Hz), 6.91 (2H, s), 6.84 (1H, dd, J = 8, 1 Hz), 6.76 (2H, d, J = 8.5 Hz), 5.22 (1H, m), 4.35 (1H, br m), 3.4−3.0 (4H, br m), 2.1−1.8 (4H, br m); ^{13}C NMR ($CDCl_3$) δ 203.8, 174.8, 170.3, 166.5, 162.3, 161.5, 154.5, 138.1, 136.3, 132.4, 130.5, 130.2, 125.7, 120.9, 118.7, 118.3, 116.1, 109.6, 77.0, 54.6, 30.3, 22.2; SIMS calcd for $C_{28}H_{26}N_2O_{10}$ − H (negative, M^+ − H) 549.1507, found 549.1500.

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Supporting Information Available: Experimental procedures and characterization of **16c** and **17a**−**c** and ^1H NMR data for all compounds (40 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.

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