Total Synthesis of (-)-Balanol

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Abstract: The total synthesis of (-)-balanol, a potent protein kinase C inhibitor, is described. The synthesis includes a radical cyclization approach to the hexahydroazepine-containing fragment and a biomimetic route to the benzophenone fragment.

Balanol **1**, isolated from the fungus *Verticillium balanoides*, has been shown to be a potent inhibitor of protein kinase C (PKC) enzymes that play an important role in cellular growth control, regulation and differentiation.[1] Since activation of PKC enzymes has been implicated in a number of diseases such as cancer, HIV infection and so on,[2] balanol and its analogues have been the new subject of synthetic studies for the development of potent and selective PKC inhibitors.[3,4] Here, we describe a total synthesis of balanol with novel routes to two distinct structural domains, a chiral hexahydroazepine-containing fragment and a benzophenone fragment (Figure 1). The preparation of enantiomerically pure hexahydroazepine-containing fragments was achieved through the SmI_2-promoted radical cyclization of the oxime ether followed by the lipase-catalyzed optical resolution of the racemic alcohols. The benzophenone fragment was prepared in short steps through a biomimetic oxidative anthraquinone ring cleavage starting from commercially available natural chrysophanic acid.

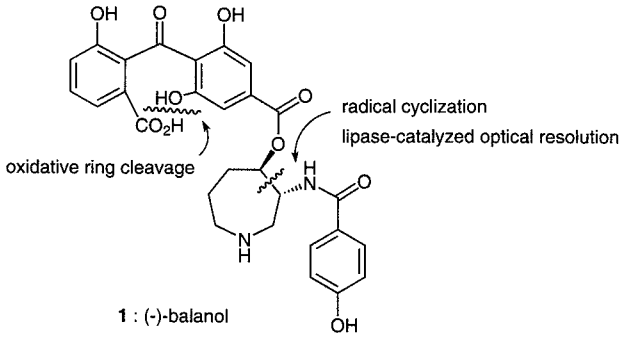
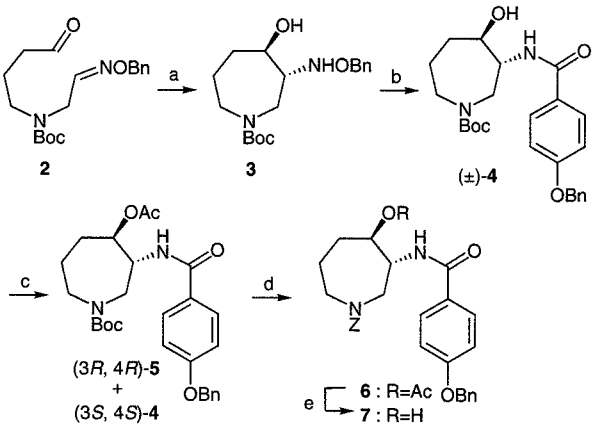


Figure 1. Synthetic routes for (-)-balanol **1**

Free radical-mediated cyclization has been an important method for the synthesis of various types of cyclic compounds which were mainly concentrated on five- or six-membered rings.[5] Thus, the radical-mediated construction of seven-membered compounds and its stereocontrol are subjects of considerable interest. In continuation of our studies on the stannyl radical cyclization of the aldehyde connected with oxime ether,[6] we now investigated the SmI_2-promoted radical cyclization for the *trans*-selective synthesis of the seven-membered cyclic amino alcohol (Scheme 1). The cyclization of the aldehyde **2**[6b] with SmI_2 took place smoothly in the presence of HMPA to give the *trans*-cyclized product **3** in 46% yield accompanied by a minor amount of the *cis*-product in 7% yield. In this case, the presence of HMPA as a ligand was found to be essential for the successful cyclization. It is thought that the chelation of the Sm(III) cation to the carbonyl and the oxime ether moieties is of critical importance for the sense of expected preferential formation of *trans*-seven-membered ring. Hydrogenolysis of the benzyloxyamino group in the *trans*-product **3** in the presence of platinum dioxide followed by *N*-acylation with *p*-(benzyloxy)benzoyl chloride afforded the racemic azepine (±)-**4**[3a] in 58% yield.



Scheme 1. *Reagents and conditions*: a) SmI_2, HMPA, *t*-BuOH, -78 °C - rt, 5 h, 46%; b) H_2, PtO_2, MeOH, rt, 5 h and then *p*-(benzyloxy)benzoyl chloride, $NaHCO_3$, H_2O, CH_2Cl_2, rt, 2 h, 58%; c) immobilized lipase, vinyl acetate, *t*-BuOMe, 20 - 45 °C, 20 h, 42% ((3*R*, 4*R*)-**5**, 96% *e.e.*) + 49% ((3*S*, 4*S*)-**4**, 82% *e.e.*); d) TFA, CH_2Cl_2, rt, 2 h and then ZCl, Na_2CO_3, H_2O, Me_2CO, rt, 14 h, 87%; e) KOH, MeOH, rt, 5 min, quant.

For the large-scale preparation of chiral hexahydroazepine, we focused our attention to the lipase-catalyzed optical resolution such as the enzymatic esterification of the racemic azepine (±)-**4**. Among several conditions investigated, the enzymatic esterification using the immobilized lipase from *Pseudomonas* sp. (Wako Pure Chemical Industries, Ltd.) was found to be effective and afforded the acetate (3*R*, 4*R*)-**5** in 42% (96% *e.e.*)[7] with the recovered (3*S*, 4*S*)-**4** in 49% (82% *e.e.*).[7] Treatment of the *N*-Boc acetate (3*R*, 4*R*)-**5** with trifluoroacetic acid gave the deprotected product which was then reprotected with benzyloxycarbonyl chloride to afford the *N*-Z acetate **6** in 87% yield. Alkaline hydrolysis of the acetate **6** gave the alcohol **7** which was found to be identical with an authentic chiral sample upon comparison of their spectral data including optical rotation.[3b,c]

From the fact that the conversion of anthraquinones to benzophenones *via* the Baeyer-Villiger type reaction has been recognized as a key step in the biosynthesis of fungus metabolites,[8] we next planned to explore the biomimetic route to the synthesis of the benzophenone fragment of balanol and succeeded in its short-step synthesis *via* a route involving the oxidation of anthraquinone derivatives with singlet oxygen. In general, Baeyer-Villiger reaction of anthraquinones is known to proceed slowly to give the unstable seven-membered lactones in poor yields.[9] A few successful examples of anthraquinone ring cleavage are the experiments using an enzyme or singlet oxygen.[8a,10]

Our synthesis of the benzophenone fragment of balanol started from natural chrysophanic acid **8** as the corresponding commercially available natural anthraquinone (Scheme 2). Chrysophanic acid **8** was first protected by methylation to give the methyl ether **9** in quantitative yield which was then reductively methylated to the corresponding anthracene **10** in 85% yield under standard conditions.[11] According to the known method,[10] irradiation of an etheral solution of an anthracene **10**, which also serves as a sensitizer, under bubbling oxygen with a halogen lamp followed by treatment of the resulting oxygen adduct with

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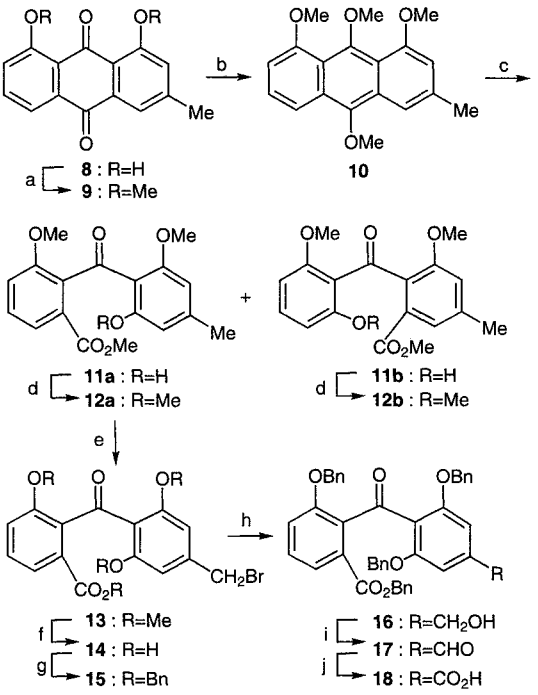
a catalytic amount of sulfuric acid in acetone gave an inseparable mixture of two regioisomeric benzophenones **11a** and **11b** in 57% combined yield in addition to 30% yield of the starting anthraquinone **9** which could be recycled.[12] Fortunately, the benzophenones **11a** and **11b** were characterized as the corresponding methyl ethers **12a** and **12b** which were readily separated by column chromatography.

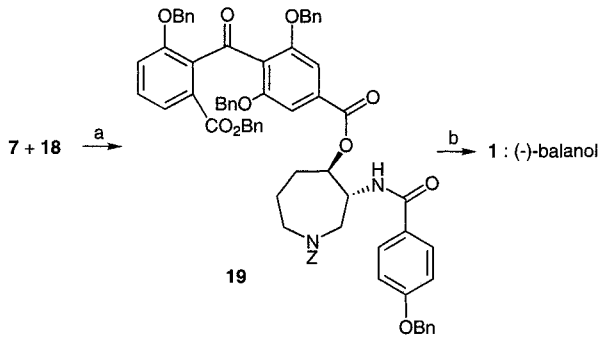


Scheme 2. *Reagents and conditions*: a) Me_2SO_4, K_2CO_3, acetone, reflux, 10 h, quant.; b) $Na_2S_2O_4$, $Bu_4N^+Br^-$, THF, H_2O, rt, 15 min; 6 *N* KOH, rt, 5 min; Me_2SO_4, rt, 12 h, 85%; c) O_2 / *hv*, Et_2O, 30 °C, 7 h; cat. H_2SO_4, acetone, rt, 10 h, 57%(**11a**+**11b**) + 30%(**9**); d) NaH, MeI, DMF, rt, 30 min, 39%(**12a**) + 41%(**12b**); e) NBS, cat. AIBN, CCl_4, reflux, 30 min, 57% (67%)[13]; f) BBr_3, CH_2Cl_2, rt, 5 days; g) BnBr, K_2CO_3, DMF, rt, 5 h, 28% from **13**; h) $CaCO_3$, H_2O, dioxane, reflux, 10 h, 79%; i) Pr_4NRuO_4, 4-methylmorpholine *N*-oxide, MeCN, rt, 30 min, 61%; j) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene,THF, *t*-BuOH, H_2O, rt, 1 h, 84%

Thus, we succeeded in the biomimetic synthesis of the desired benzophenone **12a** which is then converted into the known key intermediate[3b] for the synthesis of balanol. Bromination of **12a** with NBS in the presence of a catalytic amount of AIBN proceeded smoothly to give the bromide **13** in 57% (67%)[13] yield which was then treated with boron tribromide to give the triphenolic acid **14**. The resulting crude deprotected phenolic acid **14** was reprotected by benzylation to afford the tetrabenzyl derivative **15** in 28% yield from **13**. Hydrolysis of **15** under mild conditions provided the desired alcohol **16** in 79% yield which was found to be identical with an authentic sample upon direct comparison of their spectra.[3b] The alcohol **16** was then converted into the acid **18** under Nicolaou's conditions.[3b]

Finally, the coupling of two fragments **7** and **18** was accomplished by Mukaiyama's procedure[14] to afford the protected balanol **19** which was then deprotected by palladium-catalyzed hydrogenolysis into (-)-balanol under Nicolaou's conditions (Scheme 3).[3b] The synthetic (-)-balanol was identical spectroscopically with an authentic samples.[3]

In conclusion, we succeeded in the total synthesis of (-)-balanol by the large-scale preparation of chiral hexahydroazepine fragment through the radical cyclization followed by the enzymatic esterification and by the facile preparation of benzophenone fragment through a biomimetic route.



Scheme 3. *Reagents and conditions*:a) 2-chloro-1-methylpyridinium iodide, Et_3N, DMAP, CH_2Cl_2, rt, 3 h, 77%; b) HCO_2H, Pd-black, rt, 30 h, 79%

Acknowledgements

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References and Notes

(1) a) Nishizuka, Y. *Nature* **1984**, *308*, 693. b) Nishizuka, Y. *Science* **1986**, *233*, 305. c) Nishizuka, Y. *Nature* **1988**, *334*, 661. d) Kikkawa, U.; Kishimoto, A.; Nishizuka, Y. *Annu. Rev. Biochem.* **1989**, *58*, 31. d) Farago, A.; Nishizuka, Y. *FEBS Lett.* **1990**, *268*, 350. e) Bell, R. M.; Burns, D. J. *J. Biol. Chem.* **1991**, *266*, 4661. f) Asaoka, Y.; Nakamura, S.; Yoshida, K.; Nishizuka, Y. *Trends Biochem. Sci.* **1992**, *17*, 414.

(2) Bradshaw, D.; Hill, C. H.; Nixon, J. S.; Wilkinson, S. E. *Agents Actions.* **1993**, *38*, 135.

(3) Balanol has been independently synthesized by three groups.
a) Lampe, J. W.; Hughes, P. F.; Biggers, C. K.; Smith, S. H.; Hu, H. *J. Org. Chem.* **1994**, *59*, 5147. Hu, H.; Jagdmann, Jr. G. E.; Hughes, P. F.; Nichols, J. B. *Tetrahedron Lett.* **1995**, *36*, 3659. Hollinshead, S. P.; Nichols, J. B.; Wilson, J. W. *J. Org. Chem.* **1994**, *59*, 6703. Lampe, J. W.; Hughes, P. F.; Biggers, C. K.; Smith, S. H.; Hu, H. *J. Org. Chem.* **1996**, *61*, 4572. b) Nicolaou, K. C.; Bunnage, M. E.; Koide, K. *J. Am. Chem. Soc.* **1994**, *116*, 8402. Nicolaou, K. C.; Koide, K.; Bunnage, M. E. *Chem. Eur. J.* **1995**, *1*, 454. c) Adams, C. P.; Fairway, S. M.; Hardy, C. J.; Hibbs, D. E.; Hursthouse, M. B.; Morley, A. D.; Sharp, B. W.; Vicker, N.; Warner, I. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2355.

(4) Other preparations of the hexahydroazepine-containing fragment. a) Tanner, D.; Almario, A.; Högberg, T. *Tetrahedron* **1995**, *51*, 6061. b) Albertini, E.; Barco, A.; Benetti, S.; De Risi, C.; Pollini, G. P.; Zanirato, V. *Synlett* **1996**, 29. c) Tuch, A.; Saniére, M.; Merrer, Y. L.; Depezay, J. C. *Tetrahedron Asymmetry* **1996**, *7*, 2901.

(5) Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*; Translated by Lomas, J.; John Wiley&Sons: New York, 1995; pp. 151-158 and pp. 243-255.

(6) We reported the first example of the synthesis of five- to seven-membered cyclic amino alcohols *via* the tributyltin hydride-induced radical cyclization of oxime ethers. a) Naito, T.; Tajiri, K.; Harimoto, T.; Ninomiya, I.; Kiguchi, T. *Tetrahedron Lett.* **1994**,

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35, 2205. We reported the application of this procedure to the preparation of the hexahydroazepine-containing fragment. In this case, a *trans-cis* mixture of cyclized products was obtained in 58% yield. b) Naito, T.; Torieda, M.; Tajiri, K.; Ninomiya, I.; Kiguchi, T. *Chem. Pharm. Bull.* **1996**, *44*, 624.

(7) The enantiomeric purity of (3*R*, 4*R*)-**5** and (3*S*, 4*S*)-**4** was checked by chiral chromatography (Chiral Pack AD column) eluting with ethanol-heptane (15:85, v/v). The absolute configuration of (3*R*, 4*R*)-**5** was determined by comparison of the optical rotation of the corresponding alcohol (3*R*, 4*R*)-**4** with that of authentic sample.[6b] (3*R*, 4*R*)-**4** was readily obtained by saponification of (3*R*, 4*R*)-**5**.

(8) a) Fujii, I.; Ebizuka, Y.; Sankawa, U. *J. Biochem.* **1988**, *103*, 878. b) Franck, B. *The Biosynthesis of Mycotoxins*; Steyn, P. S. Ed.; Academic Press: New York, 1980; pp. 151-191.

(9) Svensson, L. Å. *Acta Chem. Scand.* **1972**, *26*, 2372.

(10) Franck, B.; Berger-Lohr, B. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 818.

(11) Blankespoor, R. L.; Schutt, D. L.; Tubergen, M. B.; De Jong, R. L. *J. Org. Chem.* **1987**, *52*, 2059. Kraus, G. A.; Man, T. O. *Synth. Commun.* **1986**, *16*, 1037.

(12) The reaction pathway from **10** to **11ab** can be rationalized by [4+2] cycloaddition of singlet oxygen to anthracene **10**, regioselective hydrolysis of the ketal moiety at 9-position, and Baeyer-Villiger type of rearrangement of the resulting hydroperoxide. The formation of this peroxide intermediate was also confirmed by EI and high-resolution mass spectra as follows.

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.

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

(14) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 707.

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