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TETRAHEDRON: *ASYMMETRY*

Formal enantioselective synthesis of tacamonine starting from asymmetrized 2-substituted propane-1,3-diols

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Abstract

2-Substituted propanediols monoacetates, derived from enzymatic asymmetrization of the corresponding diols, have been obtained in high yields and enantiomeric excesses by using lipases and vinyl acetate as both solvent and acylating agent. These chiral building blocks have been transformed into the advanced intermediate **3**, useful for the enantioselective synthesis of tacamane alkaloids.

1. Introduction

The strategy of using C_S-symmetric precursors in the asymmetric synthesis of complex natural molecules is based on the ability to identify simple symmetrical units as starting materials through a correct retrosynthetic analysis.[1] Following this concept, over the last decade, our group has been interested[1,2] in the applications of optically active C_1-synthons, obtained through enzyme-mediated transesterification or hydrolysis of the corresponding *meso*-precursors. However, for certain synthetic purposes, examination of the target structure suggests more appropriate chiral synthons, possibly accessible by enzymatic discrimination of enantiotopic groups linked to an achirotopic carbon atom, such as in the case of 2-substituted propanediols or malonates. Following this approach, we report here an efficient lipase-mediated preparation of the new chiral synthons **5** and **6** and their conversion into an advanced intermediate for the enantiosynthesis of tacamane alkaloids.

Tacamonine **1**, one of the few indole alkaloids of the tacamane type, was isolated in 1984 from *Tabernaemontana eglandulosa*[3] and has been found to show a structural similarity to eburnamonines,[4] which are *Hunteria* alkaloids possessing vasodilator and hypotensive activities. Even if a great deal of

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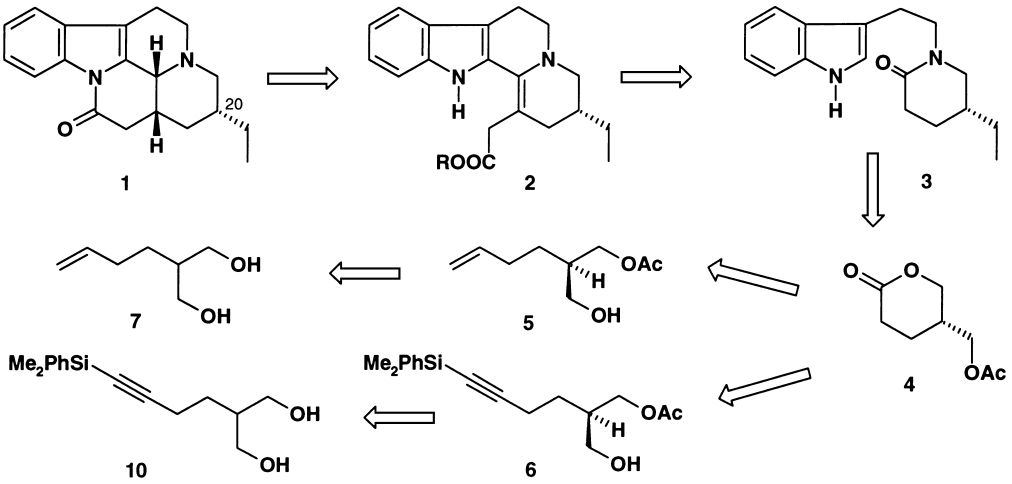
effort has been devoted to the development of strategies for the synthesis of **1**, few stereoselective routes have been published to date.[5,6]

2. Results and discussion

We envisaged the optically active lactam **3** as a key synthetic intermediate for the enantiosynthesis of **1**. In the pioneering work of Levy et al.,[7] **3** has been prepared in racemic form by condensation of tryptamine with 4-formyl hexanoate. The conversion to **1** was performed using standard chemistry, leading to all the four possible tacamonine isomers, well before the isolation of the naturally occurring isomer **1**. In our retrosynthetic plan (Scheme 1), preparation of **3** could involve chemoselective nucleophilic attack of chiral lactone **4** by tryptamine, subsequent cyclization of the produced hydroxyamide and homologation of the C20 side chain. In turn, lactone **4** could be produced by two different approaches, both utilizing enzymatic asymmetrization of 2-substituted 1,3-propanediols[8] as the key step.



Scheme 1.

The PPL-catalyzed transesterification of diol **7**[9a] was reported by Tombo et al.[9b] leading to **5** in 70% yield and 90% e.e. With the aim of improving both the yield and enantioselectivity of the process, we carried out a comparative study using some commercially available enzymes (Table 1), and we found that, using vinyl acetate both as solvent and acyl donor, and Amano PS lipase from *Pseudomonas cepacea*, a substantial increase in the rate and enantioselection was achieved (Table 1).

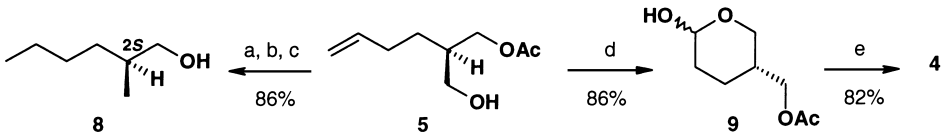
In order to confirm its 2*R* absolute configuration, **5** was converted to 2-methylhexan-1-ol **8** through the mesylate derivative, subsequent reduction with $LiAlH_4$ and hydrogenation of the double bond (overall yield 86%). The specific rotation was found to be $[\alpha]_D^{25}=-10.5$ (c=1, $CHCl_3$) {lit.[10] $[\alpha]_D^{25}=-10.7$ (c=1, $CHCl_3$)}, thus establishing the absolute configuration as 2*S* (Scheme 2) for **8**.

Having found an efficient procedure for preparing **5** in high yield and e.e., we performed chemical transformations in order to obtain the key intermediate **4**. Compound **5** was reacted with ozone leading to lactol **9** as a mixture of C2 epimers. Oxidation of **9** was strongly dependent upon the reagent and conditions: reactions with $KMnO_4$ and with CrO_3–Py_2 left the substrate substantially unaltered, while a partial oxidation was achieved using catalytic tetra-*n*-propylammonium perruthenate (TPAP) in the presence of *N*-methylmorpholine *N*-oxide. Finally, oxidation of **9** worked smoothly on a small scale using freshly prepared $AgCO_3$ supported on Celite, yielding 82% of **4**. Since the Fetizon[11] reagent is

Table 1
Results of the lipase-catalyzed acetylation of **7** and **10**

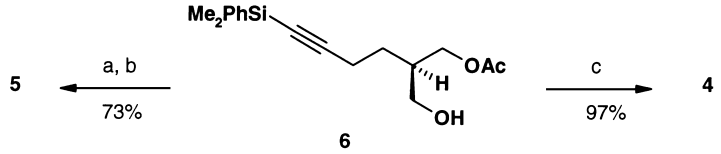
entry	substrate[a]	lipase[b]	time (h)	product (yield%)[c]	%e.e.
1	**7**	PPL	4	**5** (78)	90
2	**7**	PFL	5	**5** (95)	85
3	**7**	Amano PS	1	**5** (98)	>99
4	**10**	PPL	2	**6** (98)	>99
5	**10**	PFL	4	**6** (99)	95
6	**10**	Amano PS L.	3	**6** (98)	93

[a] 1.0 mmol of substrate in vinyl acetate at 25°C, as described in the Experim. Section. [b] PPL = Porcine pancreas lipase, PFL = lipase from *Pseudomonas Fluorescens*; Amano PS = lipase from *Pseudomonas Cepacea*. [c] Isolated yields.



Scheme 2. (a) MsCl, pyridine; (b) $LiAlH_4$, THF, 0°C; (c) H_2, Pd (C), EtOH; (d) O_3, MeOH/CH_2Cl_2, −78°C; (e) $AgCO_3$/Celite, benzene, Δ

expensive and not suitable for large scale preparations, the more direct approach depicted in Scheme 3 was examined.

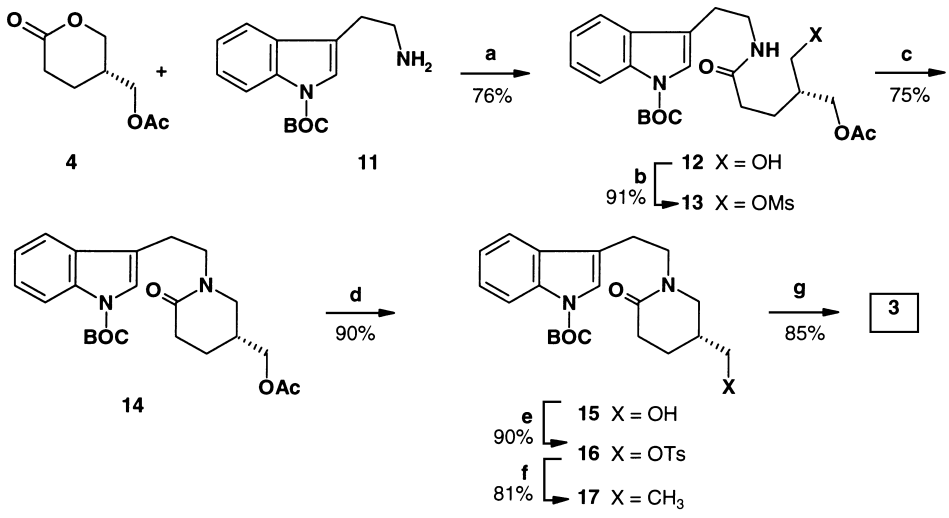


Scheme 3. (a) aq. 10% H_2SO_4, THF; (b) Pd/$BaSO_4$, quinoline, MeOH; (c) O_3, MeOH/CH_2Cl_2, −78°C

At this stage, we have studied the enantioselective transesterification of **10**, easily prepared by standard methodologies.[12] Under the same conditions already applied for the desymmetrization of **7**, PPL proved to be the most promising enzyme for providing monoacetate **6** with extremely high enantiomeric excess and in good yield. Chemical correlation of **6** to **5** via desilylation and partial hydrogenation of the triple bond indicated that **6** also possesses the 2*R* configuration. Ozonization of **6** afforded **4** in quantitative yield, overcoming the difficulties related to the oxidation of lactol **9**.

The attack of *N*-Boc-tryptamine **11** at the lactonic carbonyl group of **4** could be successfully effected in refluxing THF, giving **12** in good yield. The next step in our synthetic plan was the transformation of the hydroxyl group into an efficient leaving group, enabling the preparation of the lactam ring of intermediate **14** via cyclization in basic conditions. Thus, alcohol **12** was converted into mesylate **13** and then subjected to deprotonation with *t*BuOK to give the desired cyclization product **14** in 75% yield. Finally, in order to homologate the C20 acetoxymethyl side chain, the acetoxy group was hydrolyzed and then converted into the corresponding tosylate **16**. Cross-coupling condensation with dimethyllithium cuprate,[13] followed by *N*-Boc deprotection proceeded smoothly to give the desired chiral lactam **3** (Scheme 4).

Bischler–Napieralski cyclization of **3**, followed by a few other steps affording the fifth ring has been described[7] to give a diastereoisomeric mixture of pseudovincamones, from which the natural



Scheme 4. (a) THF, Δ; (b) MsCl, pyridine; (c) *t*BuOK, THF; (d) 0.5N NaOH, THF; (e) TsCl, Et_3N, CH_2Cl_2, 0°C; (f) CuI, MeLi, Et_2O, −40°C; (g) TFA, CH_2Cl_2

all-*cis* isomer could be separated. Thus, the synthesis of **3** secured a formal enantioselective entry to (+)-tacamonine. Despite this achievement, studies are in progress aimed at obtaining a completely stereocontrolled formation of C3 and C14 stereocentres, with the required *cis D*/*E* ring junction, and avoiding in this way the final step of diastereoisomeric separation.

3. Experimental[14]

3.1. Materials

Porcine pancreatic lipase (PPL, EC 3.1.1.3. of type II) was obtained from Sigma Chemical Co., *Pseudomonas fluorescens* lipase (PFL EC 3.1.1.3.) was purchased from Fluka and lipase Amano PS from *Pseudomonas cepacea* was provided by Amano Pharmaceutica (Japan). All enzymes were used without further purification.

3.2. General methods

Analytical liquid chromatography was carried out with a Kontron HPLC system equipped with a UV detector and a Chiracel ODH HPLC column, using *n*-hexane:*i*PrOH (97:3) as an eluant. Progress of the acetylations was monitored by HPLC analysis, and the reactions were stopped when they came to a near standstill. All separations were carried out under flash-chromatographic (FC) conditions on silica gel 60 (230–400 mesh) using the indicated eluents. The organic extracts were dried over anhydrous Na_2SO_4 prior to solvent removal on a rotary evaporator.

*3.3. General procedure for the enzymatic acetylation of 2-(but-3-enyl)-propane-1,3-diol **7** and 2-(4-dimethylphenyl silanyl-but-3-ynyl)-propane-1,3-diol **10***

To a solution of **7** or **10** (1 mmol) in dry vinyl acetate (10 ml) was added an appropriate enzyme (PPL, 45670 units/mmol substrate; PFL, 236 units/mmol substrate; Amano PS lipase, 5400 units/mmol

substrate) and the mixture was shaken at room temperature. After the appropriate time, the enzyme was filtered off, the solvent was evaporated, and the reaction product purified by FC. The optical purities of monoacetates **5** and **6** were determined by chiral HPLC (after conversion into its *p*-nitrobenzoic ester for **5**).

*3.3.1. (2*R*)-2-(Acetoxymethyl)hex-5-en-1-ol **5***

Oil; R_f (AcOEt:hexane, 1:1) 0.43; $[\alpha]_D^{25}$=+11.1 (c=1, $CHCl_3$), $[\alpha]_{365}^{25}$=+36.3 (c=1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86–5.71 (m, 1H), 5.08–4.93 (m, 2H), 4.19 (dd, 1H, *J*=11.0, 4.5 Hz), 4.09 (dd, 1H, *J*=11.0, 6.5 Hz), 3.61 (dd, 1H, *J*=11.0, 4.5 Hz), 3.52 (dd, 1H, *J*=11.0, 7.0 Hz), 2.18–2.08 (m, 2H), 2.06 (s, 3H), 1.95 (br s, 1H), 1.88–1.78 (m, 1H), 1.52–1.32 (m, 2H); HRMS calcd for $C_9H_{16}O_3$: 172.1099, found 172.1113. Anal. calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.37. Found: C, 62.68; H, 9.48.

*3.3.2. (2*R*)-2-(Acetoxymethyl)-6-dimethylphenylsilyl-hex-5-yn-1-ol **6***

Oil; R_f (AcOEt:hexane, 1:1) 0.40; $[\alpha]_D^{25}$=+10.8 (c=1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 2H), 7.36 (m, 3H), 4.19 (dd, 1H, *J*=11.2, 5.0 Hz), 4.12 (dd, 1H, *J*=11.2, 6.2 Hz), 3.63 (dd, 1H, *J*=11.2, 4.5 Hz), 3.55 (dd, 1H, *J*=11.2, 5.5 Hz), 2.38 (t, 2H, *J*=7.2 Hz), 2.07 (s, 3H), 2.03–1.93 (m, 1H), 1.70–1.52 (m, 2H), 0.4 (s, 6H); HRMS calcd for $C_{17}H_{24}O_3Si$: 304.1495, found 304.1508. Anal. calcd for $C_{17}H_{24}O_3Si$: C, 67.06; H, 7.95; O, 15.76. Found: C, 67.21; H, 8.01; O, 15.70.

*3.4. (5*S*)-2-Hydroxy-5-(acetoxymethyl)tetrahydropyran **9***

A solution of **5** (600 mg, 3.5 mmol) in MeOH (15 ml) and CH_2Cl_2 (8 ml) was cooled to −78°C. Ozone was bubbled into the solution until persistence of a blue colour. After further bubbling of O_3 for 5 min, Me_2S (2.5 ml) and pyridine (30 μl) were added. After 2 min the flask was put under a nitrogen atmosphere, allowed to warm to rt, and stirred for 2 h. The solution was concentrated under reduced pressure, the residue was dissolved in AcOEt and washed with water to give, after evaporation of the solvent, crude **9** (525 mg, 86%, mixture of epimers A:B, 1:1) which was used as such at once for further reactions: oil; R_f (AcOEt:hexane, 7:3) 0.28; $[\alpha]_D^{25}$=−5.1 (c=1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.12 (br s, $0.5H_B$), 4.75 (dd, *J*=8.4, 2.4 Hz, $0.5H_A$), 3.99 (dd, *J*=12.2, 5.6 Hz, $0.5H_{eqA}$), 3.95–3.85 (m, 2H), 3.77 (dd, *J*=11.2, 9.1 Hz, $0.5H_{eqB}$), 3.61 (dd, *J*=11.2, 4.2 Hz, $0.5H_{axB}$), 3.28 (dd, *J*=12.2, 9.0 Hz, $0.5H_{axA}$), 2.02 (s, 3H), 2.00–1.85 (m, 2H), 1.75–1.55 (m, 2H), 1.50–1.35 (m, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 171.0, 95.4, 92.0, 66.7, 65.4, 64.9, 62.6, 34.4, 34.2, 30.8, 29.2, 24.0, 20.8, 20.7; EIMS *m/z* (relative intensity) 174 (2, M^+), 157 (100), 114 (53). Anal. calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.11. Found: C, 55.21; H, 8.01.

*3.5. (5*S*)-5-(Acetoxymethyl)tetrahydropyran-2-one **4***

Method A: A mixture of **9** (500 mg, 2.87 mmol) and Ag_2CO_3/Celite (22.8 mmol, freshly prepared according to a literature procedure[11]) in benzene (90 ml) was heated under reflux for 8 h. The solid was collected by filtration, washed with CH_2Cl_2, and the combined filtrates evaporated to give, after purification by FC (eluent: AcOEt), pure **4** (406 mg, 82%).

Method B: Into a solution of **6** (500 mg, 1.6 mmol) in MeOH (15 ml) and CH_2Cl_2 (8 ml) ozone was bubbled until persistence of a blue colour. After further bubbling of O_3 for 5 min, the flask was put under a nitrogen atmosphere and stirred for 2 h. The solution was concentrated, the residue was dissolved in AcOEt and washed with aq. $NaHCO_3$ to give, after evaporation of the solvent and purification by FC (eluent: AcOEt), pure **4** (267 mg, 97%): oil; R_f (AcOEt:hexane, 7:3) 0.19; $[\alpha]_D^{25}$=+4.0 (c=1, $CHCl_3$); ^{1}H

NMR (300 MHz, $CDCl_3$) δ 4.37 (ddd, *J*=11.5, 6.8, 2.3 Hz, 1H), 4.14 (dd, *J*=11.4, 8.0 Hz, 2H), 3.99 (dd, *J*=11.5, 7.8 Hz, 1H), 2.60 (m, 2H), 2.33 (m, 1H), 2.08 (s, 3H), 2.07 (m, 1H), 1.68 (m, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 70.6, 64.7, 32.7, 28.9, 22.2, 21.2; EIMS *m/z* (relative intensity) 172 (15, M^+), 130 (100), 112 (45). Anal. calcd for $C_8H_{12}O_4$: C, 65.45; H, 5.50. Found: C, 65.58; H, 5.70.

*3.6. (4*R*)-*N*-[2-(*N*-Boc-indol-3-yl)ethyl]-4-acetoxymethyl-5-hydroxypentanamide **12***

A solution of *N*-Boc-tryptamine (670 mg, 2.6 mmol) in THF (5 ml) was added to a solution of **4** (370 mg, 2.2 mmol) in THF (4 ml). After heating at 60°C for 4 h, the solvent was evaporated and the residue was flash-chromatographed (eluent: AcOEt:hexane, 9:1) to give pure **12** (866 mg, 76%): oil; R_f (AcOEt) 0.30; $[\alpha]_D^{25}$=+6.8 (c=1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, *J*=8.7 Hz, 1H), 7.53 (d, *J*=8.7 Hz, 1H), 7.41 (s, 1H), 7.31 (t, *J*=7.5 Hz, 1H), 7.22 (t, *J*=7.5 Hz, 1H), 5.60 (br s, 1H), 4.11 (dd, *J*=12.0, 4.8 Hz, 1H), 4.04 (dd, *J*=12.0, 6.3 Hz, 1H), 3.64–3.57 (m, 2H), 3.56–3.51 (m, 2H), 2.91 (t, *J*=6.7 Hz, 2H), 2.36 (br s, 1H), 2.32–2.12 (m, 2H), 2.02 (s, 3H), 1.82–1.75 (m, 1H), 1.75–1.62 (m, 2H), 1.66 (s, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.1, 171.7, 149.8, 135.6, 130.3, 124.5, 122.6, 119.0, 117.9, 115.8, 93.9, 64.9, 62.3, 40.0, 39.4, 33.5, 28.4, 25.2, 23.1, 21.0; EIMS *m/z* (relative intensity) 432 (4, M^+), 187 (21), 143 (100). Anal. calcd for $C_{24}H_{34}N_2O_6$: C, 64.55; H, 7.68; N, 6.27. Found: C, 64.51; H, 7.65; N, 6.14.

*3.7. (4*S*)-*N*-[2-(*N*-Boc-indol-3-yl)ethyl]-4-acetoxymethyl-5-mesyloxypentanamide **13***

To a solution of **12** (600 mg, 1.4 mmol) in pyridine (6 ml), methanesulfonyl chloride (243 mg, 1.7 mmol) was added. After stirring at rt for 30 min, the reaction mixture was poured into aq. $NaHCO_3$ and extracted with AcOEt; the organic phase was washed with 1N HCl and then with brine to give, after evaporation, pure **13** (650 mg, 91%): oil; R_f (AcOEt) 0.60; $[\alpha]_D^{25}$=+4.2 (c=1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, *J*=8.4 Hz, 1H), 7.55 (d, *J*=8.4 Hz, 1H), 7.45 (s, 1H), 7.32 (t, *J*=7.5 Hz, 1H), 7.24 (t, *J*=7.5 Hz, 1H), 5.65 (br s, 1H), 4.19 (d, *J*=6.5 Hz, 2H), 4.15 (dd, *J*=12.0, 4.5 Hz, 1H), 4.11 (dd, *J*=12.0, 6.5 Hz, 1H), 3.58 (q, *J*=7.0, 2H), 2.99 (s, 3H), 2.91 (t, *J*=7.0 Hz, 2H), 2.23 (t, *J*=7.1 Hz, 2H), 2.04 (s, 3H), 2.15–2.03 (m, 1H), 1.79–1.66 (m, 2H), 1.66 (s, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 172.4, 170.9, 149.7, 135.5, 130.4, 124.5, 122.5, 118.9, 117.5, 115.3, 83.6, 68.9, 63.0, 39.4, 37.3, 33.0, 28.2, 25.0, 23.7, 20.8, 14.2; HRMS calcd for $C_{25}H_{36}N_2O_8S$: 524.2192, found 524.2205. Anal. calcd for $C_{25}H_{36}N_2O_8S$: C, 57.23; H, 6.92; N, 5.34; O, 24.40. Found: C, 57.12; H, 6.98; N, 5.32; O, 24.32.

*3.8. (5*R*)-1-[2-(*N*-Boc-indol-3-yl)ethyl]-5-acetoxymethyl-piperidin-2-one **14***

To a solution of **13** (600 mg, 1.2 mmol) in THF (15 ml), 1 M *t*BuOK in THF (1.76 ml, 1.8 mmol) was added dropwise. After stirring at rt for 2 h, the reaction mixture was diluted with aq. NH_4Cl and extracted with AcOEt; the solvent was evaporated to give, after FC (eluent: AcOEt:hexane, 8:2), pure **14** (373 mg, 75%): oil; R_f (AcOEt) 0.50; $[\alpha]_D^{25}$=+27.9 (c=1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, *J*=8.0 Hz, 1H), 7.60 (d, *J*=8.0 Hz, 1H), 7.41 (s, 1H), 7.30 (t, *J*=7.5 Hz, 1H), 7.23 (t, *J*=7.5 Hz, 1H), 4.01 (dd, *J*=11.0, 5.4 Hz, 1H), 3.86 (dd, *J*=11.0, 7.9 Hz, 1H), 3.73–3.54 (m, 2H), 3.21 (dd, *J*=11.8, 4.6 Hz, 1H), 3.05–2.94 (m, 3H), 2.56–2.32 (m, 2H), 2.15–2.01 (m, 1H), 2.00 (s, 3H), 1.92–1.80 (m, 1H), 1.66 (s, 9H), 1.60–1.48 (m, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 171.2, 169.8, 150.2, 136.1, 131.1, 125.0, 123.1, 119.6, 118.4, 115.8, 84.0, 66.1, 51.7, 48.6, 34.1, 31.6, 28.8, 24.5, 23.4, 21.3; EIMS *m/z* (relative intensity) 414 (13, M^+), 243 (52), 187 (100). Anal. calcd for $C_{26}H_{28}N_2O_5$: C, 69.62; H, 6.30; N, 6.24. Found: C, 69.70; H, 6.42; N, 6.28.

3.9. (5R)-1-[2-(N-Boc-indol-3-yl)ethyl]-5-hydroxymethyl-piperidin-2-one **15**

To a stirred solution of **14** (300 mg, 0.72 mmol) in THF (5 ml), aq. 0.5N NaOH (2.2 ml, 1.09 mmol) was added. After 2 h at rt, the reaction was acidified with 1N HCl and extracted with AcOEt to give pure **15** (242 mg, 90%): oil; R_f ($CHCl_3$:MeOH, 95:5) 0.40; $[\alpha]_D^{25}$=+28.4 (c=1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, *J*=8.3 Hz, 1H), 7.61 (d, *J*=8.3 Hz, 1H), 7.41 (s, 1H), 7.30 (t, *J*=7.8 Hz, 1H), 7.23 (t, *J*=7.8 Hz, 1H), 3.64 (t, *J*=7.5 Hz, 2H), 3.58 (dd, *J*=10.5, 7.2 Hz, 1H), 3.47 (dd, *J*=10.5, 5.5 Hz, 1H), 3.32 (dd, *J*=12.0, 5.1 Hz, 1H), 3.08 (dd, *J*=12.0, 9.1 Hz, 1H), 2.96 (t, *J*=8.5 Hz, 2H), 2.53–2.31 (m, 2H), 2.03–1.91 (m, 1H), 1.91–1.80 (m, 1H), 1.66 (s, 9H), 1.58–1.46 (m, 1H); EIMS *m/z* (relative intensity) 373 (15, MH^+), 188 (35), 143 (100). Anal. calcd for $C_{24}H_{26}N_2O_4$: C, 70.91; H, 6.45; N, 6.89. Found: C, 71.00; H, 6.47; N, 6.94.

3.10. (5R)-1-[2-(N-Boc-indol-3-yl)ethyl]-5-tosyloxymethyl-piperidin-2-one **16**

A solution of **15** (97 mg, 0.26 mmol) in CH_2Cl_2 (4 ml), cooled to 0°C, was treated with Et_3N (138 μl, 1.0 mmol) and *p*-toluenesulfonyl chloride (99 mg, 0.52 mmol). After stirring at rt overnight, the reaction mixture was quenched with aq. NH_4Cl and extracted with AcOEt to give, after FC (eluent: $CHCl_3$:MeOH, 99:1), pure **16** (123 mg, 90%): oil; R_f ($CHCl_3$:MeOH, 95:5) 0.48; $[\alpha]_D^{25}$=+19.1 (c=1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, *J*=8.3 Hz, 1H), 7.74 (d, *J*=8.8 Hz, 2H), 7.60 (d, *J*=8.3 Hz, 1H), 7.41 (s, 1H), 7.32 (d, *J*=8.8 Hz, 2H), 7.31 (t, *J*=7.5 Hz, 1H), 7.23 (t, *J*=7.5 Hz, 1H), 3.94 (dd, *J*=9.5, 5.5 Hz, 1H), 3.83 (dd, *J*=9.5, 7.5 Hz, 1H), 3.68–3.49 (m, 2H), 3.26 (dd, *J*=12.0, 5.0 Hz, 1H), 3.01 (dd, *J*=12.0, 9.2 Hz, 1H), 2.90 (t, *J*=7.5 Hz, 2H), 2.50–2.29 (m, 2H), 2.43 (s, 3H), 2.22–2.09 (m, 1H), 1.83–1.76 (m, 1H), 1.66 (s, 9H), 1.55–1.49 (m, 1H); EIMS *m/z* (relative intensity) 526 (64, M^+), 472 (45), 426 (100). Anal. calcd for $C_{31}H_{32}N_2O_6S$: C, 66.41; H, 5.76; N, 5.00; O, 17.12. Found: C, 66.33; H, 5.69; N, 5.08; O, 17.29.

3.11. (5R)-1-[2-(N-Boc-indol-3-yl)ethyl]-5-ethyl-piperidin-2-one **17**

A suspension of CuI (145 mg, 0.76 mmol) in dry Et_2O (4 ml), cooled to −10°C, was treated with a 1.6 M solution of MeLi in Et_2O (950 μl, 1.5 mmol). During this addition a yellow precipitate formed first, which, upon completion of the addition, dissolved completely forming a brown solution. After stirring for 10 min at −10°C, this solution was added to a solution of **16** (80 mg, 0.152 mmol) in Et_2O (2 ml), cooled to −40°C. The temperature was allowed to rise slowly to rt and the mixture was stirred overnight. After dilution with aq. NH_4Cl and Et_2O, the mixture was stirred for 1 h to give two homogeneous phases, which were separated. After usual work up and FC (eluent: $CHCl_3$:MeOH, 99:1), pure **17** (46 mg, 81%) was obtained: oil; R_f ($CHCl_3$:MeOH, 95:5) 0.53; $[\alpha]_D^{25}$=+29.3 (c=1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, *J*=8.2 Hz, 1H), 7.61 (d, *J*=8.2 Hz, 1H), 7.41 (s, 1H), 7.30 (t, *J*=7.3 Hz, 1H), 7.24 (t, *J*=7.3 Hz, 1H), 3.70–3.52 (m, 2H), 3.17 (dd, *J*=12.0, 5.5 Hz, 1H), 2.96 (t, *J*=7.6 Hz, 2H), 2.88 (dd, *J*=12.0, 9.5 Hz, 1H), 2.47 (ddd, *J*=12.8, 6.0, 3.8 Hz, 1H), 2.33 (ddd, *J*=12.8, 11.0, 6.2 Hz, 1H), 1.90–1.81 (m, 1H), 1.66 (s, 9H), 1.62–1.54 (m, 1H), 1.44–1.32 (m, 1H), 1.26 (q, *J*=7.0 Hz, 2H), 0.85 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.4, 150.3, 136.1, 131.2, 125.0, 123.7, 123.1, 119.7, 118.6, 115.8, 84.0, 54.6, 48.5, 36.2, 32.3, 28.8, 27.6, 26.6, 23.4, 11.9; EIMS *m/z* (relative intensity) 370 (6, M^+), 187 (41), 143 (100). Anal. calcd for $C_{25}H_{28}N_2O_3$: C, 74.23; H, 6.98; N, 6.93. Found: C, 74.11; H, 7.10; N, 6.98.

3.12. (5R)-1-[2-Indol-3-yl-ethyl]-5-ethyl-piperidin-2-one **3**

At 0°C, **17** (46 mg, 0.12 mmol) was dissolved in CH_2Cl_2 (2 ml) and TFA (0.5 ml) was added. After stirring for 1 h at rt, the solution was poured into aq. 10% NaOH and extracted with CH_2Cl_2 to give **3** (29 mg, 85%): oil; R_f ($CHCl_3$:MeOH, 95:5) 0.21; $[\alpha]_D^{25}$=+21.0 (c=1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, *J*=8.2 Hz, 1H), 7.61 (d, *J*=8.2 Hz, 1H), 7.39 (s, 1H), 7.30 (t, *J*=7.3 Hz, 1H), 7.24 (t, *J*=7.3 Hz, 1H), 3.72–3.53 (m, 2H), 3.17 (dd, *J*=12.0, 5.4 Hz, 1H), 2.90 (t, *J*=7.5 Hz, 2H), 2.87 (dd, *J*=12.0, 9.5 Hz, 1H), 2.45 (ddd, *J*=12.8, 6.0, 3.7 Hz, 1H), 2.31 (ddd, *J*=12.8, 11.0, 6.2 Hz, 1H), 1.93–1.80 (m, 1H), 1.62–1.52 (m, 1H), 1.46–1.32 (m, 1H), 1.26 (q, *J*=7.0 Hz, 2H), 0.85 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.4, 150.3, 136.0, 131.3, 125.0, 123.7, 123.4, 118.5, 117.9, 115.8, 83.0, 54.3, 48.5, 35.2, 32.3, 27.1, 26.6, 23.4, 11.8; HRMS calcd for $C_{17}H_{22}N_2O$: 207.1732, found 207.1725. Anal. calcd for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.21; N, 10.36. Found: C, 75.68; H, 8.15; N, 10.34.

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References

1. Danieli, B.; Lesma, G.; Passarella, D.; Riva, S. Chiral Synthons via Enzyme-Mediated Asymmetrization of *meso*-Compounds. In *Advances in the Use of Synthons in Organic Chemistry*; Dondoni, A., Ed.; 1993; Vol. 1, pp. 143–219.
2. Danieli, B.; Lesma, G.; Passarella, D.; Silvani, A. *J. Org. Chem*. **1998**, *63*, 3492–3496 and references cited therein.
3. Van Beek, T. A.; Verpoorte, R.; Baerheim Svendsen, A. *Tetrahedron* **1984**, *40*, 737–748.
4. Lounasmaa, M.; Tolvanen, A. The Eburnamine–Vincamine Alkaloids. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1992; Vol. 42, pp. 1–116.
5. Lounasmaa, M.; Din Belle, D.; Tolvanen, A. *Tetrahedron Lett*. **1995**, *36*, 7141–7144.
6. (a) Ihara, M.; Setsu, F.; Shohda, M.; Taniguchi, N.; Fukumoto, K. *Heterocycles* **1994**, *37*, 289–292. (b) Ihara, M.; Setsu, F.; Shohda, M.; Taniguchi, N.; Tokunaga, Y.; Fukumoto, K. *J. Org. Chem*. **1994**, *59*, 5317–5323.
7. Massiot, G.; Sousa Oliveira, F.; Lévy, J. *Bull. Soc. Chim. Fr. II* **1982**, 185–190.
8. Schoffers, E.; Golebiowski, A.; Johnson, C. R. *Tetrahedron* **1996**, *52*, 3769–3826.
9. (a) The diol **5** was prepared by treatment of 4-bromobutene with sodium diethyl malonate in abs. ethanol and subsequent reduction with $LiAlH_4$ in THF. (b) Ramos Tombo, G. M.; Schär, H.-P.; Fernandez, X.; Busquets, I.; Ghisalba, O. *Tetrahedron Lett*. **1986**, *27*, 5707–5710.
10. Fuganti, C.; Grasselli, P.; Servi, S.; Zirotti, C. *Tetrahedron Lett*. **1982**, *23*, 4269–4272.
11. (a) Balogh, V.; Fetizon, M.; Golfier, M. *J. Org. Chem*. **1971**, *36*, 1339. (b) Mc Killop, A.; Young, D. W. *Synthesis* **1979**, 401–422.
12. The diol **10** was prepared by treatment of 1-dimethylphenylsilyl-4-tosyloxybutyne with sodium diethyl malonate in dioxane and subsequent reduction with $LiAlH_4$ in THF.
13. Hanessian, S.; Thavonekham, B.; DeHoff, B. *J. Org. Chem*. **1989**, *54*, 5831–5833.
14. For typical experimental protocols, see: Danieli, B.; Lesma, G.; Passarella, D.; Silvani, A. *J. Org. Chem*. **1998**, *63*, 3492–3496.