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A STEREOCONTROLLED SYNTHESIS OF HAPALOSIN

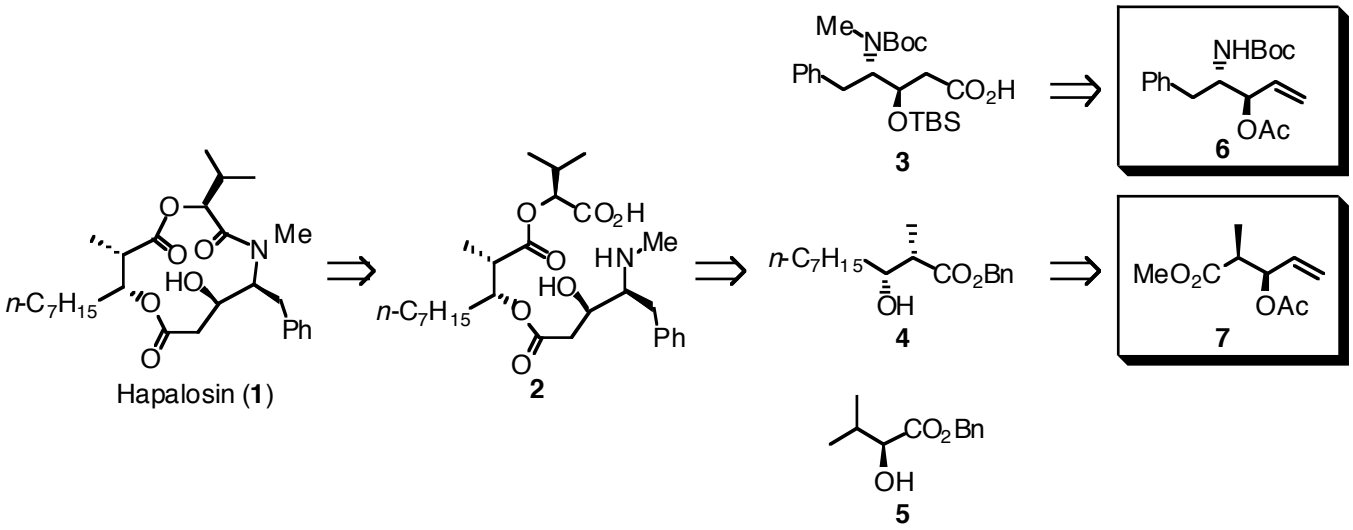
Tetsuta Oshitari, Saiyinbilige, and Tadakatsu Mandai*

Department of Chemistry and Bioscience, Kurashiki University of Science and the Arts, 2640 Nishinoura, Tsurajima, Kurashiki 712-8505, Japan
Fax: +81(86)4401062; E-mail: ted@chem.kusa.ac.jp

Abstract – A facile synthetic method for two components of hapalosin, that is, □-hydroxy-□-amino acid and □-hydroxy acid, has been established by utilizing chiral building blocks efficiently resolved in a lipase-catalyzed transesterification. Furthermore, the synthesis of hapalosin through macrolactamization of the seco acid derived from these two components and *(S)*-2-hydroxy-3-methylbutyric acid has thus been demonstrated.

A 12-membered cyclic depsipeptide hapalosin (**1**), isolated by Moore and co-workers, has shown remarkable reversing activity against P-glycoprotein-mediated multidrug resistance (MDR) of cancer cells.[1] Due to the important biological activity and the unique structural features, many research groups have pursued syntheses of **1** and its analogues.[2-11] Most of them reasonably adopted the macrolactamization of seco acid (**2**) which consists of three components, that is, □-silyloxy-□-amino acid (**3**), □□hydroxy ester (**4**), and □-hydroxy ester (**5**) as depicted in Scheme 1.

Scheme 1

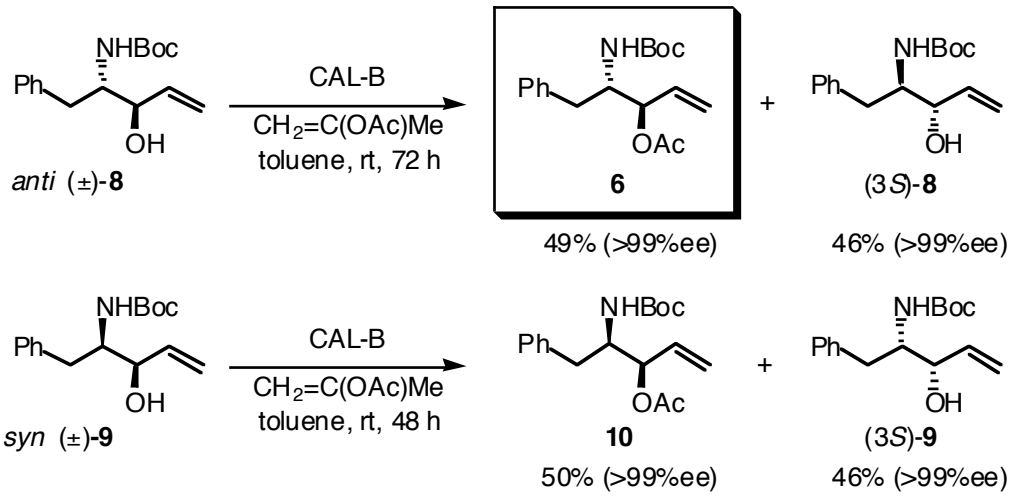


The compound (**3**) was prepared in several ways, some of which started from stereodefined compounds such as L-phenylalanine,[2-6] L-serine,[7] or the chiral epoxides accessible by the Sharpless' protocols.[12,13] Others depend on asymmetric reactions using the chiral auxiliaries such as Williams' oxazine[14] and Evans' oxazolidinone.[15] On the other hand, **4** was elaborated by means of either the Cram-selective addition of Grignard reagent to *(R)*-2-phenylpropanal[7] or the asymmetric reactions involving Evans-type

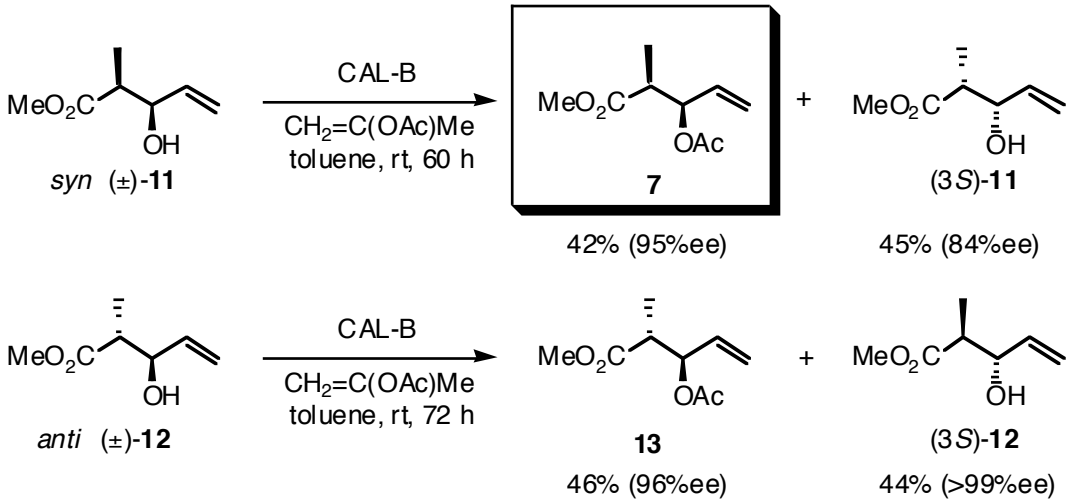
syn-aldol protocol[3-5,8] and Brown's allylboration of 1-octanal.[2] These preparative methods for **3** and **4**, however, require careful handling of moisture-sensitive reagents under low temperatures and/or manipulation of easily racemizing compounds. In the light of the important biological activity of **1**, a more intensive structure-activity relationship (SAR) study would be indispensable for further biological information. Thus, it is highly desired to develop a more flexible and concise approach to a wide range of diastereomers, enantiomers, and congeners of **3**, **4** and **5** leading to a variety of analogues of **1**.

The reasonable retrosynthetic analysis of **1** is illustrated in Scheme 1, in which compounds (**6**) and (**7**) seem to be the superb precursors for **3** and **4**, respectively, because **3** can be synthesized through hydroboration/oxidation and **4** through cross-metathesis/hydrogenation. In our efforts to expand the usefulness of lipase-catalyzed kinetic resolutions, we have recently disclosed that methyl 2-substituted 3-hydroxy-4-pentenoates[16] and 4-amino-1-alken-3-ols[17] can efficiently be resolved by use of CAL-B (*Candida antarctica*, fraction B), which seemingly allows access to **6** and **7** with high optical purity together with all the possible stereoisomers. In the event, racemic amino alcohols (**8**),[18, 19] (**9**),[18, 19] racemic β-hydroxy esters (**11**),[20, 21] and (**12**)[20, 21] were efficiently resolved with high enantiomeric purity as outlined in Schemes 2 and 3.

Scheme 2

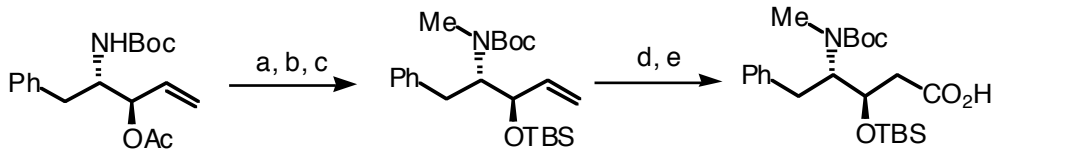


Scheme 3



Encouraged by these successful results, we then examined the transformation of **6** and **7** into **3** and **4**, respectively. As shown in Scheme 4, compound (**6**) was transformed into silyl ether (**14**) through alkaline-hydrolysis followed by silyl protection and *N*-methylation. Hydroboration of **14** followed by TEMPO-mediated oxidation[22] gave rise to **3** uneventfully, whose ^{1}H and ^{13}C NMR spectra and $[\alpha]_D$ were in good accordance with those in the literature.[4b]

Scheme 4



6 (>99%ee) **14** **3**

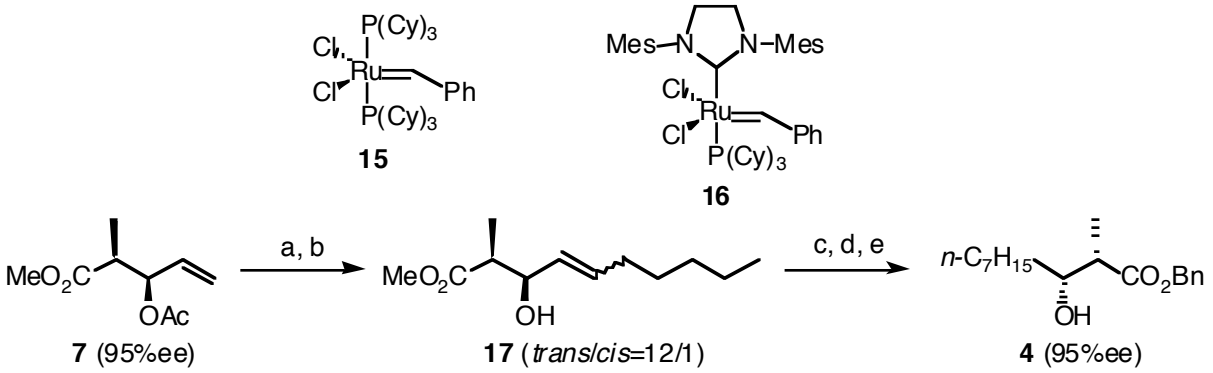
$[\alpha]_D^{23}$ -42.4° (*c* 1.32, $CHCl_3$)

lit.[4b] $[\alpha]_D^{24}$ -41.2° (*c* 1.00, $CHCl_3$)

(a) 1 M NaOH/MeOH, rt, 1 h, 98%; (b) TBSCl/imidazole/DMF, rt, 10 h, 97%;
(c) NaH/MeI/DMF, rt, 12 h, 98%; (d) 9-BBN/THF, rt, 12 h; NaOOH, 50 °C, 3 h, 82%;
(e) cat. TEMPO/cat. $NaOCl/NaClO_2$/MeCN/pH 6.8 phosphate buffer, rt, 4.5 h, 66%.

On the other hand, compound (**4**) was prepared by the procedure depicted in Scheme 5. The initially attempted cross-metathesis of **7** with 1-heptene (3 eq.) resulted in poor yield (20-40%) even at the refluxing temperature of dichloromethane in the presence of 5 mol% of cata;yst (**15**).[23] However, the reaction with catalyst (**16**)[24] smoothly afforded β-hydroxy ester (**17**) even at room temperature. Hydrogenation of **17** followed by alkaline-hydrolysis gave a carboxylic acid which was alkylatively esterified to afford **4** (95%ee),[25] whose ^{1}H and ^{13}C NMR spectra were identical to those in the literature.[4b] This procedure implies the high synthetic potential of **7** leading to a wide range of stereodefined β-hydroxy esters with high enantiomeric purity in place of Evans' asymmetric aldol protocol.

Scheme 5



15 **16**

7 (95%ee) **17** (*trans*/*cis*=12/1) **4** (95%ee)

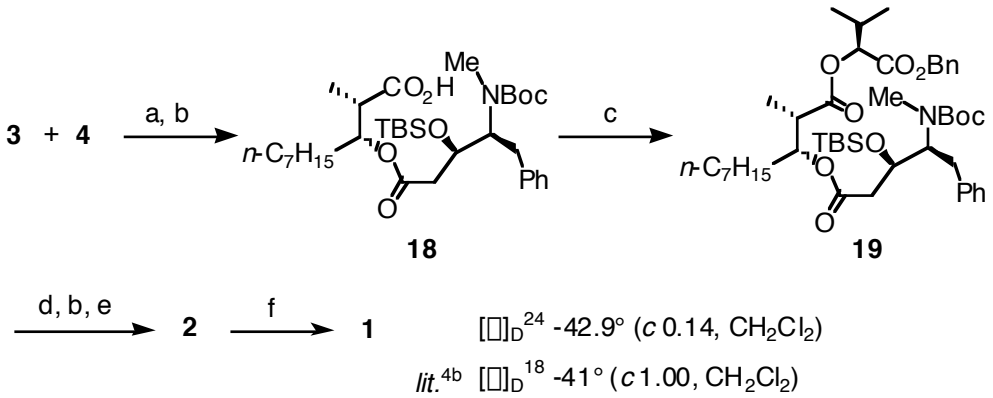
$[\alpha]_D^{24}$ +7.1° (*c* 1.04, $CHCl_3$)

lit.[4b] $[\alpha]_D^{24}$ +3.7° (*c* 1.00, $CHCl_3$)

(a) K_2CO_3/MeOH, rt, 1 h, 85 %; (b) **16** (5 mol%)/1-heptene (3 eq.)/CH_2Cl_2, rt, 12 h, 71%;
(c) H_2 (1 atm)/10%Pd-C /EtOH, 2 h, 82%; (d) 1 M NaOH/MeOH, rt, 5 h; (e) Cs_2CO_3/BnBr/DMF, rt, 12 h, 86% in two steps.

With components (**3**) and (**4**) in hand, the stage was set for macrolactamization. As depicted in Scheme 6, **1** was synthesized through the slightly modified procedure of the Nishiyama's protocol.[4] Condensation of **3** with **4** followed by reductive cleavage of the benzyl ester afforded carboxylic acid (**18**), which was condensed with **5**[26] to give fully-protected seco acid (**19**). Sequential treatment with TABF, H_2/$Pd(OH)_2$, and TFA gave seco acid (**2**) as a trifluoroacetic acid salt. Finally, the macrolactamization of **2** was accomplished by means of DPPA[27] in DMF under high dilution condition to afford **1** in 32% yield, whose ^1H and ^{13}C NMR spectra and $[\alpha]_D$ were fully identical to those reported.[1, 2, 4, 7, 8]

Scheme 6



(a) EDCI/DMAP/CH_2Cl_2, 40 °C, 8 h, 89% (b) H_2 (1 atm)/cat. $Pd(OH)_2$/EtOH, rt, 1 h; (c) **5**/EDCI/DMAP/CH_2Cl_2, rt, 12 h, 97%; (d) TBAF/THF, rt, 1.5 h, 77%; (e) TFA (10 eq.) /CH_2Cl_2, rt, 2 h, 90%; (f) DPPA (2 eq.)/*i*-Pr_2NEt (6 eq.)/DMF (1 mM soln of **2**), rt, 72 h, 32%.

In summary, we have achieved an efficient synthesis of hapalosin utilizing chiral building blocks obtained by lipase-catalyzed kinetic resolutions of methyl 2-substituted 3-hydroxy-4-pentenoates and 4-amino-1-alken-3-ols. We believe that our strategy constitutes an advantageous route to various congeners of hapalosin required for SAR studies, which will be reported in due course.

ACKNOWLEDGMENTS

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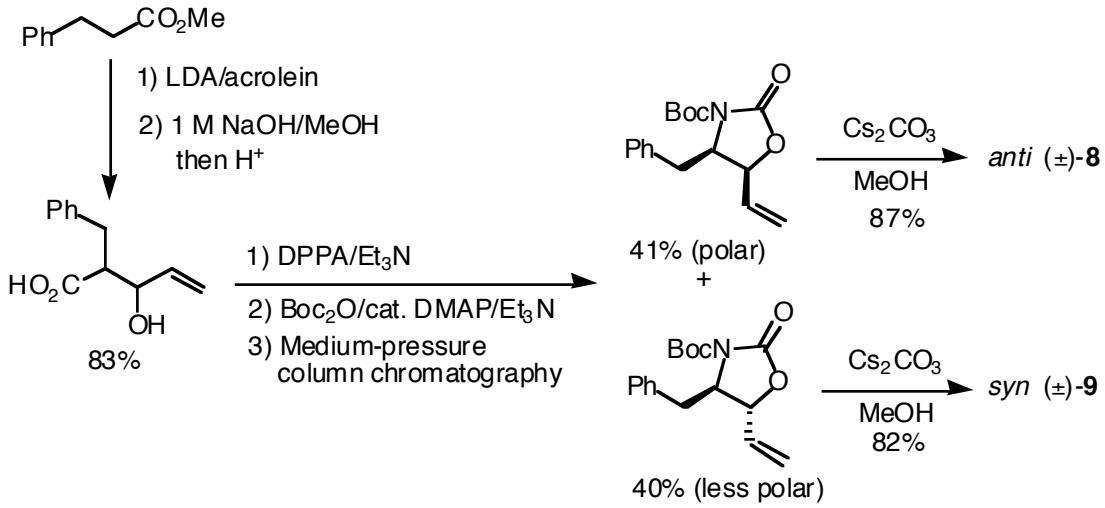
18. Prepared as follows.



For the ring opening with Cs_2CO_3/MeOH, see:
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19. The typical procedure is as follows. A mixture of (±)-**8** (3.17 g, 11.4 mmol), 2-propenyl acetate (3.78 mL, 34.2 mmol), and CAL-B [1.14 g, 0.1 g per 1 mmol of (±)-**8**] in toluene (34 mL) was stirred at rt for 72 h. The lipase was filtered off and the filtrate was concentrated to give solids which were chromatographed (SiO_2) to afford acetate (**6**) (1.78 g, 49%) and alcohol (3*S*)-(**8**) (1.45 g, 46%). Treatment of **6** with K_2CO_3/MeOH (rt, 40 min) gave rise to alcohol (3*R*)-(**8**) in a quantitative yield. The %ee of (3*R*)-**8** and (3*S*)-**8** was determined by HPLC using Chiralcel OD-H (hexane/2-propanol=20/1, 230 nm). The reaction of (±)-**9** was performed in an almost similar manner. Compound **10** was converted to alcohol (3*R*)-(**9**) by the treatment with K_2CO_3/MeOH (rt, 40 min). The %ee of (3*R*)-**9** and (3*S*)-**9** was determined by HPLC using Chiralcel OD-H (hexane/2-propanol=50/1, 254 nm) after conversion to benzoates.
20. Prepared by the aldol condensation of methyl propionate with acrolein (LDA/THF, –78 °C). The aldols thus obtained revealed to be a *ca.* 1:1 mixture of diastereomers, which were isolated by

medium-pressure column chromatography (SiO_2, hexane/EtOAc=6/1-4/1).

21. The typical procedure is as follows. A mixture of (±)-**11** (4.89 g, 31.8 mmol), 2-propenyl acetate (7.01 mL, 63.6 mmol), and CAL-B [3.18 g, 0.1 g per 1 mmol of (±)-**11**] in toluene (48 mL) was stirred at rt for 60 h. The lipase was filtered off and the filtrate was concentrated to give an oil which was chromatographed (SiO_2) to afford acetate (**7**) (2.50 g, 42%) and alcohol (3*S*)-(**11**) (2.05 g, 45%). The compound (**7**) was treated with K_2CO_3/MeOH (rt, 40 min) to give (3*R*)-**11** in quantitative yield. The %ee of (3*R*)-**11** and (3*S*)-**11** was determined by HPLC using Chiralcel OD-H (hexane/2-propanol=20/1, 230 nm). The reaction of (±) **12** was performed in an almost similar manner. The %ee of (3*R*)-**12** and (3*S*)-**12** was determined by HPLC using Chiralcel OD-H (hexane/2-propanol=20/1, 230 nm).
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25. Determined by HPLC using Chiralcel OD-H (hexane/2-propanol=9/1, 0.8 mL/min, 220 nm). **4**: t_R=6.60 min, the enantiomer of **4**: t_R=5.85 min.
26. Commercially available from Aldrich. For the preparation, see: (a) K. Mori, *Tetrahedron*, 1976, **32**, 1101. (b) P. Koch, Y. Nakatani, B. Luu, and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1983, **11**, II-189. (c) W.-R. Li, W. R. Ewing, B. D. Harris, and M. M. Joullié, *J. Am. Chem. Soc.*, 1990, **112**, 7659.
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