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TETRAHEDRON: *ASYMMETRY*

Formal enantioselective synthesis of (+)-vincamine. The first enantioselective route to (+)-3,14-epivincamine and its enantiomer

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Abstract

A formal synthesis of (+)-vincamine (**1**) from (*S*)-(+)-2-ethyl-2-(2-methoxycarbonylethyl) cyclopentanone (**6a**) is described. This intermediate had previously been obtained by our research group in 90% ee through d'Angelo's deracemizing alkylation of the chiral imine **7**, easily prepared from (*R*)-(+)-α-methylbenzylamine and 2-ethyl cyclopentanone with methyl acrylate. A potencial advanced intermediate for the synthesis of (+)-**4**, an epimer of (+)-**1** at positions C-3 and C-14, has also been prepared from **6a**.

1. Introduction

(+)-Vincamine (**1**) and (−)-eburnamonine (**2**) (Fig. 1) are among the most important naturally occurring indole alkaloids. They show a strong vasodilation activity which brings about powerful central oxygenation.[2] Vinpocetin (**3**), the semisynthetic analog of (+)-**1**, has a similar biological activity. These compounds have been therapeutically used in cases of central sclerosis and cerebral vascular accidents. In addition, **3** showed activity on gastric ulcers, probably due to an effect on prostaglandins release.[3]

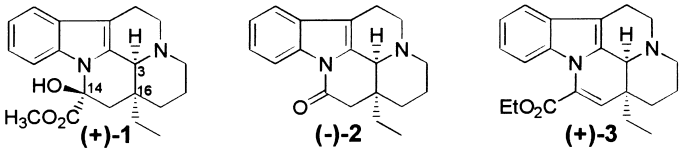

Figure 1.

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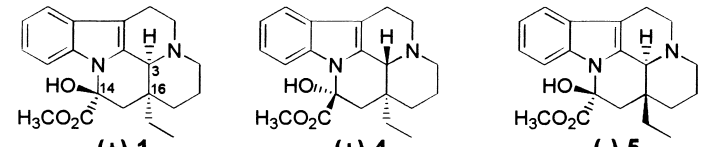


Figure 2.

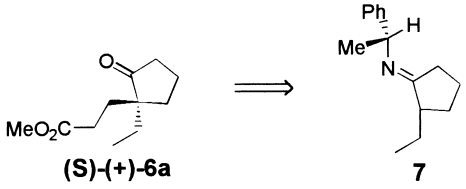


Figure 3.

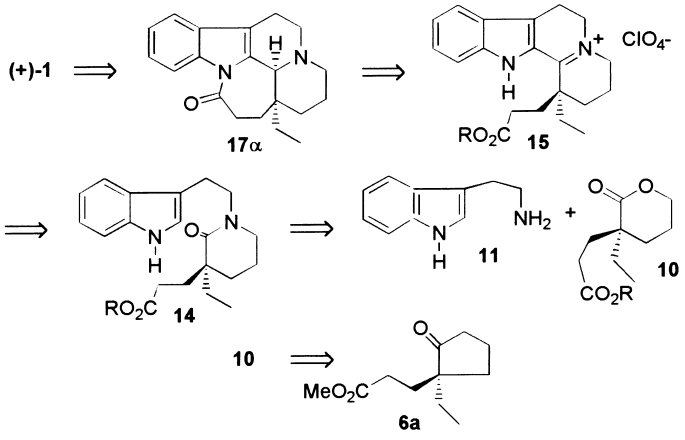
A common feature of these compounds is the presence of a *cis* junction of rings D/E, with absolute configuration *S* at both C_3 and C_{16} stereocenters. Recently, Nemes et al.[4] reported a study involving the obtention, through resolution, of all the stereoisomers of **1** (Fig. 2). The effect of these compounds on the femural blood flow (FBF) and internal carotid blood flow (ICBF) were used to evaluate their action as peripheric and central vasodilators, respectively. Two new substances, (+)-**4** and (−)-**5**, presenting a *trans* D/E ring junction, emerged from this study as interesting synthetic targets. They proved to be more selective than **1** in the mentioned biological assays. While (+)-**4** is more active and selective as a central vasodilator than **1**, (−)-**5** has no central activity, but it is a peripheric vasodilator about seven times as active as **1**.

In this paper, we report the formal enantioselective synthesis of (+)-**1** from (*S*)-(+)-2-ethyl-2-(2-methoxycarbonylethyl) cyclopentanone (**6a**) (Fig. 3).[5] This intermediate had been previously[6] obtained by our research group in 90% ee through d'Angelo's deracemizing alkylation[7] of the chiral imine **7** (easily prepared from (*R*)-(+)-α-methylbenzylamine and 2-ethyl cyclopentanone) with methyl acrylate. Moreover, a potential advanced intermediate for the synthesis of (+)-**4** has been prepared from a late intermediate of the formal synthesis of **1**.

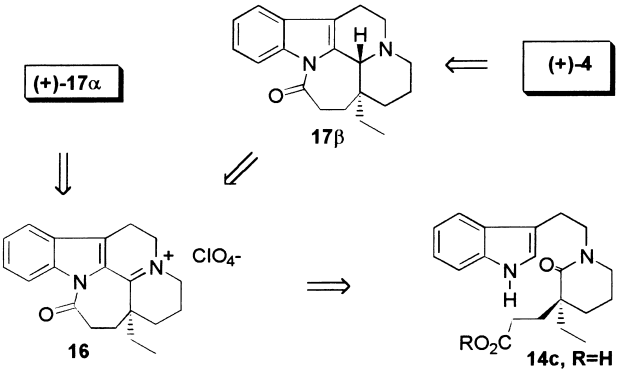
2. Synthetic strategy

A great deal of effort has been devoted to the development of synthetic strategies to control the relative and absolute configuration of stereocenters C_3 and C_{16} of eburnane alkaloids such as **1**.[8,9] A useful approach for the synthesis of **1** involves pentacyclic lactam **17α**[10] (Scheme 1). We envisioned that the preparation of this intermediate could be obtained by a stereoselective reduction of imminium intermediate[11] **15**, followed by cyclization. Substance **15** would be the result of Bischler–Napieralski cyclization[12] of lactam **14**. Our approach for the synthesis of **14** would involve chemoselective nucleophilic attack of chiral lactone **10** by tryptamine **11** and further cyclization of the produced hydroxyamide. At last, **10** might be prepared from already mentioned chiral cyclopentanone **6a** via oxidative ring expansion of the corresponding silyl enol ether.

Alternatively, we decided to explore the stereoselective reduction of novel pentacyclic imminium salt **16** (Scheme 2) which might enable the preparation of both lactam **17α** and **17β**. Intermediate **16** could evolve from double cyclization of acid **14c** effected under Bischler–Napieralski conditions. The latter compound is a potential intermediate for the synthesis of (+)-**4**.



Scheme 1.

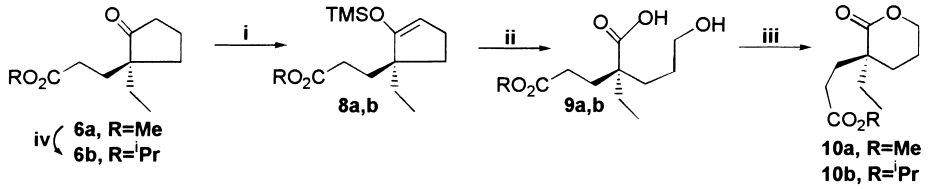


Scheme 2.

3. Results

Compound **6a** was transformed, in high yield, into the silyl enol ether **8a** (R=Me) (Scheme 3) by reaction with TMSCl in CH_3CN, in the presence of Et_3N and NaI.[13] This crude intermediate was allowed to react with ozone in CH_2Cl_2–MeOH solution, followed by reduction of the resulting ozonide with $NaBH_4$, leading to the hydroxy acid **9** (R=Me). Cyclization of crude **9** to **10a** was easily achieved by acid catalysis with concentrated HCl in CH_2Cl_2 (80% yield for the three steps). The next step in our synthetic strategy would be the chemoselective attack of tryptamine **11** at the lactonic carbonyl group of **10a**. Due to its neopentylic nature, contrasting with the unhindered methyl ester at the side chain, an opposite chemoselectivity might result. In order to protect the side chain carbonyl group and direct the reaction to the ring carbonyl function, we also prepared lactone **10b**, presenting a carboisopropoxy propanoate side chain. Thus, the starting material for the synthesis of **10a**, cyclopentanone **6a**, suffered transesterification with substoicheometric sodium isopropoxide in isopropanol to afford compound **6b**. This substance was transformed into **10b** through the same route employed in the preparation of **10a** with a similar overall yield.

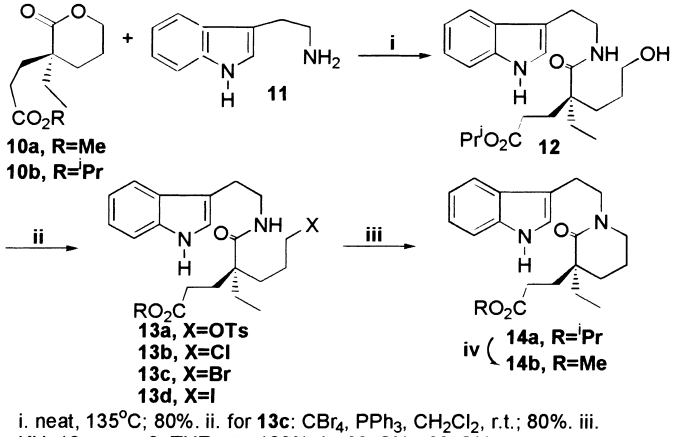
The reaction of **10a** with tryptamine **11** (Scheme 4) was studied. In the absence of solvent[14] at 135°C, a mixture of products was formed. Analysis of the crude product by ^1H NMR showed a decrease in the absorption of the methyl group indicating that the methyl ester in **10a** was, at least in part, touched. Therefore, employment of **10b** was studied. Solventless reaction of **10b** and **11** under the same conditions led to hydroxyamide **12** in good yield. Thus, the presence of the more bulky isopropoxide moiety at the



i. TMSCl-NaI, Et_3N, CH_3CN, r.t.; 95% (for **8b**) . ii. a) O_3, MeOH,CH_2Cl_2, -78°C. b) $NaBH_4$, -78°C-r.t.. iii. HCl conc., CH_2Cl_2; 80% from 8b. iv. ^iPrONa, ^iPrOH, r.t.; 80% (for **10b**).

Scheme 3.

ester function in **7b** was actually able to protect this group against the attack of **11**. Unfortunately, this transformation was only compatible with small scales (100–500 mg of **10b**), supposedly for medium homogeneity reasons. Nevertheless, the same reaction could also be successfully effected in DMF at 100°C for 2 h, resulting in **12**. The next step would be the transformation of the hydroxyl group into an efficient leaving group, enabling the preparation of the lactam ring, to afford intermediate **14** via cyclization in basic condition.



i. neat, 135°C; 80%. ii. for **13c**: CBr_4, PPh_3, CH_2Cl_2, r.t.; 80%. iii. KH, 18-crown-6, THF, r.t.; 100%. iv. MeONa, MeOH, r.t.; quant.

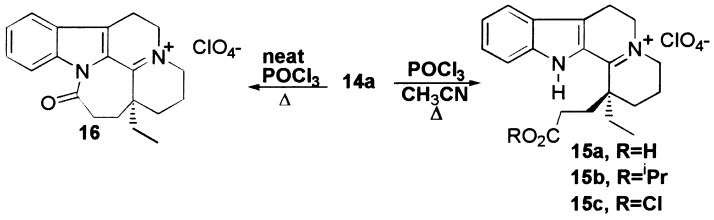
Scheme 4.

The conversion of alcohol **12** (Scheme 4) into tosylate **13a** was not successful. In one procedure [TsCl (5 equiv.), DMAP, pyridine, rt] we observed surprisingly low conversion to the desired product. Thus, a second procedure was employed [TsCl (5 equiv.), Et_3N, DMAP, CH_2Cl_2] but, after 20 h at rt, there still remained a considerable amount of starting material. So, the reaction mixture was heated at 80°C in an attempt to completely consume **12**. However, this led to formation of a mixture containing chloride **13b** along with desired product **13a**. Then, we found that the use of the CBr_4 bromination method[15] could afford us substance **13c** efficiently. We also prepared iodide **13d** by a similar procedure (I_2, PPh_3, imidazol, CH_2Cl_2, 0°C–rt),[16] but this reaction only led to a moderate yield (50%). When bromide **13c** was subjected to deprotonation with LDA (LDA, HMPA, THF, −78°C–rt), the desired cyclization product **14** was obtained in 30% yield. The employment of iodide **13d** as starting material under the same conditions did not provide a sensibly higher yield (35%). Fortunately, the cyclization of **13c** with KH in the presence of 18-crown-6 led to lactam **14a** quantitatively. We observed that the use of 18-crown-6 ether was a requisite for a clean reaction, although the reaction in the absence of it was also quite satisfactory (TLC, ^1H NMR of the crude product).[17]

At the time we achieved the preparation of lactam **14a**, d'Angelo's group was independently finishing their synthesis of **1**.[8b] In their work, they employed lactam **14b** as an intermediate. As the chemistry

they used for conversion of **14b** into the final target relied basically on literature procedures, we felt that there might not be much place for improvement by our own work. Therefore, we effected the transformation of the isopropyl ester **14a** into **14b** through transesterification with catalytic NaOMe in MeOH, which occurred quantitatively. Physical and spectroscopic data of **14b** were compatible with those obtained for the same substance prepared by d'Angelo's group. So, the synthesis of **14b** secured a formal enantioselective synthesis of **1**.

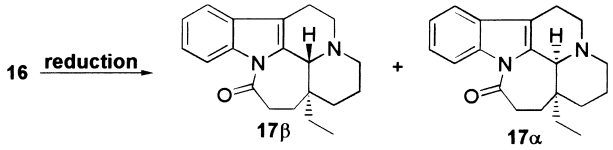
Despite having attained the formal synthesis of **1**, we decided to investigate whether we could obtain a more advanced intermediate of **1** avoiding the transesterification of **14a**. Thus, we turned to the Bischler–Napieralski reaction of this substance (Scheme 5) and the reduction of the generated imminium salt. Lactam **14a** was heated in the presence of a large excess of $POCl_3$ in CH_3CN for several hours and the reaction mixture was treated according to the usual workup. The product of this reaction consisted of a mixture of perchlorates **15a** and **15b**. The formation of acid **15a** indicated the lability of the carboisopropoxy group under the cyclization conditions, which forbids the preparation of a tetracyclic precursor **15** of our synthetic strategy carrying an isopropyl ester side chain. It is important to note that the bulky isopropyl group might be needed for high stereoselectivity in the reduction of this intermediate. Even under milder conditions, a considerable amount of the isopropyl substituent cleavage product **15a** was formed. Thus, we decided to apply forceful conditions on **14a** so that all **15b** was converted to acid chloride **15c** (the actual precursor of **15a**), which could eventually cyclize in situ to the seven-membered ring lactam. Indeed, heating of **14a** in neat $POCl_3$ at 120°C for 2 days brought about C-ring formation, complete cleavage of the isopropyl group and cyclization of the in situ generated acid chloride **15c**, giving the expected product **16**. This is the first report of the pentacyclic imminium lactam **16**.



Scheme 5.

Reduction of **16** with Zn in AcOH[18] led to an easily separable 3:2 mixture of diastereomers **17β** and **17α**,[19] respectively (Scheme 6). Unfortunately, compound **17α**,[10] a known precursor of **1**, is the minor product of that reaction. Furthermore, reaction of **16** with the bulky aluminum hydride[14] afforded amine **17β** as a single product. The overall yield of this reaction is quite satisfactory as it concerns three reaction events. Compound **17β** presents both stereocenters C_3 and C_{16} in the same absolute configuration as that of (+)-epivincamine **4**. Use of the literature procedures [4,8b,10a] for conversion of **17α** into **1** might also produce (+)-**4** from **17β**. As the methodology we employed in the synthesis of chiral starting material **6a** enables equally easy access to *ent*-**6a**, we may say that we have also formally achieved the preparation of *ent*-**17β**, a potentially advanced precursor of peripheric vasodilator (−)-**5**.

In summary, we have successfully employed the imine deracemization reaction in the synthesis of chiral lactam **14b**. The preparation of that intermediate configures a formal synthesis of (+)-vincamine. Moreover, we have been able to convert lactam **14a** into potential (+)-epivincamine's precursor **17β** in only two steps. The first step of the process involved a double cyclization under Bischler–Napieralski conditions, which afforded novel pentacyclic imminium **16**. This compound could be stereoselectively reduced to lactam **17β**.



Reduction Condition	Yield *	14β : 14α ratio
Zn, AcOH, r.t.	30%	3 : 2
$LiAl(OtBu)_4$, THF, 0°C	35%	1 : 0

* from lactam **14a**.

Scheme 6.

4. Experimental

4.1. General

All nonaqueous reactions were conducted under an atmosphere of nitrogen. Solvents/reagents were dried as follows: CH_3CN, CH_2Cl_2, Et_3N, $POCl_3$ (under vacuum) and TMSCl were distilled from CaH_2; THF was distilled from sodium/benzophenone; MeOH and ^{i}PrOH were treated with sodium and the resulting solution was distilled; NaI was heated at 100°C under vacuum. Unless otherwise noted, chromatographic purifications were performed under medium pressure on 230–400 mesh silica gel (flash chromatography).

*4.2. (S)-2-Ethyl-2-(2-methoxycarbonylethyl) cyclopentanone (**6a**)*

A mixture of 2-ethylcyclopentanone (4.0 g, 35.71 mmol), (*R*)-(+)-1-phenylethylamine (5.06 mL; 39.28 mmol) and a catalytic amount of *p*-toluenesulfonic acid in toluene (35 mL) was heated to reflux in a Dean–Stark apparatus for 5 h. Then, the volatiles were removed under vacuum to afford crude imine **7** (6.38 g) as a brownish oil. To this substance, neat methyl acrylate (26.7 mL, 0.296 mol) was added at rt and the resulting mixture was stirred for 48 h. Finally, 10% aqueous AcOH (25 mL) and THF (15 mL) were added to the reaction mixture. After 1 h, the product was extracted with CH_2Cl_2 (5×15 mL). The combined organic layers were successively washed with 10% aqueous HCl and 5% aqueous $NaHCO_3$, dried (Na_2SO_4) and concentrated under vacuum. The obtained residue was chromatographed (eluent 1:9 EtOAc:hexanes) to furnish **6a** (4.06 g, 70%) as a yellowish oil. The enantiomeric excess of **6a** was found to be 90% and was measured by ^{1}H NMR employing $Eu(tfc)_3$ as a chiral shift reagent.

$[\alpha]_D^{20}$=+8.1 (c=5.92, CH_2Cl_2); IR (thin film) 1735 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.63 (3H, s), 2.15–2.37 (4H), 1.60–1.90 (6H), 1.35–1.45 (2H, m), 0.76 (3H, t); ^{13}C NMR (75 MHz, $CDCl_3$) δ 222.3, 173.9, 51.6, 50.9, 38.1, 33.2, 28.9, 26.8, 18.5, 8.3; LRMS (EI, 70 eV) 198 (M^+), 55; HRMS calcd mass for $C_{11}H_{18}O_3$=198.125595, found=198.125504.

*4.3. (S)-2-Ethyl-2-(2-isopropoxycarbonylethyl) cyclopentanone (**6b**)*

Cyclopentanone **6a** (10.04 g, 50.72 mmol) in isopropanol (80 mL) at rt was treated with a solution of sodium isopropoxide (2.83 mmol) in isopropanol. After 15 min, the solvent was evaporated. EtOAc was then added to the residue and the mixture was washed with 10% aqueous HCl and water. The organic layer was dried over Na_2SO_4 and concentrated to give **6b** as a yellow oil (9.16 g, 80%) in satisfactory purity.

$[\alpha]_D^{25}$=+9.5 (c=2.0, EtOH); IR (thin film) 2971, 1734 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.99 (1H, m), 2.10–2.40 (4H), 1.62–2.00 (6H), 1.39–1.54 (2H, m), 1.23 (6H, d, *J*=6.3 Hz), 0.84 (3H, t, *J*=7.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 222.0, 172.6, 67.3, 50.7, 37.9, 32.9, 29.2, 28.6, 26.6, 21.5, 18.2, 8.0; LRMS (EI, 70 eV) 226 (M^+), 167, 111; HRMS (EI) calcd mass for $C_{13}H_{22}O_3$=226.156895, found=226.156493.

4.4. Silyl enol ether **8**

TMSCl (3.8 mL, 29.34 mmol) was added to a suspension of NaI (6.76 g, 45.15 mmol) in acetonitrile (5 mL) at 0°C. The resulting mixture was then stirred at rt for 10 min. Afterwards, Et_3N (6.3 mL, 45.15 mmol) followed by cyclopentanone **6b** (5.1 g, 22.57 mmol) dissolved in acetonitrile (15 mL) was added. The reaction was allowed to proceed at rt for 30 min. Then, the reaction mixture was poured over an aqueous saturated solution of $NaHCO_3$. The product was extracted with hexanes and the organic layer was dried over Na_2SO_4. Finally, the volatiles were evaporated to give **8** (6.39 g, 95%) as a brownish oil.

IR (thin film) 2960, 1730, 1645 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.02 (1H, m), 4.51 (1H, t, *J*=2.3 Hz), 2.22–2.44 (2H, m), 1.80–2.20 (4H), 1.27–1.70 (4H, m), 0.99–1.08 (6H), 0.84 (3H, t, *J*=7.4 Hz), 0.12 (9H, s).

4.5. Lactone **10b**

MeOH (10 mL) was added to a solution of silyl enol ether **8** (6.35 g, 21.3 mmol) in CH_2Cl_2 (50 mL) at −78°C. Then, the obtained solution was treated with an ozone/O_2 flow until it became blue. An O_2 flow was passed through the reaction mixture in order to drive the ozone excess out and $NaBH_4$ (1.61 g, 42.6 mmol) was added. Stirring proceeded for 15 min at −78°C, 30 min at 0°C, and after that, the reaction mixture was allowed to warm up to rt. After 2.5 h, a 5% aqueous HCl solution was added until pH 1.0 and the product was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated to afford **9** as a brownish oil (5.96 g). This crude material was dissolved in CH_2Cl_2 (50 mL) and 5 drops of concentrated aqueous HCl was added. After 3 h at rt under stirring, the mixture was diluted with CH_2Cl_2 and washed with H_2O, aqueous saturated $NaHCO_3$ and H_2O, in that order. Finally, the organic layer was dried over Na_2SO_4 and concentrated to give lactone **10b** (4.16 g, 80%) as a yellowish oil. This residue proved to be fairly pure by ^1H NMR and it could be successfully employed in crude form for the preparation of amide **12**. We found that this compound is sensitive towards silica gel which forbade chromatography as a means of purification.

IR (thin film) 2976, 1728 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.99 (1H, m), 4.32 (2H, t, *J*=5.3 Hz), 2.34 (2H, m), 1.45–2.10 (8H), 1.22 (6H, d, *J*=6.3 Hz), 0.92 (3H, t, *J*=7.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.8, 172.3, 69.8, 67.5, 45.1, 33.0, 31.1, 29.5, 29.0, 21.4, 20.7, 8.2; LRMS (EI, 70 eV) 214, 183, 128.

4.6. Hydroxyamide **12**

A mixture of lactone **10b** (0.4 g, 1.65 mmol) and tryptamine (0.317 g, 1.98 mmol) was fused at 135°C under stirring (by means of a small magnetic bar). After 3 h, the reaction mixture was allowed to cool to rt. This material was chromatographed (eluent 1:1 EtOAc:hexanes). The desired product **12** (0.531 g, 80%) was obtained as a brown oil.

$[\alpha]_D^{25}$=−1.1 (c=4.5, EtOH); IR (thin film) 3333, 2939, 1713, 1637 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.17 (1H), 7.60–7.67 (1H, m), 7.35–7.43 (1H, m), 7.04–7.28 (3H, m), 5.86 (1H), 4.97 (1H, m), 3.63

(2H, m), 3.48 (2H, m), 2.99 (2H, m), 2.13 (2H, m), 1.30–1.85 (9H), 1.22 (6H, d, *J*=6.2 Hz), 0.76 (3H, t, *J*=7.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.0, 173.1, 136.3, 127.0, 122.2, 121.7, 119.0, 118.4, 112.2, 111.2, 67.7, 62.3, 47.7, 39.6, 30.0, 29.3, 29.0, 26.8, 25.1, 21.6, 8.0; LRMS (EI, 70 eV) 402 (M^+), 254, 143.

*4.7. Bromoamide **13c***

A solution of PPh_3 (3.32 g, 12.69 mmol) in CH_2Cl_2 (50 mL) was slowly added to a mixture of hydroxyamide **12** (3.40 g, 8.46 mmol) and CBr_4 (8.42 g, 25.38 mmol) in CH_2Cl_2 (80 mL) at rt. After 2 h, the resulting mixture was concentrated. The residue was chromatographed (eluent 3:7 EtOAc:hexanes) to afford the desired bromide **13c** (3.14 g, 80%) as a yellow oil.

$[\alpha]_D^{25}$=+3.8 (c=2.1, EtOH); IR (thin film) 3290, 2971, 1733, 1612 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.23 (1H), 7.58–7.66 (1H, m), 7.34–7.42 (1H, m), 7.02–7.26 (3H), 5.79 (1H), 4.97 (1H, m), 3.62 (2H, m), 3.28 (2H, m), 2.98 (2H, m), 2.04–2.20 (2H, m), 1.36–1.84 (8H), 1.22 (6H, d, *J*=6.3 Hz), 0.76 (3H, t, *J*=7.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.2, 172.8, 136.3, 127.1, 122.0, 119.3, 118.5, 112.6, 111.2, 67.7, 47.7, 39.5, 33.9, 32.7, 29.3, 29.0, 27.1, 26.6, 25.2, 21.6, 7.9; LRMS (CI) 466 (M^++1).

*4.8. (S)-3-Ethyl-1-[2-(1H-indol-3-yl)ethyl]-2-oxo-3-piperidine propanoic acid isopropyl ester (**14a**)*

A solution of bromide **13c** (1.29 g, 2.78 mmol) in THF (200 mL) was slowly added to a suspension of KH (0.167 g, 4.17 mmol) in THF (50 mL) containing 18-crown-6 (0.44 g, 1.67 mmol) at rt. Ten minutes later, H_2O was carefully added and the product was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated. The resulting residue was filtered on a silica gel column, which was eluted with EtOAc. Concentration of the filtrate afforded lactam **14a** (1.06 g, 100%) as a colorless oil.

$[\alpha]_D^{25}$=+10.3 (c=1.55, EtOH); IR (thin film) 3268, 2936, 1729, 1614 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.48 (1H), 7.64–7.72 (1H, m), 7.33–7.40 (1H, m), 7.01–7.23 (3H, m), 5.00 (1H, m), 3.65 (2H, m), 3.20 (2H, m), 3.00 (2H, m), 2.16–2.44 (2H, m), 1.40–2.10 (6H), 1.23 (6H, d, *J*=6.2 Hz), 0.86 (3H, t, *J*=7.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.6, 173.4, 136.2, 127.3, 122.1, 121.6, 119.0, 118.5, 112.8, 111.1, 67.4, 48.7, 48.4, 44.1, 33.1, 30.9, 30.0, 29.3, 23.0, 21.7, 19.6, 8.4; LRMS (EI, 70 eV) 384 (M^+), 325, 143.

*4.9. (S)-3-Ethyl-1-[2-(1H-indol-3-yl)ethyl]-2-oxo-3-piperidine propanoic acid methyl ester (**14b**)*

This compound was prepared by a similar procedure (sodium methoxide in the place of sodium isopropoxide) as that employed in the preparation of cyclopentanone **6b**.

$[\alpha]_D^{25}$=+15.5 (c=2.0; EtOH) {literature $[\alpha]_D$=+15.3 (c=1.9, EtOH)}; IR (thin film) 3269, 2948, 1734, 1615 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.25 (1H), 7.62–7.72 (m, 1H), 7.32–7.40 (m, 1H), 7.00–7.24 (m, 3H), 3.48–3.80 (m, 5H), 3.20 (m, 2H), 3.00 (m, 2H), 2.18–2.48 (m, 2H), 1.40–2.10 (8H), 0.85 (3H, t, *J*=7.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.2, 173.5, 136.2, 127.2, 122.1, 121.5, 118.8, 118.4, 112.5, 111.1, 51.4, 48.6, 48.5, 44.0, 33.0, 30.7, 29.4, 29.3, 22.9, 19.5, 8.3; LRMS (EI, 70 eV) 356 (M^+), 325, 279, 143.

*4.10. Perchlorate **16***

Lactam **14a** (0.066 g, 0.173 mmol) was dissolved in $POCl_3$ (1.0 mL) and heated at 120°C for 48 h. Then, the volatiles were removed and H_2O was added. The resulting mixture was heated to reflux for

30 min, cooled down to rt and poured into a 2 M aqueous solution of $NaClO_4$ (2.0 mL). The product was extracted with CH_2Cl_2 several times. The combined organic layers were dried over Na_2SO_4 and concentrated to give a brown crystalline residue (0.06 g), which was partially characterized as imminium perchlorate **16**. This substance in crude form was subjected to two reduction procedures, which follow.

*4.11. (3*R,*17*S*)-14-Oxo-3*-epi-E-*homoeburnan (17β)*

tert-Butanol (0.5 mL, 5.19 mmol) was added dropwise to a suspension of LAH (0.066 g, 1.73 mmol) in THF (1.5 mL) at 0°C. The resulting mixture was stirred for 2 h under the same conditions. Then, crude perchlorate **16** (0.06 g) in THF (1.0 mL) was slowly added to the solution of the just prepared reduction reagent. The reaction mixture was maintained at 0°C for 4 h. Afterwards, a 10% aqueous solution of acetic acid (2.0 mL) was added and stirring proceeded for further 30 min. Eventually, the reaction mixture was filtered through a short Celite pad, which was eluted with CH_2Cl_2. The filtrate was washed once with water. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by preparative TLC (eluent 3:7 EtOAc:hexanes), which gave lactam **17β** (18 mg, 35%) as a yellowish oil.

$[\alpha]_D^{25}$=+135.3 (c=1.7, CH_2Cl_2); IR (thin film) 1698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.42–8.54 (1H, m), 7.36–7.46 (1H, m), 7.20–7.36 (2H, m), 3.43 (1H, s), 2.30–3.20 (8H), 1.20–2.20 (6H), 0.95 (2H, m), 0.70 (3H, t, *J*=7.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.7, 136.1, 133.1, 129.3, 124.3, 123.4, 118.4, 117.4, 117.0, 67.7, 56.4, 52.2, 37.5, 35.4, 33.6, 33.1, 25.5, 22.1, 21.9, 6.6; LRMS (EI, 70 eV) 308 (M^+).

4.12. Reduction of perchlorate 16 with Zn/aqueous acetic acid: preparation of D*-homoeburnamen-14(15*H*)-one 17α*

A mixture of crude perchlorate **16** (0.12 g) and zinc powder (0.336 g) in acetic acid:H_2O (1:2) was stirred at rt for 1 day. The obtained mixture was filtered and the filtrate was treated with a 10% aqueous NaOH solution until pH 11. The products were extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated to afford a residual oil containing lactams **17α** and **17β**. These compounds were separated by chromatography (eluent 1:9 EtOAc:hexanes) which led to pure **17α** (11 mg) and **17β** (17 mg) in 30% overall yield from **14a**. $[\alpha]_D^{25}$ of **17α**=+18 (c=0.5, CH_2Cl_2) {literature $[\alpha]_D$=+17.0 (c=1.00, CH_2Cl_2)}. All other physical data of **17α** are consistent with those in the literature.

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