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Highly Diastereoselective Alkylation of a Pyroglutamate Derivative with an Electrophile Obtained from Indole. Synthesis of a Potential Intermediate for the Preparation of the Natural Sweetener (-)-Monatin

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HIGHLY DIASTEREOSELECTIVE ALKYLATION OF A PYROGLUTAMATE DERIVATIVE WITH AN ELECTROPHILE OBTAINED FROM INDOLE. SYNTHESIS OF A POTENTIAL INTERMEDIATE FOR THE PREPARATION OF THE NATURAL SWEETENER (-)-MONATIN

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ABSTRACT: The synthesis of a potential intermediate for the preparation of the very intensive sweetening agent (-)-Monatin is described. The synthesis is based on a highly diastereoselective alkylation reaction of a pyroglutamate derivative with an electrophile obtained from indole.

The detrimental effects of high consumption of sucrose and glucose-based sugars, such as obesity and tooth decay in humans have resulted in the present day extensive research on synthetic, non-nutritive sweeteners.[1]

In this context the search for new sweetening agents from natural sources seems to be very promising. In 1992, Vleggaar and cols.[2] isolated from the roots of the African tree *Schlerochiton ilicifolius* (-)-Monatin (**1**, Scheme 1), a glutamic acid derivative with a high-intensity sweetening property (1200-1400 times sweeter than glucose). Despite of the biological activity of Monatin, which can be potentially used as a commercial sweetener agent and as lead compound for a structure-activity studies, there is only one report in the literature describing a racemic total synthesis of **1**.[3]

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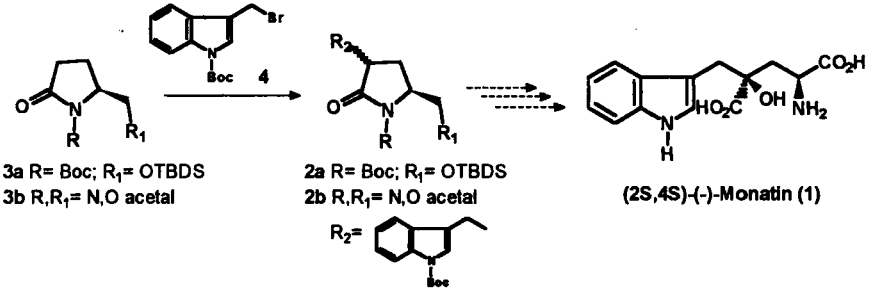
In our view, (-)-Monatin (**1**, scheme 1) can be synthesized from intermediate **2**, which can be obtained by a diastereoselective alkylation reaction of the pyroglumate derivatives **3a/b** (Scheme 1) with an electrophile **4** prepared from indole.

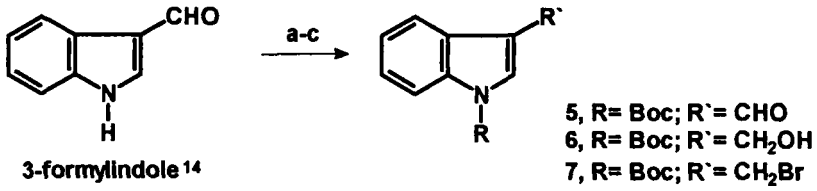
Pyroglutamic acid and its derivatives are versatile starting materials and in the last years there have been many reports concerning their utilization as substrate in alkylation reactions.[4] To our surprise there is only one report in the literature[5] which exploits the chemoselectivity in alkylation reactions of pyroglutamates with indole derivatives as electrophile, with moderate diastereoselectivity. This report encouraged us to disclose our results concerning a highly diastereoselective alkylation reaction of a pyroglutamic derivative (**3**), with N-Boc-3-bromomethylindole, which furnished compound **2**. In our point of view, the latter substrate can be used as a possible precursor towards **1**.

SCHEME 1



N-Boc-3-bromomethylindole (**4**) was prepared from commercial 3-formylindole, in three steps, by adaptation of a methodology described by Schöllkopf et al.[6] in 76% overall yield. This bromide is very unstable and, under normal conditions, must be prepared just before use.[7] (Scheme 2).

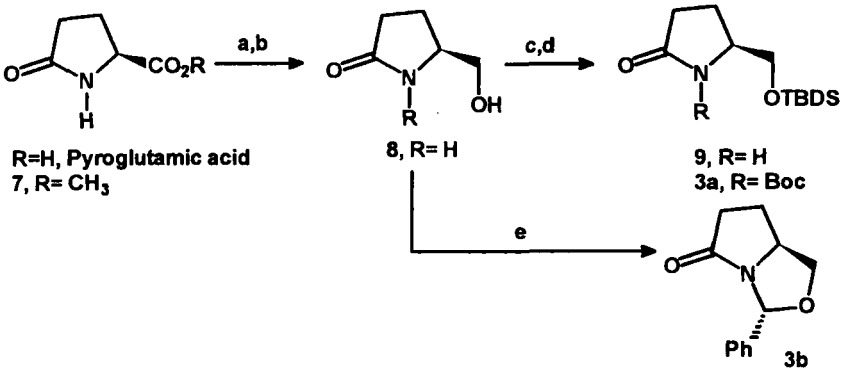
SCHEME 2



Reagents and conditions: a. NaOH, $(Bu)_4NHSO_4$, CH_2Cl_2, 2h, quantitative; b. $NaBH_4$, EtOH, 6h, 20°C, 92%; c. Br_2, PPh_3, CCl_4, 3 days, rt, 83%.

The pyroglutamate derivative **3a** was prepared according to Saijo *et al.*[8] and Tamm *et al.*[9] in 3 steps from (S)-pyroglutamic acid or from (S)-glutamic acid. In order to avoid the double protection of **8** we decided to prepare **3b**, where the N- and the hydroxyl groups were protected as N,O-acetal (Scheme 3)[10a].

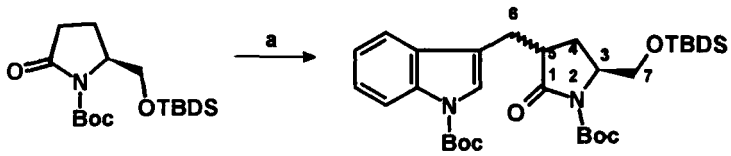
SCHEME 3



Reagents and conditions: a) $SOCl_2$, MeOH, rt., 48h, 80%; b) $NaBH_4$, i-PrOH, rt., 20h, 86%; c) Imidazole, DMF, TBSCl, rt, 20h, 95%; d) $(Boc)_2O$, DMAP, Et_3N, rt., 3h, quantitative; e) PhCHO (10eq.), PPTA, toluene, reflux, 4 days, 65%.

It is well known that enolates generated from cyclic lactams can be alkylated with high degree of diastereoselectivity.[11] In our first trials the enolate was generated using standard conditions (LDA, THF, -78°C), unfortunately compounds **2a** (*syn* and *anti*) were not isolated, instead substrates **3a/3b** were almost quantitatively recovered. Then we decided to change the base to lithium bis(hexamethyldisilazide) in place of LDA. Once again we were unable to isolate alkylation products from the reaction medium. We then tried to use HMPA (1 eq.) as co-solvent. At this time we were able to isolate the product of alkylation as a mixture of diastereoisomers (3:1; *anti:syn*, separable by tlc) in 34% yield (Scheme 4).

SCHEME 4

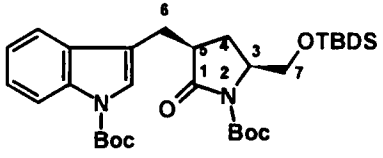


3a **2a *syn* + 2a *anti***

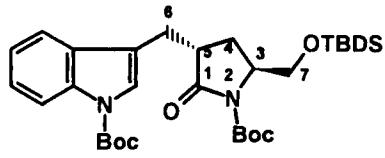
Reagents and conditions: a) i. LHMDS, THF, -78°C, 30min; ii. HMPA (1 eq.), 45min; iii. bromide **4**, -78°C → rt, 1h.

After separation of the diastereoisomers by usual purification methods (preparative thin layer chromatography or silica gel column chromatography), ^{1}H NMR spectra analysis[10a] indicated that the more polar product was *anti* and the minus polar was *syn*. The ^{1}H NMR data for the two diastereisomers are summarized in table I.

Table 1: ^{1}H NMR data[10a*] for the diastereoisomers **2a** (*syn* and *anti*)



2a *syn*



2a *anti*

2a	H_3	H_4			H_5	H_6			H_7		
Syn	3.98	1.94			3.14 ($J_{5,6\alpha}$=3.6Hz; $J_{5,6\beta}$=10.8Hz)	H_α	H_β	$J_{\alpha,\beta}$(Hz)	H_α	H_β	$J_{\alpha,\beta}$(Hz)
						3.28	2.68	13.8	3.46	3.94	9.6
Anti	3.96	H_α	H_β	J(Hz)	3.08 ($J_{5,6\alpha}$=9.0Hz; $J_{5,6\beta}$=3.0Hz)	H_α	H_β	$J_{\alpha,\beta}$(Hz)	H_α	H_β	$J_{\alpha,\beta}$(Hz)
		2.02	1.74	10.2		2.59	3.22	13.2	3.52	3.90	9.6

All the spectra were recorded on a Varian Gemini BB-300 at 300MHz in CDCl3 as solvent.

Searching for improved diastereoselectivity and yield we increased the amount of HMPA to 10 equivalents and kept the reaction temperature at -78°C for 26 hours. Preliminary analysis by tlc showed the presence of a single diastereoisomer, which was confirmed by ^{1}H NMR analysis of the crude mixture. The NMR data were compatible with those of the *anti* diastereoisomer[10a]. The diastereoisomeric excess (d.e..≥95%) of *anti*-**2a** was determined by chiral HPLC (Chrompack-CP-Chirasil-Dex CB column) by comparing with those obtained for the racemic product. The absolute configuration of this new stereogenic center was not determined yet, but if we take in consideration that the enolate attack occured from the *si* face[5b], it should be R.

This modification allowed us to prepare **2** with a high degree of diastereoselectivity (≥ 95%), and good chemical yield (73%). We have tried to work with a smaller quantity of HMPA (2-9 equiv.), however in these cases the observed diastereoselectivity was comparable to that observed when 1 equivalent of HMPA was used (3:1, *anti*:*syn*). Amounts of HMPA greater than 10 equivalents have no effect on stereoselectivity and on the yield of the reaction.

The obtained results are summarized on Table II

Table II: Conditions for the alkylation of pyroglutamate derivative ***3a*** *with the electrophile* ***4****.*

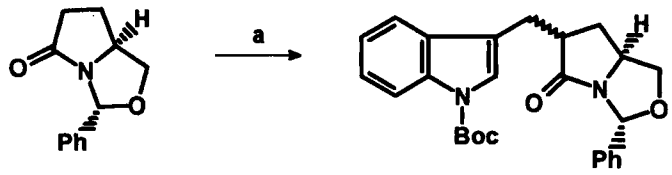
Conditions	Base	Co-solvent	d.r.	Yield (%)
A[a]	LDA/THF	-	-	0[c]
B[b]	LHDMS/THF	HMPA (1 eq.)	3:1 (*syn*:*anti*)	34
C[d]	LHDMS/THF	HMPA (10 eq.)	*anti* (≥ 95%)	73

a: -78°C; b: bromide ***4*** *added at -78°C. then room temperature (1h); d: lactam* ***3a*** *recovered; d: bromide* ***4*** *was added at -78°C then 26h at the same temperature*

The optimized condition C was employed for the alkylation of the lactam **3b**, however the diastereoselectivity and the chemical yield were lower than that obtained for the lactam **3a** (scheme 5).

This low chemical yield is attributed to degradation of compound **3b** in the reaction medium. We were unable to isolate any unreacted starting material. These results are reproducible and the diastereoselection and chemical yield achieved are better than those described by Braña et al.[5].

SCHEME 5



3a **2b (*syn* and *anti*)**

Reagents and conditions: a) i. LHMDS, THF, -78°C, 30 min; ii HMPA (10 eq.), 45 min -78°C; iii. bromide **4**, -78°C, 26h, 34% diastereoisomeric ratio (*anti*:*syn*; 7:3).

The synthetic strategy to transform **2a** in (-)-Monatin is under investigation in our laboratory.

EXPERIMENTAL

General: The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian GEMINI BB-300 at 300MHz and 75.1 MHz respectively. The ^{1}H NMR spectra were also recorded in an AW-80 Bruker at 80MHz and Inova 500MHz. The mass spectra were recorded on CG/MS HP model 5988A and Autospec-Micromass - EBE - High Resolution. The melting points were measured in open capilary tubes using an Electrothermal apparatus model 9100, and are uncorrected. The $[\alpha]_D$ are corrected and measured in Polamat A polarimeter. Purification and separations by column chromatography were performed on silica gel, using flash chromatography. Ether and THF were distilled from benzophenone ketyl under nitrogen. Tlc visualization was achieved by spraying with 5% ethanolic phosphomolybdic acid and heating. (S)-Pyroglutamic acid and (S)-Glutamic acid were purchased from Aldrich Company.

1-(tert-Butyloxycarbonyl)-3-formylindole **5**

To a suspension of 1.65 g (41.25 mmol) of sodium hydroxide and 0.1g (0.29 mmol) of tetrabutylammonium hydrogen sulfate in 20 mL of CH_2Cl_2, 2.18 g (15 mmol) of 3-formylindole[14] was added at 0°C. Subsequently a solution of 3.6 g (16.5 mmol) of di-*tert*-butyl-dicarbonate in 10 mL of CH_2Cl_2 was added (the temperature should not rise above 10°C). Stirring was continued for 20 min. at 0°C, and the mixture was then diluted with 10 mL of CH_2Cl_2 and stirring was maintained for additional 90 min. The dichloromethane layer was separated and the aqueous layer extracted twice with 20 mL of CH_2Cl_2 each. The combined organic layers were dried over magnesium sulfate. Concentration under reduced pressure furnished 3.84g (100%) of **5**, as white solid that was pure by tlc and used for the next step without additional purification.

M.p. 124°C (lit[15]. 124-125°C); IR(KBr, λ_{max}): 1735, 1670 cm^{-1}; ^1H NMR (80MHz, $CDCl_3$): δ 1.84 (s, 9H), 7.2-8.4 (m, 5H), 10.2 (s, 1H).

1-(*tert*-Butyloxycarbonyl)-3-(hydroxymethyl)indole **6**

1-(*tert*-Butyloxycarbonyl)-3-formylindole (3,67 g, 15mmol) was suspended in 10 mL of ethanol, sodium borohydride (1,13g, 30 mmol) was added during which the temperature did not rise above 20°C. Stirring was continued for 6h. The solvent was evaporated *in vacuo*. The residual oil was shaken with 80 mL of 1,0N NaOH and the alkaline solution extracted 3 times with 50 mL of ether each. The combined organic extracts were dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the residual oil heated *in vacuo* (10 Torr, 36h, room temperature, or ca. 40°C) to remove small amounts of triethoxyborane . The hydroxymethyl derivative crystallized slowly; yield 3.41g (92%).

IR(KBr, λ_{max}): 3381, 2978, 1732 cm^{-1}; ^1H NMR (80MHz, $CDCl_3$): δ 1.75 (s, 9H), 4.90 (s, 2H), 7.20-8.40 (m, 5H).

1-(tert-Butyloxycarbonyl)-3-(bromomethyl)indole **4**

A solution of bromine (0,504g, 3.15 mmol) in 5 mL of dry tetrachloromethane was added with stirring to a solution of triphenylphosphine (0,78 g, 3 mmol) in 7 mL of dry tetrachloromethane. To the resulting yellow suspension was added 0.44 mL (3.15 mmol) of triethylamine. A solution of the **6** (0.74 g, 3 mmol) in 5 mL of dry tetrachloromethane was added to the yellow suspension. Stirring was continued for 3 days at the room temperature. The triphenylphosphine was removed by filtration, the solvent removed *in vacuo*, and the solid residue treated with 50 mL of hexane, filtered and the hexane evaporated. This procedure was repeated to remove the triphenylphosphine oxide. The bromomethyl derivative was unstable to the usual purification conditions and was purified by crystallization in hexane to furnish 0.256 g (83%) of **4**, as a white amorphous solid.

M.p. 96°C (with decomposition) [(Lit.[6] 96°C (dec.)]; IR (KBr, λ_{max}): 2978, 1732 cm^{-1}; ^1H NMR (80MHz, $CDCl_3$): δ 1.65 (s, 9H), 4.64 (s, 2H), 7.0-8.25 (s, 1H).; MS (high resolution): m/e 309.0365 (M^+ calculated for $C_{14}H_{16}BrNO_2$ 309.0365)

Methyl-(2S)-5-oxopyrrolidine-2-carboxylate (**7**)

A solution of 12 g (81.63 mmol) of (S)-glutamic acid in water (60 mL) was heated under reflux for 63 hours; the solvent was then evaporated at 70°C. The residue was dried by dissolving 3 times in 40 mL of absolute methanol and

evaporating at 60°C. The colorless (S)-pyroglutamic acid was dissolved in 150 mL of absolute methanol, and 0,4 mL (5.50 mmol) of thionyl chloride ($SOCl_2$) were added (pH 0). The mixture was stirred at room temperature for 3h. The pH was corrected to 7 by addition of a saturated $NaHCO_3$ solution. The solvent was evaporated and the residue dried by dissolving in 20 mL of methanol and evaporating at 40°C. The residue was dried under *vaccum* in an oil bath (120-30°C) for 12h to furnished 9.93g (80%) of **7** of a colorless oil that was pure by tlc and was used for the next step without additional purification. The optical purity of **7** (≥ 99%) was determined by chiral HPLC (Chrompack-CP-Chirasil-Dex CB column).

$[\alpha]^{20}_D$ = + 0.88 (c 2.8, H_2O) [lit.[8] +0.9 (c 2.8, H_2O)]; IR (neat, λ_{max}): 3256, 1956,1743, 1703, 1437, 1216, 714 cm^{-1}.; ^1H NMR (300MHz, $CDCl_3$): δ 2.4 (m, 4H), 3.8 (s, 3H), 4.3 (m, 1H), 7,5 (br. signal, 1H).; ^{13}C NMR (75.1MHz, $CDCl_3$): δ 24.4, 29.0, 52.3, 55.3, 172.8, 179.0.; MS (70eV, m/e, %): 143 (M^+, 10), 84(100), 41(10).

(5S)-5-(Hydroxymethyl)pyrrolidin-2-one (**8**)

To a solution of 10.0g (69.93 mmol) of **7** in 100 mL of absolute isopropanol, 5.3 g (140.0 mmol) of $NaBH_4$ were added. After 20h at room temperature, acetic acid (13 mL) was slowly added and the mixture stirred for 1h. Then, water (18 mL) was added and the mixture stirred for 1h at room temperature. The pH value was adjusted to 7 by adding 2N NaOH, and the solvents were evaporated under reduced pressure. The residue was extracted with hot ethyl acetate (6 x 100 mL) and after evaporation a colorless solid was obtained, which was purified by silica gel column chromatography with ethyl acetate-ethanol (2:1) to furnish 6.9 g (87%)

of **8**, as colorless crystals. The optical purity of **8** was determined to be ≥ 98% by chiral HPLC (Chrompack-CP-Chirasil-Dex CB colum).

M.p. 85.5-87.5°C (recrystallized from acetone) (lit[9]. 85.5-87.5°C); $[\alpha]^{20}_D$ = + 32.0° (c 1.76, EtOH) [Lit.[8] + 32.4° (c 1.76g, EtOH)]; IR (nujol, $\lambda_{max,}$): 3333, 2933, 1676, 1420, 1282, 651 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): δ 1.80 (dddd, J_1= 5.5Hz, J_2= 7.4Hz, J_3= 9.4Hz, J_4= 12.9Hz, 1H), 2,20 (dddd, $J_1 \approx J_2 \approx J_3$= 8.0Hz, J_4= 12.4Hz, 1H), 3.46 (ddd, $J_1 \approx J_2$= 5.7Hz, J_3= 11.8Hz, 1H), 2.37 (m, 2H), 3.46 (ddd, $J_1 \approx J_2$ = 5.7Hz, J_3 = 11.8Hz), (m, 1H), 3.68 (ddd, J_1= 3.2Hz, J_2= 5.7Hz, J_3= 11.4Hz, 1H), 4.14 (dd, $J_1 \approx J_2$= 5.7Hz, 1H), 7.28 (d, J= 3.0Hz, 1H); ^{13}C NMR (75.1MHz, $CDCl_3$): δ 22.3, 30.0, 56.3, 65.7, 179.8

(5S)-5-[(1,1,2,2-tetramethyl-1silapropoxy)methyl]pyrrolidin-2-one (**9**)

To a solution of 1.72 g (15 mmol) of **8** and 2.55 g (37.5 mmol) of imidazole in 4.5 mL of DMF, 2.71 g (18 mmol) of (*tert*-butyl)dimethylsilyl chloride were added. After 24h at room temperature, 45 mL of Et_2O were added. The ethereal solution was washed with H_2O (1 x 20 mL), brine (1 x 20 mL) and dried over anhydrous sodium sulfate. Concentration under reduced pressure followed by column chromatography on silica gel with ethyl acetate:CH_2Cl_2 (15:1) yielded 3.29 g (95%) of **9** as a pale yellow oil. The optical purity of **9** was determined to be ≥ 99% by chiral HPLC (Chrompack-CP-Chirasil-Dex CB column).

$[\alpha]^{20}_D$ = + 4.2° (c 2.14, EtOH) (Lit.[9] + 4.3° (c 2.14, EtOH); IR (neat, $\lambda_{max,}$): 3242, 2856, 1700, 1462, 1255, 1117, 777 cm^{-1}.; ^1H NMR (300MHz, $CDCl_3$): δ 1. 0 (s, 9H), 1.80 (m, 2H), 2.20 (m, 2H), 3.55 (d, J= 4.0Hz, 2H), 3.65 (m, 1H), 8.18 (br signal, 1H); ^{13}C NMR (75.1MHz, $CDCl_3$): δ 17.8, 22.6, 25.5, 29.4, 52.2, 65.9, 178.1.

tert-Butyl-(5S)-2-oxo-5[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]pyrrolidine carboxylate (**3a**)

To a solution of 1.60 g (7 mmol) of **7** in 15 mL of CH_2Cl_2, 2.03 g (9.33 mmol) of di-*tert*-butyl-dicarbonate [$(Boc)_2O$], 0.25 g (2.1 mmol) of 4-dimetylaminopyridine (DMAP) and 1.4 mL of trietylamine (Et_3N) were added at room temperature. After 24h under stirring at room temperature, 135 mL of Et_2O were added, and the mixture was washed with 10% citric acid (1 x 50 mL), saturated NaHCO3 (1 x 50 mL) solution, brine (1 x 50 mL) and dried over anhydrous magnesium sulfate. Concentration under reduced pressure furnished a residue, which was purified by column chromatography on silica gel with hexane-ethyl acetate (95:5) to provide 2.46 g (98%) of **3a**, as a colorless viscous oil. The optical purity of **3a** was determined to be ≥ 99% by chiral HPLC (Chrompack-CP-Chirasil-Dex CB column). $[\alpha]^{20}_D$ = -61° (c 1.1, $CHCl_3$) (Lit.[13] -61° (c 1.1, $CHCl_3$); IR (neat, λ_{max},): 1760, 1720, cm^{-1}.; ^1H NMR (80MHz, $CDCl_3$): δ 0.90 (s, 9H), 1.50 (s, 9H), 1.70-2.80 (m, 4H), 3.50-4.20 (m, 3H).

(7aS,5R)-5-phenyl-2,5,6,7,7a-pentahydro-6-oxapyrrolizin-3-one (**3b**)

A mixture of alcohol **5** (1.15g, 10 mmol), benzaldehyde (freshly distilled, 1.4 mL, 13 mmol) and PTSA (0.254 g, 1.0 mmol) in 14 mL of dry toluene was refluxed for 3 days in a Dean-Stark apparatus. After cooling the mixture and diluting with 50 mL of toluene, the organic phase was washed with a saturated solution of NaHCO3 (20 mL) and dried over anhydrous magnesium sulfate. Concentration under reduced pressure furnished 1.42 g (65% yield) of **3b**, as a tinged yellow oil which was used for the next step without additional purification. The optical purity

of **3b** was determined to be ≥ 99% by chiral HPLC (Chrompack-CP-Chirasil-Dex CB column)

$[\alpha]^{20}_D$ = +269° (c 1, $CHCl_3$) (Lit.[16] +269.6° (c 1, $CHCl_3$); IR (neat, λ_{max}): 2980, 1710, 1605, 1500, 1235 cm^{-1}; ^1H NMR (80MHz, $CDCl_3$): δ 1.6-2.6 (m, 4H), 3.5 (m, 1H), 4.0 (m, 2H), 6.2 (s, 1H), 7.2-7.8 (m, 5H, aromatics)

Alkylation of **3a** with bromide **4**.

To a solution of **3a** (0,339 g, 1 mmol) in 2 mL of anhydrous THF, at -78°C, was added 1.1 mL of a 1,0M solution of lithium bis(trimethylsilyl)amide (1.1 mmol). The mixture was kept under stirring for 30min, at the same temperature. After that 1.0 mL of anhydrous hexamethylphosphoramide (HMPA) was added and the reaction was maintained for more half hour under stirring, at -78°C, following by the slow addition of bromide **4** (0.325 g, 1.05 mmol) dissolved in 1 mL of anhydrous THF. The reaction media was kept at -78°C for 26 hours. After the reaction was warmed to room temperature and extracted with ethyl acetate (100 mL). The organic phase was washed with water (50 mL), brine (50 mL) and dried over magnesium sulfate. Concentration under reduced pressure followed by column chromatography on silica gel with hexane ethyl acetate (9:1) yielded 0.407 g (73%) of isomer *anti*-**2a**, as a slightly yellow viscous oil.

$[\alpha]^{20}_D$ = -26.7° (c 1.2, EtOH)]; IR (neat, λ_{max},): 1784, 1734, 1714, 1157cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): δ 0.85 (s, 9H), 1.55 (s, 9H), 1.67 (s, 9H), 1.80 (ddd, J_1 = 12.0Hz, J_2 = 9.0Hz, J_3 = 6.0Hz, 1H, $H_{4\beta}$), 2.10 (dd, J_1 = 12.0Hz, J_2 = 9.6Hz, 1H, $H_{4\alpha}$), 2.63(dd, J_1= 14.1Hz, J_2= 9.6Hz, 1H, $H_{7\alpha}$), 3.25 (m, 1H, H_5), 3.37 (ddd, J_1 = 14.1Hz, J_2= 6.0Hz, J_3 = 1.0Hz, 1H, $H_{7\beta}$), 3.60 (dd, J_1= 9.0Hz, J_2 = 1.5Hz, 1H, $H_{6\alpha}$),

3.90 (dd, J_1= 9.0Hz, J_2 = 3.0Hz, 1H, $H_{6\beta}$), 4.03 (m, 1H, H_3), 7.1-8.2 (m, 5H, aromatics); ^{13}C NMR (75.1MHz, $CDCl_3$): δ 18,5, 26.0, 27.0, 28.0, 28.5, 42.56, 64.0, 66.5, 115.0, 118.0, 119.0, 123.0, 123.5, 125.0, 130.0, 1251.0, 173.5

MS (70 ev, m/z): 558 ($M^{+\cdot}$, 2.5%), 458 (6%), 389 (7%), 358 (27%), 301 (58%),130 (100%); MS (high resolution): m/e 558.3125 (M^+ calculated for $C_{30}H_{46}N_2O_6Si$ 558.3125); Anal. calcd. for $C_{30}H_{46}N_2O_6Si$: C, 64.47; H, 8.30; N, 5.01. Found C, 64.45; H, 8.28; N, 4.99

Alkylation of **3b** with bromide **4**

To a solution of **3b** (0,109 g, 0.5 mmol) in 2 mL of anhydrous THF, at -78°C, was added 0.55 mL of a 1,0M solution of lithium bis(trimethylsilyl)amide (0.55 mmol). The mixture was kept under stirring for 30min, at the same temperature. After that 1.0 mL of anhydrous hexamethylphosphoramide (HMPA) was added and the reaction was maintained for more half hour under stirring, at -78°C, following by the slow addition of bromide **4** (0.195 g, 0.65 mmol) dissolved in 1 mL of anhydrous THF. The reaction media was kept at -78°C for 26 hrs. After the reaction was slowly warmed to room temperature (24 hrs) and extracted with ethyl acetate (60 mL). The organic phase was washed with water (20 mL), brine (20 mL) and dried over magnesium sulfate. Concentration under reduced pressure followed by column chromathography on silica gel with hexane ethyl acetate (8:2) yielded 0.018 g of isomer *syn*-**2b** and 0,056 g of isomer *anti*-**2b** (34%), as a viscous oil.

Anti isomer; IR (neat, $\lambda_{max.}$): 1711, 1705, 1495, 1353, 1150cm^{-1}; ^1H NMR (500MHz, CCl_4): δ 1.52 (s, 9H), 2.0 (tdd, J_1 = 10.0Hz, J_2 = 9.0Hz, J_3 = 4.5Hz, 1H, $H_{4\beta}$), 2.12 (td, J_1 = 10.0Hz, J_2 = 5.0Hz, 1H, $H_{4\alpha}$), 2.92 (dd, J_1 = 14.4Hz, J_2 = 8.9Hz, 1H, $H_{9\alpha}$),

2.98 (m, 1H, H_3), 3.24 (dd, J_1= 14.4Hz, J_2 = 2.7Hz, 1H, $H_{9\beta}$), 3.32 (t, J = 8.5Hz, 1H, $H_{6\beta}$), 3.80 (m,1H, H_5), 4.04 (dd, J_1= 8.50Hz, J_2 = 6.0Hz, 1H, $H_{6\alpha}$), 6.25 (s, 1H, H_8), 7.1 (m, 10H, aromatics); ^{13}C NMR (75.1MHz, CCl_4): δ 26.5, 28.0, 33.0, 45.0, 56.0, 72.0, 117.0, 118.0, 122.0, 123.0, 124.0, 126.0, 139.0, 176.0; MS(70eV, m/e): 432 (9.2%), 332 (25%), 244 (8.6%), 203 (7.9%), 130 (100%), 57 (19%); MS (high resolution): m/e 432.2049 (M^+ calculated for $C_{26}H_{28}N_2O_4$ 432.2049); Anal. calcd. for $C_{26}H_{28}N_2O_4$: C, 72.20; H, 6.52; N, 6.47. Found C, 72.18; H, 6.51; N, 6.46

Syn isomer: IR (neat, λ_{max},): 1711, 1705, 1495, 1353, 1150cm^{-1}; ^{1}H NMR (500MHz, CCl_4): δ 1.62 (m, 1H, $H_{4\alpha}$), 1.70 (s, 9H), 2.46 (dt, J_1 = 11.4Hz, J_2 = 7.8Hz, 1H, $H_{4\beta}$), 2.73 (dd, J_1 = 14.1Hz, J_2 = 9.6Hz, 1H, $H_{9\beta}$), 3.22 (m, 1H, H_3), 3.32 (t, J = 7.0Hz, 1H, $H_{6\beta}$), 3.36 (dd, J_1= 14.1Hz, J_2 = 4.0Hz, 1H, $H_{9\alpha}$), 3.92 (quintet, J= 7.0Hz,1H, H_5), 4.08 (t, J= 7.0Hz, 1H, $H_{6\alpha}$), 6.31 (s, 1H, H8), 7.1-8.2 (m, 10H, aromatics); ^{13}C NMR (75.1MHz, CCl_4): δ 26.5, 28.5, 35.0, 45.0, 56.0, 72.0, 117.0, 118.0, 122.0, 123.0, 124.0, 126.5, 140.0, 176.0; ; MS(70eV, m/e): 432 (9.2%), 332 (25%), 244 (8.6%), 203 (7.9%), 130 (100%), 57 (19%); MS (high resolution): m/e 432.2049 (M^+ calculated for $C_{26}H_{28}N_2O_4$ 432.2049); Anal. calcd. for $C_{26}H_{28}N_2O_4$: C, 72.20; H, 6.52; N, 6.47. Found C, 72.18; H, 6.51; N, 6.46

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