Concise Biomimetic Total Syntheses of Both Antipodes of Balasubramide

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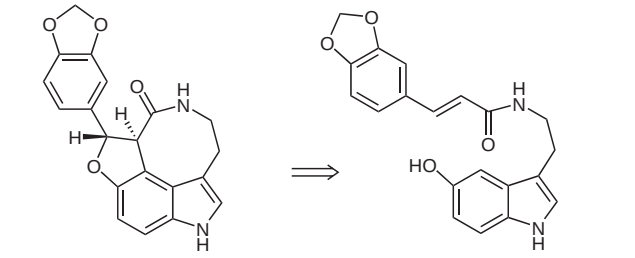
Abstract: A two-step, protecting-group-free synthesis of the natural product balasubramide, using an $Yb(OTf)_3$-catalyzed intramolecular epoxide opening, is reported. Both enantiomers of the natural product are available from the antipodal forms of the starting epoxycinnamic acid.

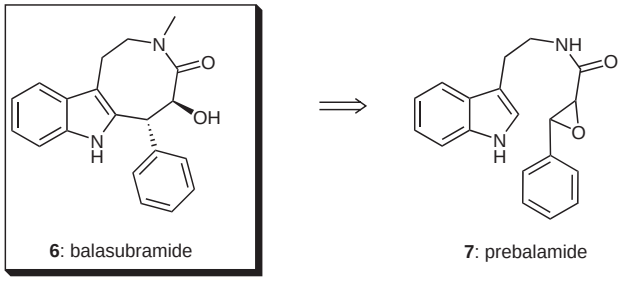
Key words: balasubramide, biomimetic synthesis, lanthanide catalysis, chiral resolution, indole natural product

Recently, we reported the total synthesis of the antimalarial indole natural product decursivine (**1**, Scheme 1).[1] Its biogenesis is likely to include the serotonin-derived cinnamide **2** via a C4-centered (indole numbering) radical cyclization. This hypothesis is strengthened by the co-isolation of the closely related serotobenine (**5**), moschaminindolol (**4**), and moschamine (**3**).[2]



Scheme 1 Biosyntheses of decursivine and serotobenine

During synthetic efforts towards decursivine, we became aware of a related natural product balasubramide (**6**, Scheme 2) isolated from *Clausena indica*.[3] It is also derived from a similar cinnamide, as evidenced by its co-isolation with prebalamide (**7**). In this case, the indole does not bear a 5-hydroxyl group, which would likely preclude the formation of a C4-centered radical. Instead, the favored biosynthetic pathway apparently involves an intramolecular electrophilic aromatic substitution of the epoxide. In recent years, our group has been successful in developing methods for the functionalization of the indole ring via lanthanide triflate catalysis.[4] We felt that such catalysis would be ideally directed towards the synthesis of balasubramide in the biomimetic fashion shown in Scheme 2. Moreover, a route proceeding via a homochiral epoxide would result in an asymmetric synthesis of the natural product in either antipodal form (providing of course that both epoxide enantiomers are accessible). Our efforts, culminating in the successful synthesis of both antipodes of balasubramide, are described herein.



Scheme 2 A proposed biomimetic retrosynthesis

Though isolated a decade ago, there has been only one (very recent) synthesis of *ent*-balasubramide to date.[5] This synthesis was completed in eight steps, in reasonable yield and high enantiomeric purity; however, the synthesis relied on a biotransformation which was incapable of producing the natural enantiomer.

Our initial synthetic efforts involved simply coupling cinnamic acid with tryptamine to form a cinnamic amide **8** (Scheme 3); however, all attempts at epoxidation of this amide to yield **7** resulted only in recovery of starting material or decomposition products. It was therefore decided to first epoxidize the acid residue and then couple it to tryptamine (Scheme 4).

To avoid problems surrounding the general instability of epoxyacids, the product was precipitated as the potassium salt following DMDO-mediated epoxidation of cinnamic acid (**9**).[6] While the exploratory work was conducted using racemic epoxide **10**, it was always the goal to prepare optically pure epoxide to provide access to either enantio-

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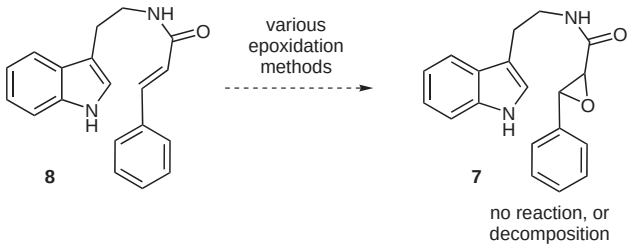
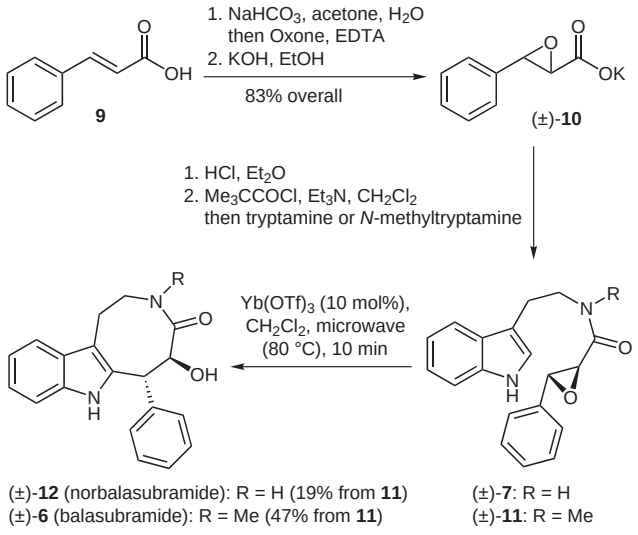


Scheme 3 The biomimetic synthesis of balasubramide

mer of the target. Coupling of epoxycinnamic acid with tryptamine was far more troublesome than anticipated and was attempted under varying conditions, including the use of DCC (which led solely to decomposition), and formation of the acid chloride, which produced only minor amounts of product. The formation of a mixed anhydride with pivaloyl chloride proved to be the most successful method for the formation of the amide **7**, the aforementioned prebalamide (Scheme 4). In the experiment, a simple acid workup of **10** followed by treatment of the resultant acid with Et_3N and pivaloyl chloride produced the mixed anhydride in situ. Addition of tryptamine directly into the reaction mixture produced the desired prebalamide **7** with an acceptable yield of 52%, but as an inseparable mixture contaminated with the pivaloyl amide of tryptamine. Compound **7** could be obtained cleanly through the use of a TFA-derived mixed anhydride, albeit in a reduced yield of 30%.

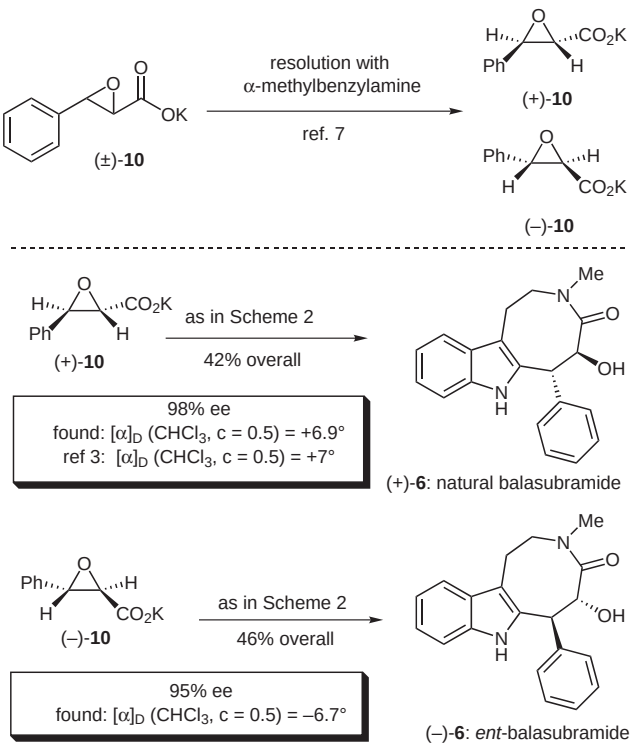


Scheme 4 Synthesis of racemic balasubramide

With prebalamide **7** in hand, attempts were made to cyclize the amide to form norbalasubramide (**12**). We were pleased to observe that cyclization took place under microwave irradiation and in the presence of catalytic ytterbium(III)triflate producing **12** (racemic norbalasubramide) in 37% yield. Alternate Lewis acids such as $Sc(OTf)_3$ were screened for this reaction, but commonly resulted in decomposition even at room temperature. Cyclization under microwave irradiation in the absence of catalyst was also unsuccessful. It was quite fortuitous that the eight-membered lactam was observed as the sole regioisomer under these conditions, with no evidence for the seven-membered lactam observed. That the eight-membered ring was formed was evident based on extensive 2D NMR analysis (HMBC, HSQC, COSY). This regioselectivity is not surprising based on electronic considerations of the epoxide opening.

With this promising result it was decided that it would be most convergent to begin the synthesis of balasubramide with commercially available *N*-methyltryptamine and thus avoid postcyclization installation of the methyl moiety. Coupling of *N*-methyltryptamine and cinnamic epoxide **10** was accomplished utilizing the same mixed anhydride used previously. Despite our best efforts, the resultant amide **11** could not be separated from at least one other unidentified compound, but the mixture could once again be subjected to microwave irradiation in the presence of catalytic $Yb(OTf)_3$ to produce racemic balasubramide (**6**) in 47% yield over two steps.

With the racemic synthesis of balasubramide completed, methods for obtaining enantiopure **10** were investigated, for this would allow access to either isomer of balasubramide. A method to resolve and isolate both enantiomers of **10** has been previously reported utilizing both antipodes of α-methylbenzylamine to sequentially precipitate each enantiomer.[7] Recrystallization of the resultant salts led to both requisite epoxides in >95% ee. The enantiopure salts were then dissolved in ethanol, reprecipitated with KOH, and taken through the previous synthetic steps (Scheme 5). Chiral HPLC analysis demonstrated that this approach led to the production of balasubramide (**6**) in 98% ee and *ent*-**6** in 95% ee.



Scheme 5 Synthesis of either antipode of balasubramide

In conclusion, we have successfully, and biomimetically completed the first total synthesis of natural (+)-balasubramide and only the second synthesis of (–)-balasubramide in two steps from epoxycinnamic acid and in excellent overall yields of 42–46%. Most importantly, this short synthesis of both enantiomers should allow for the synthesis of sufficient quantities of balasubramide or related compounds for biological screening.

General Procedure for Amide Formation: Preparation of Compound 7

A solution of chiral or racemic potassium salt **10** (227 mg, 1.12 mmol) in 5 mL distilled H_2O and ice was acidified with 3 mL of 1 M HCl and extracted with Et_2O (3 × 10 mL). The extracts were dried over anhyd Na_2SO_4 and filtered directly into a 100 mL round-bottom flask. To this solution was added Et_3N (170 mg, 1.68 mmol) and 20 mL of anhyd CH_2Cl_2 to increase solubility. Pivaloyl chloride (68.0 mg, 0.56 mmol) was added and the reaction was allowed to stir for 2 h. After 2 h, *N*-methyltryptamine (97.6 mg, 0.56 mmol) was added and the reaction was allowed to stir for a further 2 h. Regardless of the purification procedure employed, amide **11** was inseparable from at least one other compound. It was thus decided to proceed through cyclization with the mixture.

General Procedure for Cyclization: Preparation of Compound 6

A solution of amide **11** (127 mg in 5 mL CH_2Cl_2) was treated with $Yb(OTf)_3$ (25.0 mg, $4.03 \cdot 10^{-2}$ mmol) and irradiated in a microwave for 10 min at 80 °C. Once the reaction had cooled it was pre-absorbed onto silica, and then subjected to flash column chromatography with gradient elution beginning at 40% EtOAc in hexanes and increasing in 5% intervals to 50% EtOAc in hexanes yielding **6** in 46% over the two steps (82.7 mg, 0.25 mmol); mp 185–191 °C (decomp.); R_f = 0.31 (70% EtOAc in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.92 (br s, 1 H), 7.53 (dd, *J* = 6.8, 1.6 Hz, 1 H), 7.33–7.24 (m, 5 H), 7.20 (dd, *J* = 6.8 Hz, 2 Hz, 1 H), 7.15 (ddd, 7.8, 6.6, 1.2 Hz, 1 H), 7.12 (ddd, *J* = 8.4, 6.8, 1.2 Hz, 1 H), 4.96 (br d, *J* = 6.6 Hz, 1 H), 4.37 (d, *J* = 6.0 Hz, 1 H), 4.34 (v br s), 3.96 (ddd, *J* = 15.6, 10.2, 6.6 Hz, 1 H), 3.49 (ddd, *J* = 16.8, 10.8, 7.8 Hz, 1 H), 3.41 (ddd, *J* = 15.0, 7.2, 3.6 Hz, 1 H), 3.03 (ddd, *J* = 15.6, 5.4, 3.6 Hz, 1 H), 2.84 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 141.0, 135.2, 132.2, 129.3, 128.7, 127.5, 127.2, 122.1, 119.4, 117.5, 110.7, 106.6, 73.8, 54.3, 46.4, 34.2, 22.8. IR (thin film): ν_{max} = 3301, 2926, 1640, 1495, 1461, 1392, 1360, 1340, 1183, 1066, 909, 734, 700. HRMS: *m/z* calcd: 320.1525; found: 320.1530. $[\alpha]_D$ (lit.) +7 (*c* 0.5, $CHCl_3$), $[\alpha]_D^{20}$ +6.9 (*c* 0.5, $CHCl_3$). The spectral and physical data for synthetic balasubramide (**6**) match the literature data in all respects including optical rotation, and were further verified by 2D NMR. The enantiomer of balasubramide (*ent*-**6**) was found to have the same spectral and physical data but with an equal and opposite optical rotation $[\alpha]_D^{20}$ –6.7 (*c* 0.5, $CHCl_3$).

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