The Use of Sodium Chlorite in the Direct Synthesis of Glycidic Amides: Enantiopure Synthesis of Both Enantiomers of Norbalasubramide

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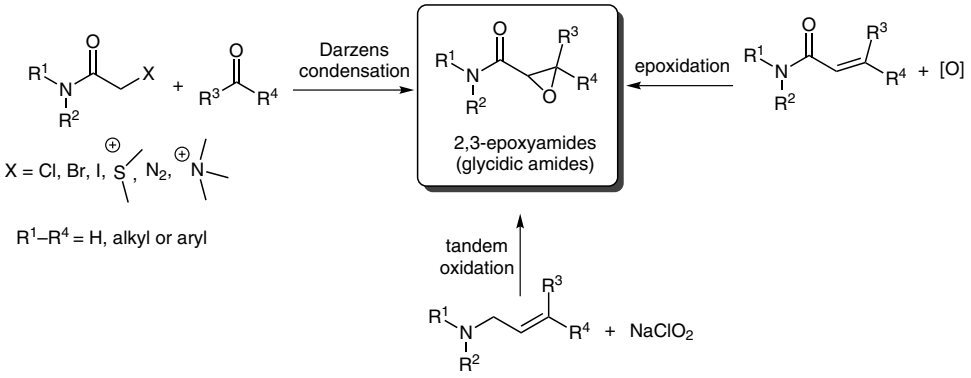
Received: 10.01.2013; Accepted after revision: 17.03.2013

Abstract: Recently, the first direct method for preparing 2,3-epoxyamides (glycidic amides) was disclosed. Now in this letter, the enantiopure synthesis of both enantiomers of norbalasubramide featuring this synthetic method is reported. To this end, chiral *N*-allyltryptamine **12** was prepared and transformed into an inseparable mixture of diastereomeric epoxyamides **13a**/**13b**, which were submitted to intramolecular cyclization with $Cu(OTf)_2$ to afford a separable mixture of eight-membered ring lactams **14a** and **14b**. Finally, after removal of the protective group and the chiral auxiliary an enantiopure synthesis of the title compounds was completed.

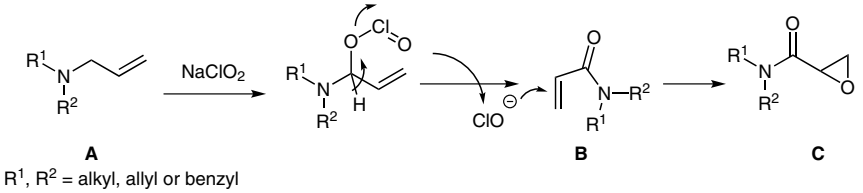
Key words: 2,3-epoxyamides, glycidic amides, tandem oxidation, sodium chlorite, balasubramide, norbalasubramide

Glycidic amides (or 2,3-epoxyamides) are very important organic compounds that are found in nature[1] or prepared in the laboratory for being used in synthesis as versatile building blocks.[2] Until very recently, the glycidic amides were prepared by only two general methods: (a) via Darzen condensation of α-halo acetamides,[3] α-sulfonium acetamides,[4] α-diazo acetamides,[5] α-ammonium acetamides[6] with either aldehyde or ketones, or (b) through the epoxidation of α,β-unsaturated amides.[7] Moreover, recently a third method was reported: (c) selective tandem oxidation of tertiary allylic amines with sodium chlorite (Scheme 1).[8] Unlike the two methods, in which at least two steps are involved, the latter represents the first direct method (one step) for preparing glycidic amides.

Apparently, the tandem oxidation reaction is initiated by $NaClO_2$-mediated C–H allylic oxidation of allylamine **A** to the corresponding α,β-unsaturated amide **B** followed by double bond epoxidation to glycidic amide **C** by hypochlorite ion, which is formed at the expense of the reduction of sodium chlorite (Scheme 2). Under this apparent logical sequence, various tertiary allylamines were transformed into their corresponding 2,3-epoxyamides in few hours with modest to good yields.[8]

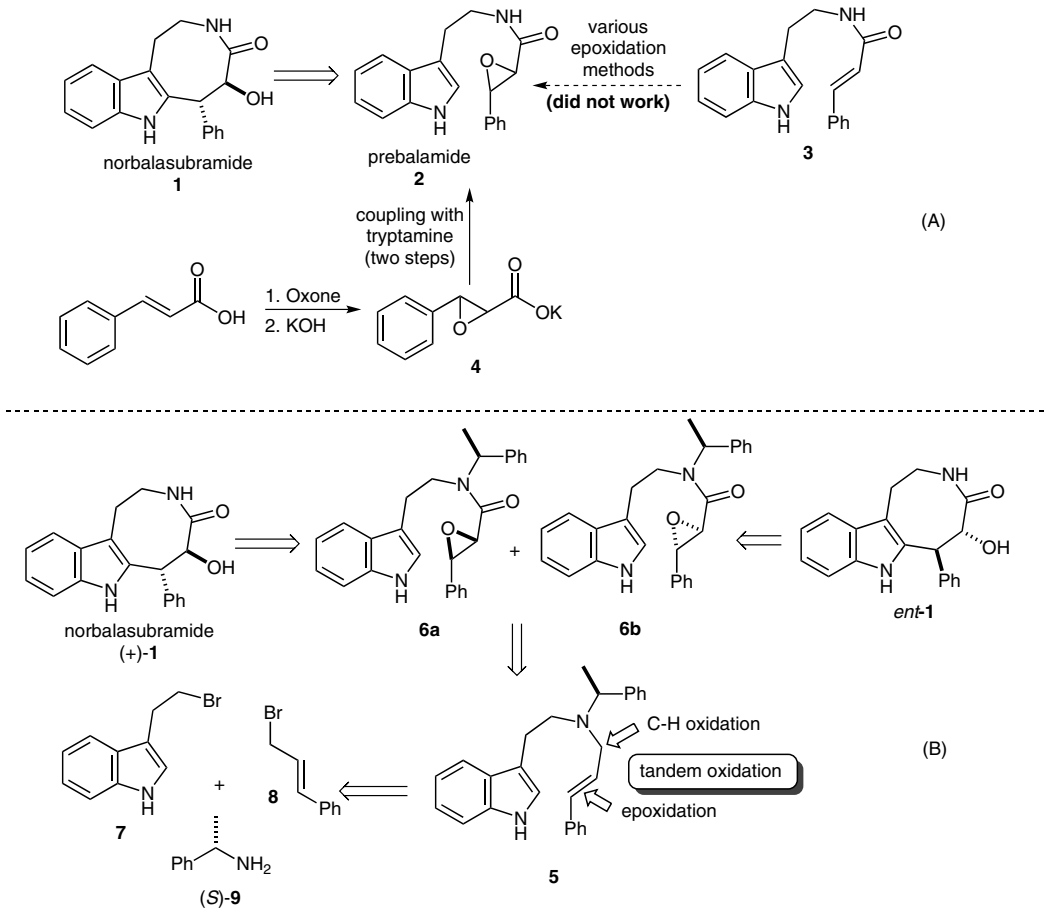


Scheme 1 Synthetic methods for preparing 2,3-epoxyamides (glycidic amides)



Scheme 2 Proposed tandem oxidation course for the direct synthesis of glycidic amides

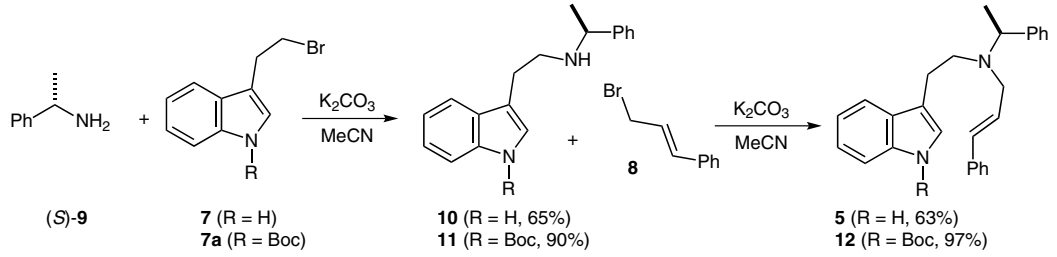
SYNLETT 2013, 24, 0878–0882
Advanced online publication: 21.03.2013
DOI: 10.1055/s-0032-1316893; Art ID: ST-2013-S0037-L



Scheme 3 Kerr's biomimetic synthesis of norbalasubramide (A) and our retrosynthetic plan (B)

Thus, motivated by these promising results, we focus now on its application to a specific synthesis of indole alkaloids. We wanted to undertake a synthesis where one of the conventional methods failed, and thus showcase some of the advantages that this chemical method offers. Going through the literature, we found an elegant biomimetic synthesis of the norbalasubramides (also of the balasubramide) developed by Kerr and co-workers.[9] They postulated to synthesize the norbalasubramide **1** (and also the balasubramide) from natural glycidic prebalamide **2** via a $Yb(OTf)_3$-catalyzed intramolecular epoxide opening, in which the prebalamide **2** would be prepared by the epoxidation of unsaturated tryptamide **3**. Unfortunately, after various attempts for conducting the epoxidation reaction, they could not obtain the prebalamide **2**. Therefore, their original strategy was modified; they decided to follow the traditional two-step synthesis of glycidic amides: first to prepare the epoxide **4** and then couple it to tryptamine (Scheme 3, A).

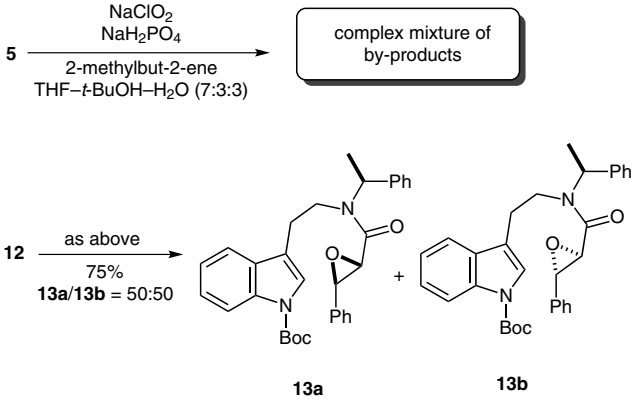
Having set up this provocative synthetic scenario, we decided to apply our tandem oxidation (C–H oxidation/double bond epoxidation) to *N*-allyltryptamine **5** in order to prepare, in only one step, the diastereomeric prebalamides **6a** and **6b**, which after Lewis acid mediated epoxide opening[9,10] followed by removing of the chiral auxiliary, would lead to the enantiopure synthesis of both enantiomers of norbalasubramide in only three steps from **5** (Scheme 3, B). To this end, both chiral allyltryptamine (*S*)-**5** and also the *N*-Boc-allyltryptamine (*S*)-**12** were prepared. The indole protection with *tert*-butyloxycarbonyl



Scheme 4 Preparation of chiral allyltryptamines **5** and **12**

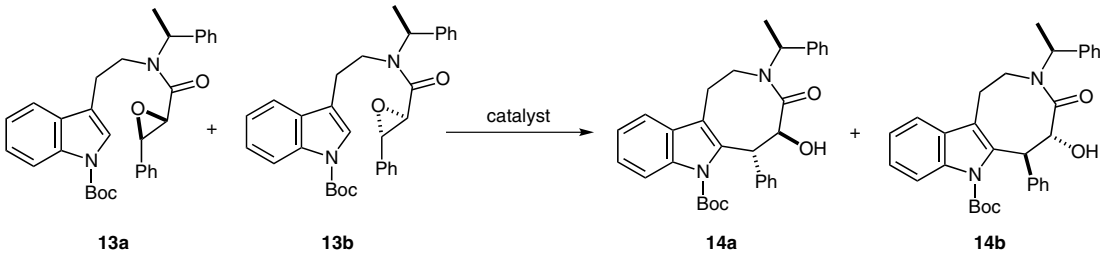
group (Boc) responds to the need for decreasing its reactivity toward the oxidizing and electrophilic conditions that the $NaClO_2/NaH_2PO_4$ system provides. Alkylation of chiral auxiliary (*S*)-**9** with both bromoethyl indole **7** and its Boc-protected derivative **7a** afforded secondary amines **10** and **11** in 65% and 90% yields, respectively; then, allylation of **10** and **11** with *trans*-cinnamyl bromide (**8**) gave the *N*-allyltryptamines **5** and **12** in good and excellent yields, respectively (Scheme 4). It is important to mention that the presence of the Boc-protecting group in **7a** increased the yields of the alkylation and allylation reactions; indeed, the sole formation of secondary amine **11** was observed; however for the alkylation of **7**, an undesirable 28% of tertiary amine (not shown) was formed.

With the chiral allylamines **5** and **12** in hand, we proceeded to apply our tandem oxidation protocol under the reaction condition that provides the best yields (8 equiv of $NaClO_2$ and NaH_2PO_4, 100 equiv of 2-methylbut-2-ene in a mixture of THF–*t*-BuOH–H_2O solvents with a ratio of 7:3:3).[8] For the case of allylamine **5**, a complex mixture of inseparable by-products was obtained; only traces of the expected glycidic amines were apparently observed. Fortunately, in the case of the Boc-protected allyltryptamine **12**, a gratifying 70% yield of a diastereomeric mixture of 2,3-epoxyamides **13a** and **13b** (ca. 50:50) was obtained (Scheme 5).[11] Since both epoxyamides had the same retention factor (R_f) in all of the common solvents, we failed to separate both epoxyamides by chromatography. Consequently, the diastereomeric mixture of epoxyamides **13a**/**13b** was submitted to intramolecular ring opening using ytterbium(III) triflate as catalyst (Kerr's conditions) obtaining thus the corresponding eight-membered ring lactams **14a** and **14b** in a low yield (entry 1, Table 1). Furthermore at this stage, both lactams were easily separated by chromatography. Because of this low yield, it was therefore decided to carry out screening experiments to find out a better catalyst that may provide better yields. As shown in Table 1, *p*-toluenesulfonic acid (PTSA) gave a modest 50% yield in two days at room temperature (entry 2); the other metal triflates catalysts showed decreased efficiency from less than traces to greater than 42% yield (entries 3–7).



Scheme 5 Synthesis of glycidic amides **13a** and **13b** via tandem C–H oxidation and double-bond epoxidation

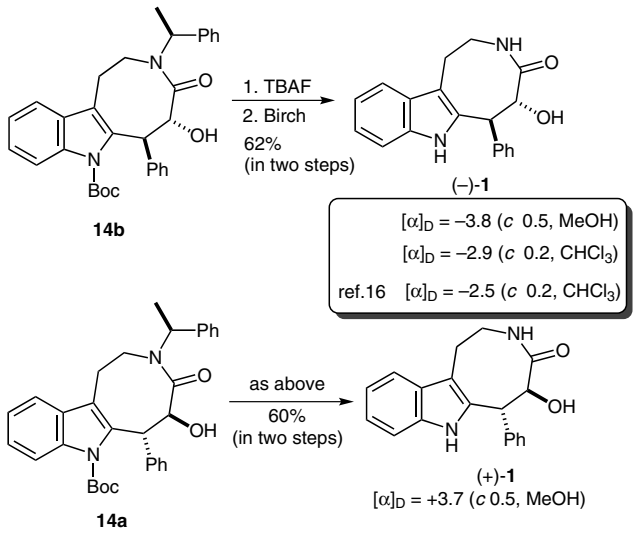
Table 1 Catalyst Screening for the Intramolecular Cyclization via Epoxide Ring Opening[a]



Entry	Catalyst	Yield of **14a** + **14b** (as 1:1 ratio)	Time (h)
1	$Yb(OTf)_3$; 20% mol	40%[b]	60
2	*p*-TsOH; 300% mol	50%[b]	48
3	$In(OTf)_3$; 20% mol	30%[b]	60
4	LiOTf; 20% mol	Trace	60
5	AgOTf; 20% mol	Trace	72
6	$Zn(OTf)_2$; 20% mol	23%[b]	72
7	$Sc(OTf)_3$; 20% mol	42%[b]	12
8	$Cu(OTf)_2$; 20% mol	82%[b]	0.5

[a] All reactions were performed in MeCN at r.t.
[b] Yields obtained after purification.

A gratifying result was obtained when $Cu(OTf)_2$ was used; in only 30 minutes at room temperature, lactams **14a** and **14b** were obtained in 82% yield (entry 8).[12] With the optically pure eight-membered ring lactams **14a** and **14b** in hand, we proceeded to remove the Boc-protective group and the chiral benzyl group to thus obtain the (+)- and (–)-norbalasubramides in enantiopure forms. Deprotection of *N*-Boc proved difficult under classic acidic condition, and decomposition of the starting material was observed. However, with the use of tetra-*n*-butylammonium fluoride (TBAF),[13] the unprotected indoles **15a** and **15b** (not shown) were obtained in 77% and 80% yields, respectively.[14] Debenzylation of **15a** and **15b** with H_2 and Pd/C or $Pd(OH)_2$ did not provide the expected results; however, under Birch conditions, both enantiomers of norbalasubramide were obtained.[15] Norbalasubramide (–)-**1** exhibited NMR spectral data identical to that reported by Zhao and co-workers,[16] as well as similar optical rotation (Scheme 6).



Scheme 6 Synthesis of both enantiomers of norbalasubramide, (–)-**1** and (+)-**1**

In summary, we have developed a highly efficient six-step synthesis of both enantiomers of norbalasubramide featuring our tandem oxidation of allylamines to glycidic amides with sodium chlorite. The application of this synthetic method clearly demonstrates some advantages over the conventional two-step synthesis of glycidic amides.

Acknowledgment

We gratefully acknowledge the financial support from CONACyT (Grant: 179074) and the Benemérita Universidad Autónoma de Puebla (BUAP-VIEP). We also thank Mr. Vladimir Carranza-Tellez for technical assistance in mass spectroscopy.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are experimental procedures for the preparation of allylamines **5** and **12** and copies of ^1H NMR and ^{13}C NMR spectra for the new compounds.

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(11) **General Procedure for the Tandem Oxidation of Allyamines**; *tert*-Butyl-3-[2-{3-phenyl-*N*-[(*S*)-1-phenylethyl]oxirane-2-carboxamido}ethyl]-1*H*-indole-1-carboxylate (13a/13b): Allylamine 12 (4.00 g, 8.32 mmol) and $NaH_2PO_4{\cdot}2H_2O$ (12.98 g, 83.22 mmol) were dissolved in a mixture of *t*-BuOH–THF–H_2O (7:3:3; 108 mL), the reaction mixture was then stirred vigorously at r.t. for 15 min after which time the solution was cooled to 0 °C followed by the addition of 2-methylbut-2-ene (58.37 g, 832.22 mmol) and the sequential addition of $NaClO_2$ (6.02 g, 66.58 mmol) dissolved in H_2O (10 mL). The reaction mixture was stirred

for 8 h, then phases were separated and the aqueous phase was extracted with EtOAc (3 × 25 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to give an inseparable mixture of diastereomeric epoxyamides 13a and 13b in a 50:50 ratio as a pale yellow oil (2.97 g, 70%); $[\alpha]_D^{20}$ –23.9 (*c* = 1.0, CH_2Cl_2). NMR data is reported as a mixture of diastereoisomers and *E*/*Z* rotamers. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.60 (d, *J* = 6.8 Hz), 1.64 (s), 1.66 (d, *J* = 6.4 Hz), 2.30–2.41 (m), 2.56–2.64 (m), 2.70–2.78 (m), 2.87–2.99 (m), 3.23–3.35 (m), 3.38–3.61 (m), 3.66 (dd, *J* = 3.6, 1.6 Hz), 3.79 (dd, *J* = 6.0, 2.0 Hz), 4.19 (ddd, *J* = 20.8, 11.6, 1.6 Hz), 5.33 (q, *J* = 6.8 Hz), 5.39 (q, *J* = 6.8 Hz), 6.13 (app quint., *J* = 7.2 Hz), 6.75 (d, *J* = 7.8 Hz), 6.88–7.03 (m), 7.18–7.45 (m), 8.04 (br). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.5, 18.3, 18.5, 23.9, 24.2, 26.7, 26.8, 28.1, 28.1, 43.4, 43.5, 44.0, 44.0, 51.8, 51.9, 54.7, 54.9, 57.4, 57.5, 57.9, 58.0, 58.1, 58.3, 83.3, 83.6, 115.0, 115.2, 115.3, 116.4, 117.9, 118.2, 119.3, 119.3, 122.4, 122.4, 123.0, 123.0, 123.1, 124.3, 124.4, 125.5, 125.6, 126.7, 127.1, 127.8, 127.9, 127.9, 128.0, 128.1, 128.6, 128.7, 128.8, 129.6, 130.3, 135.2, 135.3, 135.4, 139.2, 139.8, 140.0, 149.4, 149.7, 166.5, 166.6, 166.7. HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{32}H_{35}N_2O_4$: 511.2597; found: 511.2550.

(12) **General Procedure for the Intramolecular Ring Opening**: To a solution of **13a**/**13b** (2.00 g, 3.91 mmol) in anhyd MeCN (45 mL) at r.t. was added $Cu(OTf)_2$ (0.28 g, 0.78 mmol) dissolved in anhyd MeCN (5 mL). The reaction mixture was stirred for 30 min before H_2O (15 mL) was added. The phases were separated and the aqueous phase was extracted with EtOAc (3 × 25 mL). The organic phase was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel or recrystallized with EtOAc–hexane to give **14a** (0.80 g, 40%) and **14b** (0.84 g, 42%).
(5*S*,6*R*)-*tert*-Butyl-5-hydroxy-4-oxo-6-phenyl-3-[(*S*)-1-phenylethyl]-3,4,5,6-tetrahydro-1*H*-azocino[5,4-*b*]indole-7(2*H*)-carboxylate (14a): Obtained as a white solid (0.80 g, 40%); mp 185–186 °C; $[\alpha]_D^{20}$ –32.6 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (d, *J* = 6.8 Hz, 3 H), 1.53 (s, 9 H), 2.98–3.15 (m, 2 H), 3.30 (dt, *J* = 14.0, 9.6 Hz, 1 H), 3.60 (dd, *J* = 14.0, 9.6 Hz, 1 H), 3.97 (d, *J* = 9.2 Hz, 1 H), 4.89 (t, *J* = 9.6 Hz, 1 H), 5.29 (d, *J* = 9.6 Hz, 1 H), 5.98 (q, *J* = 6.8 Hz, 1 H), 6.51–6.60 (m, 3 H), 6.74–6.77 (m, 2 H), 6.96–7.00 (m, 1 H), 7.18–7.30 (m, 7 H), 7.98 (d, *J* = 8.4 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9, 23.0, 28.0, 39.5, 51.6, 51.9, 73.1, 84.2, 114.4, 115.5, 117.3, 122.5, 123.8, 126.8, 126.9, 127.0, 127.6, 128.0, 128.7, 129.1, 136.0, 136.5, 138.0, 139.6, 149.9, 174.8. HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{32}H_{35}N_2O_4$: 526.2597; found: 511.2613.
(5*R*,6*S*)-*tert*-Butyl-5-hydroxy-4-oxo-6-phenyl-3-[(*S*)-1-phenylethyl]-3,4,5,6-tetrahydro-1*H*-azocino[5,4-*b*]indole-7(2*H*)-carboxylate (14b): Obtained as a pale yellow oil (0.84 g, 42%); $[\alpha]_D^{20}$ +17.6 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.68 (d, *J* = 6.8 Hz, 3 H), 1.51 (s, 9 H), 2.92–3.43 (m, 4 H), 3.92 (d, *J* = 9.6 Hz, 1 H), 4.85 (t, *J* = 9.6 Hz, 1 H), 5.28 (d, *J* = 9.2 Hz, 1 H), 5.84 (q, *J* = 6.8 Hz, 1 H), 6.99–7.58 (m, 13 H), 7.94–8.19 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.3, 23.1, 28.0, 40.6, 51.4, 51.4, 73.1, 84.4, 114.6, 116.0, 117.2, 122.6, 124.2, 126.8, 127.2, 127.4, 128.1, 128.4, 128.5, 129.1, 136.0, 137.1, 139.5, 140.0, 149.8, 174.6. HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{32}H_{35}N_2O_4$: 526.2597; found: 511.2610.

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(14) ***N*-Boc Deprotection**: To a solution of lactam **14a** (0.40 g, 0.78 mmol) in anhyd THF (2 mL) at r.t. was added TBAF (7.83 mmol, 1.0 M solution). The reaction mixture was refluxed for 5 h. Then, the mixture was cooled to r.t., H_2O was added (5 mL), the phases were separated and the aqueous phase was extracted with EtOAc (2 × 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel, and then recrystallized in CH_2Cl_2–hexane to give the corresponding product.
(5*S*,6*R*)-5-Hydroxy-6-phenyl-3-[(*S*)-1-phenylethyl]-2,3,5,6-tetrahydro-1*H*-azocino[5,4-*b*]indol-4(7*H*)-one (15a): obtained as a white solid (0.25 g, 79%); mp 231–267 °C (decomp.); $[\alpha]_D^{20}$ –7.1 (*c* = 1.0, CH_2Cl_2). The NMR data is reported as a mixture of rotamers. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47 (d, *J* = 7.2 Hz), 1. 57 (d, *J* = 7.2 Hz), 1.99 (br), 2.95 (ddd, *J* = 16.0, 9.6, 4.0 Hz), 3.11 (dt, *J* = 16.0, 8.4 Hz), 3.39 (ddd, *J* = 14.4, 9.6, 8.0 Hz), 3.69 (ddd, *J* = 14.8, 8.8, 4.0 Hz), 4.28 (d, *J* = 9.6 Hz), 4.98 (d, *J* = 9.6 Hz), 5.88 (q, *J* = 7.2 Hz), 5.94 (q, *J* = 7.2 Hz), 6.34 (s), 6.53–6.59 (m), 6.82–6.91 (m), 7.04–7.08 (m), 7.15–7.34 (m), 8.40 (br), 8.55 (br). ^{13}C NMR (100 MHz, $CDCl_3$): δ =16.0, 23.1, 40.3, 42.6, 51.2, 52.4, 53.0, 72.3, 106.5, 110.2, 110.3, 110.7, 117.7, 118.6, 119.0, 121.5, 122.6, 122.9, 127.0, 127.0, 127.2, 127.5, 127.7, 127.8, 128.2, 128.4, 128.4, 128.5, 128.8, 133.8, 134.0, 135.4, 135.5, 135.7, 138.0, 138.2, 139.4, 139.8, 140.2, 169.9, 174.9. HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{27}N_2O_2$: 411.2073; found: 411.2060.
(5*R*,6*S*)-5-Hydroxy-6-phenyl-3-[(*S*)-1-phenylethyl]-2,3,5,6-tetrahydro-1*H*-azocino[5,4-*b*]indol-4(7*H*)-one (15b): obtained as a white solid (0.38 g, 80%); mp 147–150 °C; $[\alpha]_D^{20}$ –1.2 (*c* = 1.0, CH_2Cl_2). The NMR data is reported as a mixture of rotamers. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78 (d, *J* = 6.8 Hz), 1.59 (d, *J* = 7.2 Hz), 3.03–3.20 (m), 3.20–3.30 (m), 3.39–3.53 (m), 3.87 (d, *J* = 8.8 Hz), 4.27 (d, *J* = 8.8 Hz), 4.95 (t, *J* = 8.8 Hz, 1 H), 5.83 (q, *J* = 6.8 Hz, 1 H), 5.99 (q, *J* = 6.8 Hz), 7.13–7.36 (m), 7.51–7.54 (m), 8.02 (s), 8.20 (s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.6, 23.4, 41.0, 41.3, 51.6, 51.9, 53.5, 72.3, 106.8, 110.7, 110.8, 117.3, 118.7, 119.2, 119.4, 119.5, 121.9, 123.0, 127.3, 127.4, 127.5, 127.5, 127.8, 128.3, 128.5, 128.6, 128.9, 132.9, 134.3, 135.3, 135.7, 137.9, 139.4, 139.9, 140.0, 169.6, 174.7. HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{27}N_2O_2$: 411.2073; found: 411.2079.

(15) **Birch Debenzylation**: A solution of **15b** (0.26 g, 0.63 mmol) in anhyd THF (2 mL) was added dropwise to a deep blue solution of Li (0.030 g, 4.38 mmol) in condensed NH_3 (ca. 5 mL) at –78 °C. The reaction mixture was allowed to stir for 3 h at –78 °C before H_2O (3 mL) was added. The mixture was extracted with EtOAc, dried with Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, and recrystallized in CH_2Cl_2–hexane to afford the corresponding product.
(–)-Norbalasubramide: obtained as a white solid (0.15 g, 79%); mp 251–255 °C (decomp.); $[\alpha]_D^{20}$ –2.9 (*c* = 0.2, $CHCl_3$); $[\alpha]_D^{20}$ –3.8 (*c* = 0.5, MeOH), {$[\alpha]_D^{20}$ –2.5 (*c* = 0.2, $CHCl_3$); see ref. 16}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.19–3.40 (m, 4 H), 3.60–3.71 (m, 1 H), 4.20 (d, *J* = 9.2 Hz, 1 H), 4.88 (d, *J* = 9.2 Hz, 1 H), 7.10 (ddd, *J* = 8.8, 7.2, 1.6 Hz, 2 H), 7.20–7.41 (m, 6 H), 7.44–7.63 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.8, 40.1, 52.6, 71.9, 106.2, 110.8, 117.2, 119.0, 121.6, 127.2, 128.1, 128.3, 128.5, 134.2, 135.5, 140.0, 176.9. (+)-**Norbalasubramide**: obtained as a white solid (0.14 g, 76%); mp 251–255 °C (decomp.); $[\alpha]_D^{20}$ +3.7 (*c* = 0.5, MeOH).

(16) Zheng, C.; Li, Y.; Yang, Y.; Wang, H.; Cui, H.; Zhang, J.; Zhao, G. *Adv. Synth. Catal.* **2009**, *351*, 1685.

