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The asymmetric synthesis and stereochemical assignment of chelonin B

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Abstract—The first total synthesis of the marine natural product (*S*)-(+)-chelonin B is described. The key reactions employed include Sharpless asymmetric dihydroxylation of a styrene derivative, catalytic ring-opening of an epoxide and sequential deprotection–rearrangement of a phthalimido indole acetate.

The aromatic alkaloid chelonin B (**1a**) was isolated by Faulkner and Bobzin from the purple dendritic sponge *Chelonaplysilla* sp., collected from a marine lake on Kaibaku Island, Palau.[1] The structure of chelonin B (Fig. 1) was revealed by both high resolution mass measurement and ^{1}H and ^{13}C NMR techniques.[2] The specific rotation for chelonin B was never recorded and the stereochemistry of chelonin B depicted in the original paper was arbitrary.[3] Chelonin B possesses antimicrobial activity.

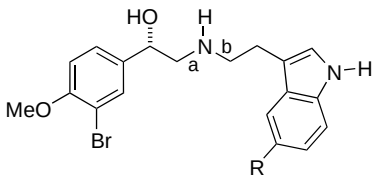
Chelonin B has not yet been prepared by asymmetric synthesis. A total synthesis would serve two purposes. Firstly, greater quantities of chelonin B and related derivatives would become available for further biological evaluation and secondly the stereochemistry of the natural product would be assigned.

The chelonin indole alkaloids have received surprisingly very little attention. Only the natural products bromochelonin B (**1b**)[4] and chelonin A[5] have been prepared (both by Somei and co-workers) but each in racemic form.

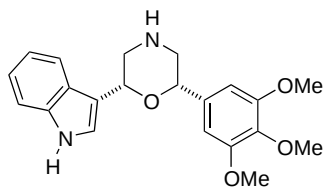
A useful strategy for the synthesis of 1,2-amino alcohols emerged from our study[6] of pyridine bis(oxazoline) catalyzed asymmetric reduction of ketones.[7] Our approach to chelonin B incorporating this strategy involves the formation of bond a via epoxide ring-opening and bond b by intramolecular $O \rightarrow N$ acyl transfer.

Sharpless dihydroxylation of the substituted styrene **3** (prepared by Wittig methylenation of the commercially available benzaldehyde **2**) using the $(DHQ)_2PHAL$ ligand gave the diol **4** (Scheme 1). The conditions used can be reasonably and reliably expected to produce the *S* enantiomer, as shown.[8]

Despite much effort we were unable to develop a convenient analytical HPLC method for separation of the enantiomers of the diol **4**. Nevertheless we were



Chelonin B 1a R = H
Bromochelonin B 1b R = Br



Chelonin A

Figure 1. Chelonin alkaloids from *Chelonaplysilla* sp.

Keywords: asymmetric dihydroxylation; oxiranes; phthalimide; natural products.

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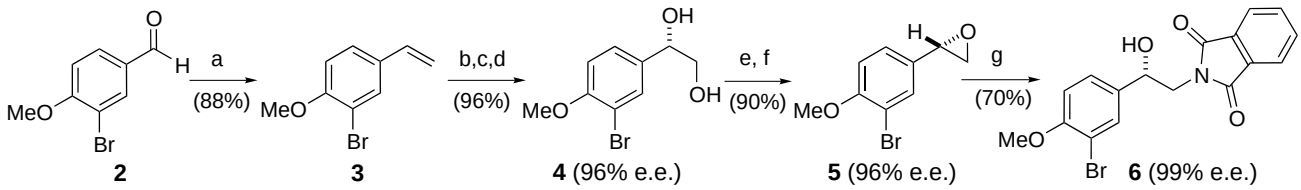


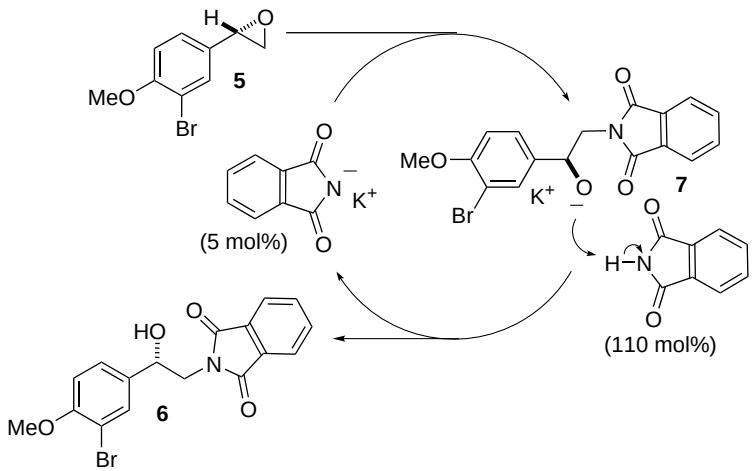
Scheme 1. *Reagents and conditions*: (a) Ph_3PMeBr (1.1 equiv.), *n*-BuLi (1.1 equiv.), THF, 0°C to rt, 1 h; (b) $K_3Fe(CN)_6$ (3 equiv.), $K_2OsO_4{\cdot}2H_2O$ (0.2 mol%), $(DHQ)_2PHAL$ (1 mol%), H_2O/*tert*-BuOH (1:1, v/v), 0°C, 4 h; (c) rt, 0.5 h; (d) Na_2SO_3 (excess), 0°C, 1 h; (e) TMSCl (1.3 equiv.), $MeC(OMe)_3$, CH_2Cl_2, 40°C to rt, 1 h; (f) K_2CO_3 (1.5 equiv.), MeOH, rt, 2 h; (g) phthalimide (1.1 equiv.), potassium phthalimide (5 mol%), DMF, 90°C, 18 h.

confident that the enantiomeric excess was high and could be determined later in the synthetic sequence. Transformation of the (*S*)-diol **4** into the corresponding enantiomerically enriched (*S*)-isomer of oxirane **5** was achieved in 90% chemical yield, according to the method of Sharpless and co-workers.[9] Fortunately, we were able to determine accurately the enantiopurity of the oxirane **5** (e.e. 96% by HPLC), so we can be certain that the enantiomeric excess of the diol **4** was at least 96%.[10]

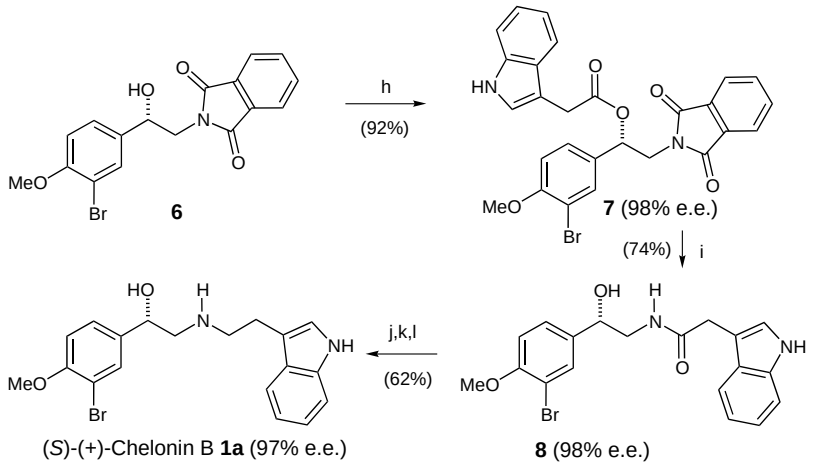
Introduction of the nitrogen atom at C-2 was achieved by reaction of the oxirane **5** with phthalimide. The use of potassium phthalimide alone was very inefficient and resulted in very poor yields of **6**. Presumably the alkoxide **7**, generated from the ring-opening process, is sufficiently nucleophilic to also react with the oxirane itself. We were keen to avoid the use of Lewis acids to catalyse the reaction, as the benzylic position of **6** is somewhat sensitive to racemization. We soon found that the ideal conditions for the transformation **5**→**6** involved the use of catalytic potassium phthalimide (5 mol%) in hot DMF. The alkoxide **7**, generated upon oxirane ring-opening in the presence of phthalimide, simply regenerates the potassium phthalimide, as illustrated in Scheme 2.[11] The acidity of these species, of course, supports this cycle (p*K*a phthalimide 13.4;[12] p*K*a secondary alcohol[13] (propan-2-ol) 30 (measured in DMSO)).

The indole acetyl group was then introduced via reaction of the C-1 hydroxyl group with inexpensive indole-3-acetic acid (Scheme 3). This was achieved efficiently by treatment of a 1:1 mixture of the alcohol **6** and indole-3-acetic acid with 1 equiv. of DCCI, in the presence of DMAP (5 mol%).[14] Treatment of the ester **7** with hydrazine monohydrate,[15] in refluxing *iso*-propanol for 12 h, furnished the optically active amide (*S*)-**8** in 74% yield. It was clear that under these reaction conditions the desired *O*→*N* acyl transfer had also taken place. The NH and OH signals in the ^1H NMR spectrum of **8** appeared as a triplet (δ 7.80 ppm, *J* 6.0 Hz, 1H) and singlet (δ 3.32 ppm, 1H), respectively. The signal for the benzylic proton (t, *J* 5.7 Hz, 1H) at C-1 was observed at δ 4.52 ppm, significantly upfield of the benzylic signal of the starting material (δ 6.06 ppm). Unequivocal proof that the *O*→*N* acyl transfer had taken place was provided by the X-ray crystal structure of **8** (Fig. 2). This also established, without doubt, that the absolute configuration of the C-1 chiral centre of **8** was indeed *S*, as expected from the initial Sharpless dihydroxylation reaction.

Finally, the chemoselective $BH_3{\cdot}SMe_2$ reduction of **8**, using a protocol developed by Bussolari and co-workers,[16] in refluxing THF, furnished the target natural product **1a** in 62% yield. HPLC analysis revealed that the enantiomeric excess of the sample was 97%, thus allaying our fears concerning the possible loss of stereo-



Scheme 2. Phthalimide oxirane ring-opening with catalytic potassium phthalimide.



Scheme 3. *Reagents and conditions*: (h) indole-3-acetic acid (1 equiv.), DCCI (1 equiv.), 4-DMAP (5 mol%), CH_2Cl_2/THF (1:1, v/v), rt, 16 h; (i) H_2NNH_2 (1.5 equiv.), ^{i}PrOH, reflux, 12 h; (j) $BH_3{\cdot}SMe_2$ (2 equiv.), THF, reflux, 20 min; (k) MeOH, rt, 2 min; (l) HCl (aq.), 0°C, 30 min.

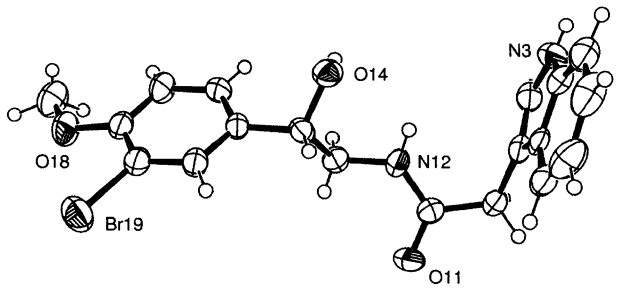


Figure 2. ORTEP representation of the X-ray crystal structure of amide **8.**

chemical integrity over the final three transformations. The ^{1}H NMR spectrum of the sample was identical to that of the natural product. HPLC analysis of a sample of the authentic natural product and the synthetic material showed that they were of the same stereochemical configuration. Indeed no (*R*)-chelonin B could be detected in the sample of the natural product.

In conclusion, we have developed a concise synthesis of chelonin B and assigned its absolute stereochemistry. We believe that the approach will be applicable to many other important classes of 1,2-amino alcohol derivatives.

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10. Enantiomeric excesses throughout were determined by HPLC: Conditions and retention times: **5**: Chiralpak AS column, 95:5 hexane:2-propanol, 0.5 cm^3 min^{-1}; 13.53 (*R*) and 14.31 (*S*); **6**: Chiralcel OD column, 9:1 hexane:2-propanol, 1.0 cm^3 min^{-1}; 26.58 (*S*) and 14.31 (*R*); **1a**: Chiralcel OJ column, 65:35 hexane:2-propanol, 1.0 cm^3 min^{-1}; 26.32 (*R*) and 38.40 (*S*).
11. (a) The use of catalytic amount of potassium phthalimide in this manner is rare, but has been used by Mosher and co-workers to ring-open without comment, see: Williams, T. M.; Crumbie, R.; Mosher, H. S. *J. Org. Chem.* **1985**, *50*, 91–97; (b) The catalytic cycle is similar in concept to that involved in the base-catalysed addition of alkynes to carbonyl compounds recently described by Babler and co-workers; see: Babler, J. H.; Liptak, V. P.; Phan, N. *J. Org. Chem.* **1996**, *61*, 416–417.

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