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(54) **FLUORINATED CATHARANTHINE DERIVATIVES, THEIR PREPARATION AND THEIR UTILISATION AS VINCA DIMERIC ALKALOID PRECURSORS**

FLUORIERTE CATHARANTHINDERIVATE, IHRE HERSTELLUNG UND IHRE VERWENDUNG ALS DIMERE VORSTUFEN FÜR VINCAALKALOIDE

DÉRIVÉS FLUORÉS DE CATHARANTHINE, LEUR PRÉPARATION ET LEUR UTILISATION EN TANT QUE PRÉCURSEURS DES ALCALOÏDES DIMÈRES DU VINCA

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Description

[0001] The present invention relates to fluorinated derivatives of catharanthine, their preparation and their use as a precursor of fluorinated dimeric Vinca alkaloids, and vinflunine in particular.

[0002] Vinflunine 1 is a wide-spectrum anticancer agent developed by Pierre Fabre laboratories. This molecule is a fluorinated analogue of vinorelbine 5 (Navelbine®) which is the reference drug for treatment of breast and lung cancer. The structure of vinflunine is very similar to that of vinorelbine, from which it differs only by the presence of a group gem-difluorinated in $C_{20'}$, and by the absence of the double bond $C_{3'}$-$C_{4'}$. Vinflunine 1 (Javlor®) is the most active fluorinated compound discovered over recent years. It is currently in phase III of clinical trials in the treatment of breast, bladder and lung cancer, and is heralded today as the most promising molecule to have originated from the family of *Vinca* alkaloids.

[0003] Vinflunine may be prepared from 3',4'-anhydrovinblastine 4 precursor which is obtained by the coupling of two sub-units catharanthine 2 and vindoline 3, which are extracted directly from the leaves of the Madagascar periwinkle (Diagram 1). Alternatively vinflunine may be prepared by direct fluorination of vinorelbine.

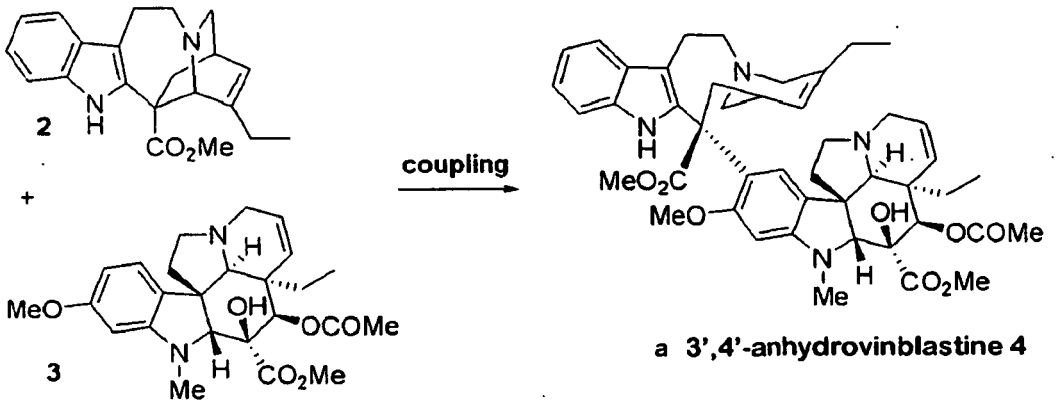


Diagram 1

[0004] 3',4'-Anhydrovinblastine 4 can then be transformed into vinorelbine 5 by ring contraction, or into vinflunine 1 by introduction of two fluorine atoms on the lateral chain of the "north" fragment followed by ring contraction (Diagram 2). This fluorination operation takes place in a superacid medium ($HF\text{-}SbF_5$) in the presence of a chlorinated solvent. These reaction conditions are particularly drastic, resulting in partial degradation of the dimeric alkaloid 4 and thus in a drop in the overall chemical yield of the transformation. The gem-difluorination in $C_{20'}$ proceeds with concomitant reduction of the $C_{3'}$-C_4 double bond. The stereocentre formed at 4' has an absolute configuration (*R*). Vinflunine can also be prepared by fluorination of vinorelbine 5 (Navelbine®). The synthesis thereof is carried out by ring contraction of 3',4'-anhydrovinblastine 4.

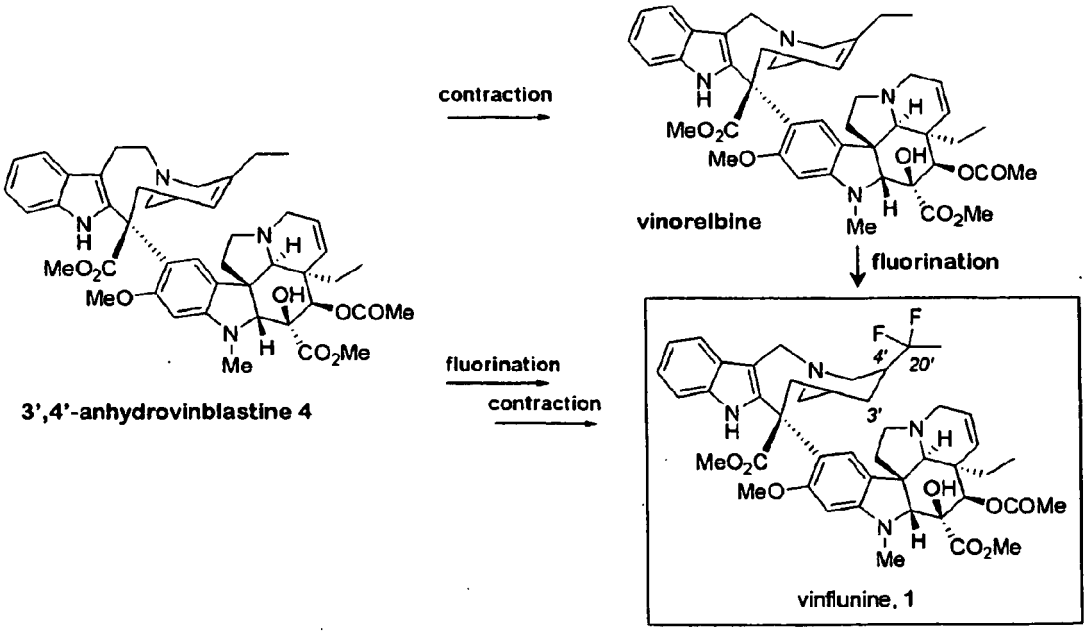


Diagram 2

[0005] 3',4'-Anhydrovinblastine 4 is a product with high added. The fluorination stage thus causes the sacrifice of a considerable quantity of this precious intermediate. This situation risks resulting at times in a strong increase in the demand for periwinkle leaves. Several strategies are being studied for continuing the development of vinflunine 1.

[0006] Based on the observation that the fluorination of 3',4'-anhydrovinblastine in a superacid mixture modifies only its "north" fragment which originates from catharanthine, a solution consisting of introducing fluorine atoms directly to the skeleton of catharanthine 2 has been advocated, within the scope of the present invention. This approach has a number of advantages: it introduces fluorine upstream in the synthesis to a product with lesser added value than 3',4'-anhydrovinblastine 4. The synthesis of vinflunine could then be accessed via a biomimetic coupling with vindoline 3. In fact, 20',20'-difluorocatharanthine 6 can then be coupled to vindoline 3 to obtain 3',4'-anhydro-20',20'-difluorovinblastine 7. The latter is finally converted into vinflunine 1, in a process familiar to the specialist, by ring contraction reaction followed by reduction of the non-saturated $C_{3'}$-C_4 double bond, (Diagram 3) .

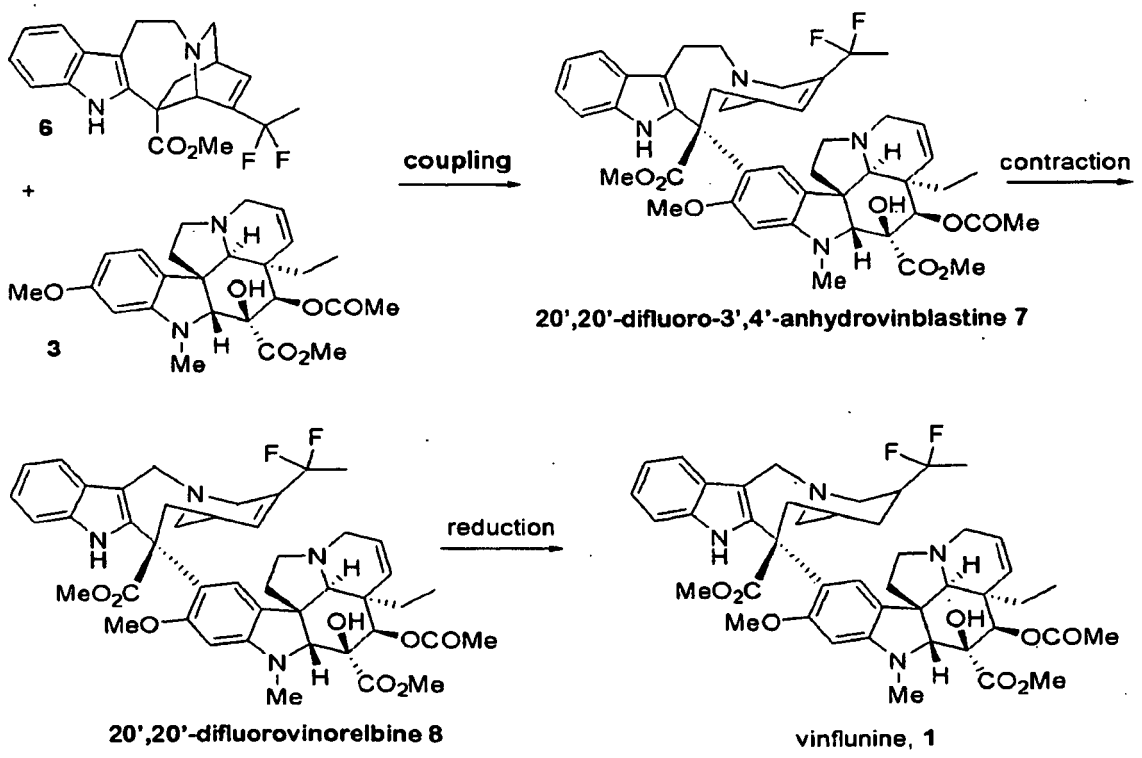
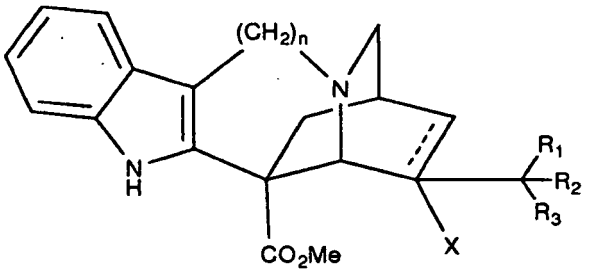


Diagram 3

[0007] This approach also allows access to other original difluorinated derivatives (3',4'-anhydro-20',20'-difluorovinblastine 7, 20',20'-difluorovinorelbine 8) which are not accessible under conventional superacid conditions. These molecules are all the more interesting since study of the structure activity relation has shown that the region 4' and 20' of the *Vinca* alkaloids is strongly associated with their anti-tumoral activity. Also, the coupling of synthesis intermediates (and derivatives) of fluorinated catharanthine likewise produces other original fluorinated derivatives of dimeric alkaloids of *Vinca.*

[0008] Therefore, the present invention relates to fluorinated derivatives of catharanthine responding to the general formula I:



I

in which:

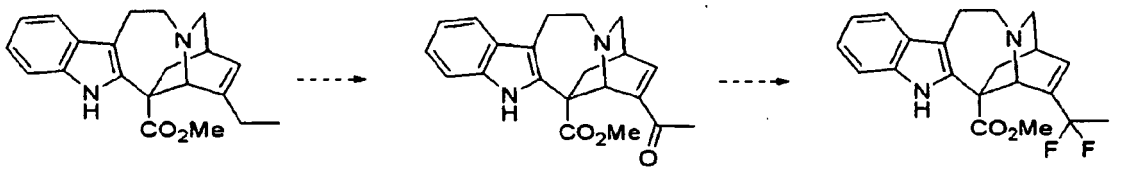
- the dotted line expresses the possibility of the presence of a double bond when the substitution -X is absent or else of a single bond when -X designates a substitution for a group:
    - H,
    - OR,
    - NR'R",

- SR, or
- an atom of halogen with R, R' and R" designating independently of one another an atom of hydrogen or a linear or branched alkyl group in C_1 to C_6,

- R_1, R_2 and R_3 represent independently of one another an atom of hydrogen, fluorine or a methylated group, on the condition all the same that at least one of the radicals R_1 and R_2 represents an atom of fluorine, and
- n = 1 or 2.

[0009] The present invention likewise relates to the utilisation of these fluorinated derivatives as synthesis intermediates useful for the preparation of fluorinated dimeric alkaloids of *Vinca,* in particular as reactive partners in coupling reactions with vindoline or with a derivative of vindoline. In particular, vinflunine will be obtained by coupling vindoline and 20,20-20,20-difluorocatharanthine, resulting in 20',20'-difluoro-3',4'-anhydrovinblastine which, in turn, will be subjected to a ring contraction reaction followed by a reduction reaction of the endocyclic double bond at position $C_{3'}$ - $C_{4'}$.

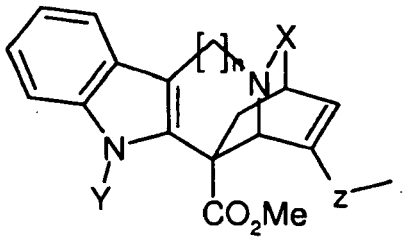
[0010] Introduction of the fluorine atoms to catharanthine 2 could be envisaged via oxidation of the lateral chain of catharanthine and fluorination.



·catharanthine 2 — 20 -oxocatharanthine 9 — 20,20-difluorocatharanthine 6

Diagram 4

[0011] The preparation of the fluorinated catharanthine derivatives of the invention implies thus an oxidation step of the lateral chain of catharanthine, which is carried out in conditions leading to an oxidised derivative of catharanthine responding to the general formula II:

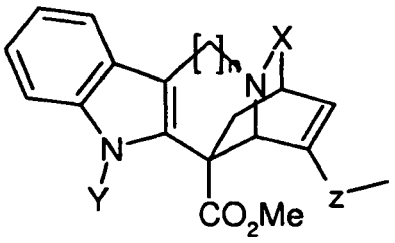


II

in which:

- n = 1 or 2,
- X designates a C=O or C=S group,
- Y designates a CO_2R, SO_2R or COR group with R designating an aryl group or a linear or branched alkyl group in C_1 to C_4, and
- Z designates a CH-OH or C=O group.

[0012] Therefore, the present invention relates also to oxidised derivatives of catharanthine responding to the general formula II:



II

in which:

- n = 1 or 2,
- X designates a C=O or C=S group,
- Y designates a CO_2R, SO_2R or COR group with R designating an aryl group or a linear or branched alkyl group in C_1 to C_4, and
- Z designates a CH-OH or C=O group.

[0013] A preferred oxidised derivative of catharanthine according to the formula II is a derivative wherein:

- n = 2,
- X designates a C=O group,
- Y designates a CO_2R group with R designating a linear or branched alkyl group in C_1 to C_4, and
- Z designates a CH-OH or C=O group.

[0014] The present invention likewise relates to the use of these oxidised derivatives as synthesis intermediates useful for the preparation of fluorinated dimeric alkaloids of *Vinca*, in particular vinflunine. This preparation implies a fluorination of the oxidised derivative of catharanthine followed by deprotection of the two nitrogen atoms, resulting in a fluorinated derivative of catharanthine of the invention. The preparation further implies a coupling reaction between the said fluorinated derivative and vindoline or a derivative of vindoline. In particular, vinflunine will be obtained by coupling vindoline and 20,20-difluoro-catharanthine, obtained by fluorination and deprotection of the two nitrogen atoms of an oxidised derivative of catharanthine as defined above for which n = 2, X = C=O, Y = CO_2R with R as defined above and Z = C=O, resulting in 20',20'-difluoro-3',4'-anhydrovinblastine which, in turn, will be subjected to a ring contraction reaction followed by a reduction reaction of the endocyclic double bond at position $C_{3'}$-$C_{4'}$.

[0015] The term "aryl" refers herein to a cyclic aromatic group of from 5 to 7 carbon atoms, comprising optionally a heteroatom, in particular an oxygen or a nitrogen, such as, for example, a phenyl or a pyridinyl group.

[0016] Thus, as an example, 20,20-difluorocatharanthine can be synthesised as follows.

[0017] Activation of the lateral chain can be achieved by isomerisation of the endocyclic double bond to the exocyclic position prior to further functionalisation. The isomerisation reaction of 2 in 10 is performed under partial hydrogen pressure in the presence of palladium on carbon. The indole ring is then protected in the form of methyl carbamate 11 and tertiary nitrogen in the form of amide 12.

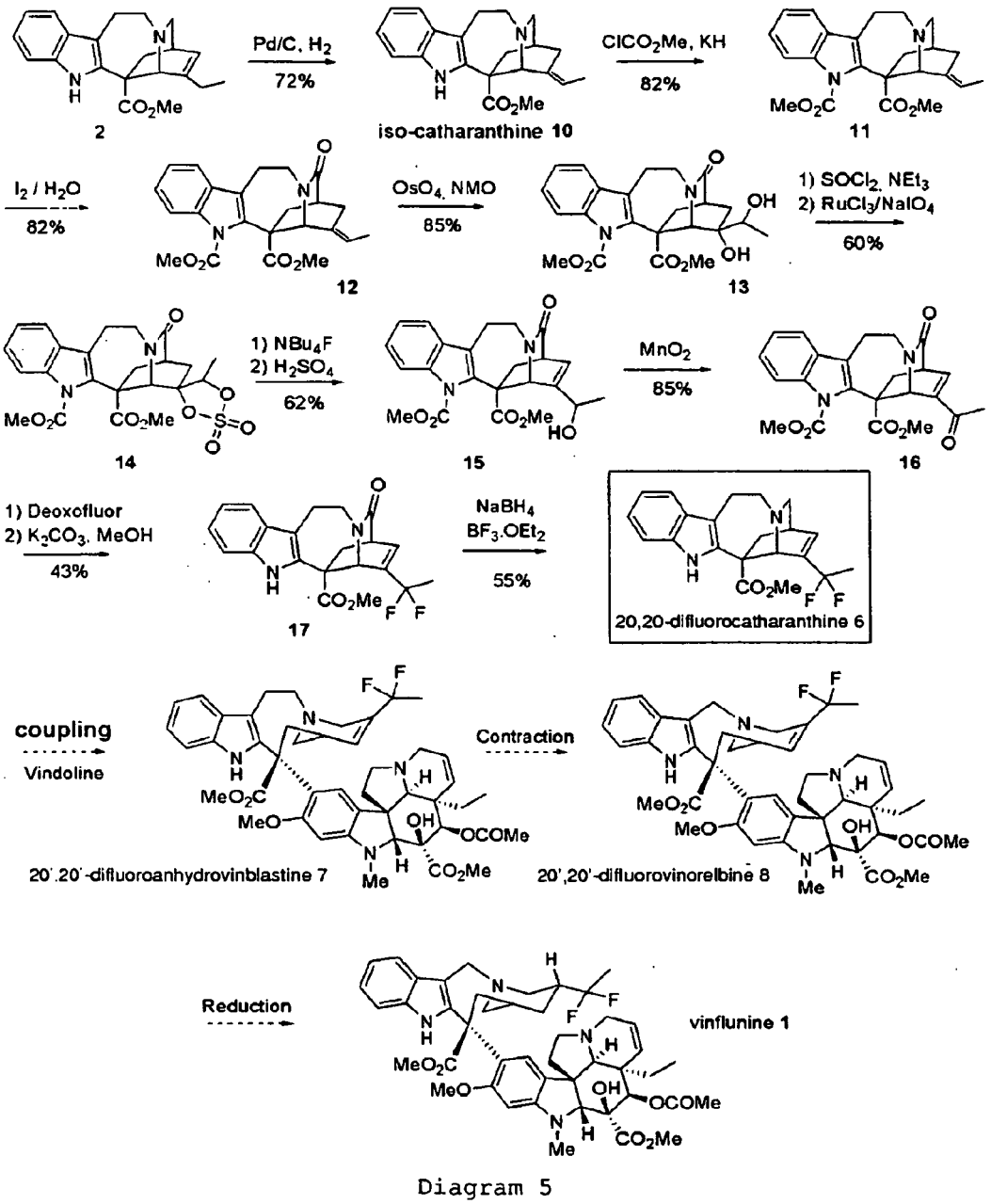


Diagram 5

[0018] The double bond of 12 is then dihydroxylated by OsO_4 and the resulting diol 13 is activated twice in the form of cyclic sulphate 14. The allylic alcohol 15 is obtained by action of tetrabutyl ammonium fluoride, followed by treatment with sulphuric acid. The alcohol function is then oxidised by MnO_2 and the resulting enone 16 is difluorinated by action of Deoxofluor™ (bis(2-methoxyethyl)aminosulfide trifluoride). The protective group of indole (carbamate) is eliminated by the action of potassium carbonate in methanol. The amide group of 17 is finally reduced to result in 20,20-difluoro-catharanthine 6. The latter can, in the same way as catharanthine of natural origin, be coupled to vindoline to provide the fluorinated analogue of 3',4'-anhydrovinblastine (7) which, after ring contraction, results in the fluorinated analogue of vinorelbine (8). Finally, selective reduction of the double bond of the north fragment results in the formation of vinflunine 1.

[0019] According to a variant synthesis route, the allylic alcohol 15 can also be obtained by an initial protection of the indole ring of catharanthine 2 by a methyl carbamate (compound 26) and of tertiary nitrogen in the form of amide 27. The latter can then be oxidised directly in allylic alcohol 15 by SeO_2 (Diagram 6).

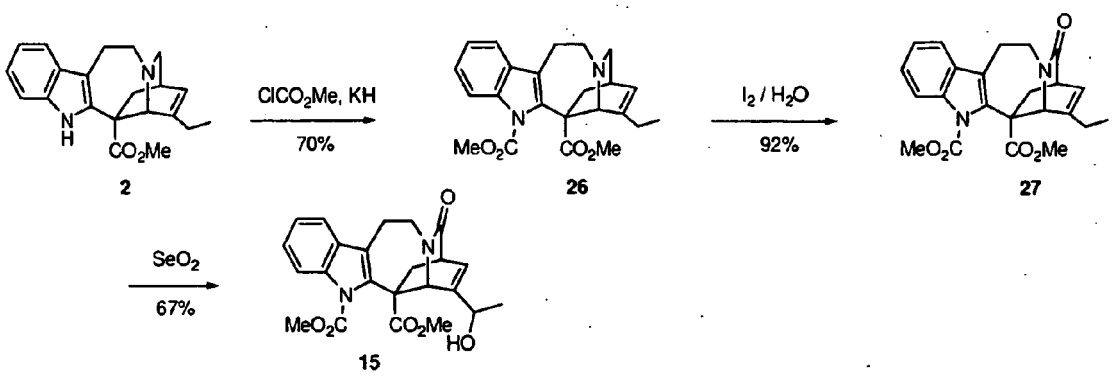


Diagram 6

[0020] The synthesis intermediates to 20,20-difluorocatharanthine 6 can be exploited by functional arrangements which do not result in 20,20-difluorocatharanthine but in structural analogues. These analogues can, in the same way as catharanthine of natural origin, be coupled to vindoline to result in the corresponding fluorinated dimeric alkaloids.

[0021] Accordingly, starting from the intermediate 13 oxidation of the secondary alcohol function gives access to ketone 18. Fluorination of the ketoalcohol 18 by DAST (diethylaminosulphide trifluoride) generates difluoro-alcohol 19. The latter could, after the usual stages of deprotection (→ 20) be coupled to vindoline to form the difluorinated analogue 21 of vinblastine which is likewise an alkaloid having notable anticancer properties (Diagram 7).

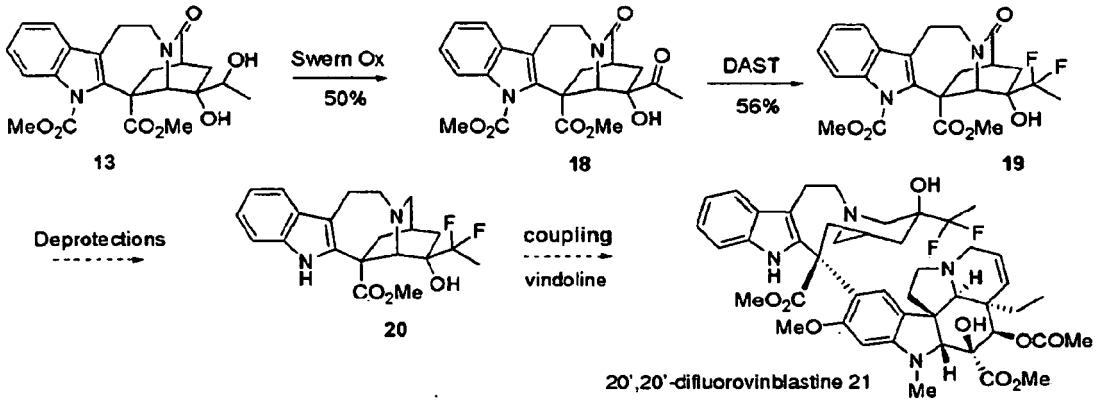


Diagram 7

[0022] Moreover, the introduction of a single fluorine atom to the catharanthine skeleton is possible from the intermediate 15 (Diagram 8). When the latter is treated by DAST, the monofluorinated product of the lateral chain (22) is formed. As already mentioned hereinabove, this product results in the mono fluoro analogues 3',4'-anhydro-20'-fluorovinblastine 24 and 20'-fluorovinorelbine 25 which can lead to the monofluorinated analogue of vinflunine by an additional stage of reduction of the double bond.

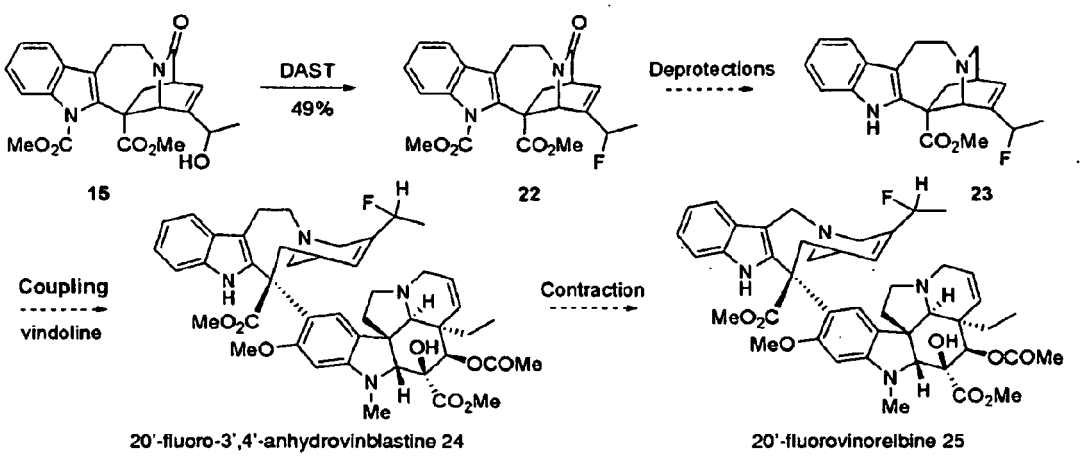


Diagram 8

[0023] Finally, isocatharanthine 10 can also be used as a synthesis intermediate in the preparation of fluorinated dimeric alkaloids of *Vinca,* and in particular vinflunine. This preparation implies a coupling reaction between the said isocathranthine and vindoline or a derivative of vindoline.

[0024] Thus, vinflunine 1 can be obtained by coupling vindoline 3 and isocatharanthine, resulting in 4',20'-anhydrovinblastine 28. This intermediate can then be difluorinated using the conditions described for the fluorination of 3',4'-anhydrovinblastine 4 (J.-C. Jacquesy et al., Journal of Fluorine Chemistry, 2002, 114, 139). The obtained product, (4'R)-4'-deoxy-20',20'-difluorovinblastine 30, is identical to the product formed by fluorination of 3',4'-anhydrovinblastine 4. Transformation of 30 in vinflunine 1 by ring contraction is described in literature (J.-C. Jacquesy et al., Journal of Fluorine Chemistry, 2002, 114, 139) (Diagram 9).

[0025] Alternately, vinflunine 1 can be also obtained by ring contraction of 4',20'- anhydrovinblastine 28, resulting in 29, followed by a gem difluorination according to the same methods as described above.

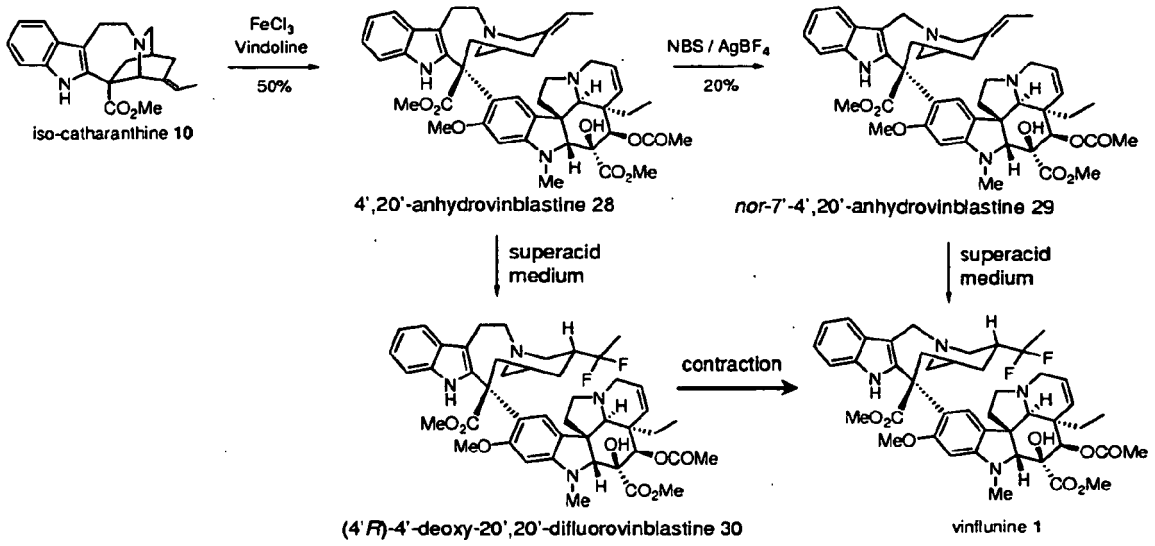


Diagram 9

[0026] It appears that the present invention offers an alternative strategy to the classic synthesis of vinflunine, allowing the use of a more efficacious and thus more economic process. In addition, the utilisation of fluorinated intermediates

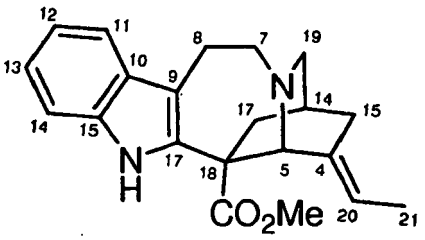
of catharanthine according to the invention, for example: 20-fluorocatharanthine 23 and 20,20-difluoro-3-hydro-4-hydroxycatharanthine 20, in coupling reactions with vindoline 3, permits preparation of novel dimeric alkaloids having potential anti-cancer activities. Other specific structural analogues of vinorelbine and vinflunine are easily accessed by this method.

[0027] All the preparation methods and reaction diagrams described hereinabove have been detailed in the case of preparation of fluorinated derivatives of catharanthine responding to the general formula (I) in which n = 2. All the corresponding derivatives responding to the general formula (I) in which n = 1 can be easily obtained by a process of ring contraction of the northern, catharanthine derived, portion of the dimers, by techniques familiar to the specialist and in particular those described by Andriamialisoa, R.Z. ; Langlois, N. ; Langlois Y. ; Potier P. Tetrahedron, 1980, 36, 3053-3060.

[0028] The present invention will now be described in greater detail by means of the preparation examples mentioned hereinbelow by way of illustration of the principal stages resulting in the fluorinated derivatives of catharanthine, and in particular in 20,20-difluorocatharanthine.

Isocatharanthine (10)

[0029]



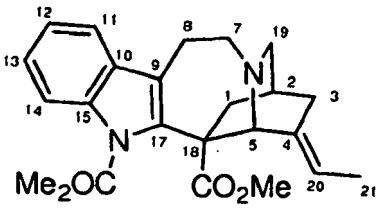
[0030] To a suspension of palladium (10% in mass) on carbon (5.7 g, 5.4 mmol, 0.2 equiv.) previously activated by hydrogen in MeOH (150 mL) is added (+)-catharanthine 2 (9.0 g, 26.8 mmol, 1 equiv.) in solution in MeOH (100 mL). The reaction mixture is placed under reduced pressure in hydrogen (0.3 bar), then isolated and left under reduced stirring at ambient temperature. The reaction is followed by ^{1}H NMR until the starting product disappears (around 2 h). The reaction mixture is then filtered on celite 545, then recrystallised in MeOH to give the compound 10 (6.5 g, 19.3 mmol, 72%) in the form of translucent crystals.

Chemical formula: $C_{21}H_{24}N_2O_2$ M = 336 g.mol^{-1}

Rf = 0.35 (Hexane/ AcOEt 3/7)
F = 78°C-81°C
^{1}H NMR ($CDCl_3$) : 8.08 (sl, 1H, NH) ; 7.53 (d, *J* = 7.3 Hz, 1H, H-11) ; 7.26 (d, *J* = 7.3 Hz, 1H, H-14) ; 7.22-7.10 (m, 2H, H-12 and H-13) ; 5.48-5.32 (m, 1H, H-20) ; 4.05 (s, 1H, H-5) ; 3.73 (s, 3H, CO_2CH_3) ; 3.62-3.46 (m, 1H, H-7) ; 3.44-3.24 (m, 2H, H-7 and H-8) ; 3.18-3.10 (m, 1H, H-19) ; 3.08-2.92 (m, 2H, H-19 and H-8) ; 2.88-2.74 (m, 1H, H-1) ; 2.44-2.26 (m, 2H, H-3); 2.20-2.08 (m, 1H, H-2) ; 1.90-1.78 (m, 1H, H-1) ; 1.62 (d, *J* = 6.7 Hz, 3H, H-21).
^{13}C NMR ($CDCl_3$): 175.2 ; 137.7 ; 135.9 ; 129.5 ; 122.6 ; 120.1; 119.4 ; 119.0 ; 111.2 ; 111.1 ; 64.2 ; 56.1 ; 53.8 ; 53.3 ; 51.1 ; 38.0 ; 30.3 ; 27.9 ; 22.0 ; 13.4.
IR (film): 3368, 2916, 2855, 1714, 1461, 1264, 740 cm^{-1}.
MS (ESI TOF): 337 [M+H$^+$] (100).
$[\alpha]_D^{20}$ = + 35 (c = 2.3 ; $CHCl_3$)

N_a-carbomethoxyisocatharanthine (11)

[0031]



[0032] To a suspension of potassium hydride (0.72 g, 6.3 mmol, 1.5 equiv.) in THF (10 mL) at 0°C is added dropwise a solution of 10 (1.35 g, 4 mmol, 1 equiv.) in THF (20 mL). After 30 minutes under stirring at 0°C, methyl chloroformate (0.5 mL, 6.3 mmol, 1.5 equiv.) is added dropwise. After 1 h under stirring at 0°C, the reaction medium is brought to ambient temperature and agitation is maintained for 18 h. An aqueous solution of saturated K_2CO_3 (10 mL) is added. The aqueous phase is extracted with CH_2Cl_2 (3x20 mL), the organic phases are collected, dried on Na_2SO_4 and concentrated under vacuum. The crude product is then purified by chromatography on silica (Eluent: CH_2Cl_2/MeOH 97/3) to give 11 (1.3 g, 3.3 mmol, 82%) in the form of a white solid.

Chemical formula: $C_{23}H_{26}N_2O_4$ $M = 394\ g.mol^{-1}$

Rf = 0.4 4 (CH_2Cl_2/MeOH 94/6)
F = 62°C-64°C

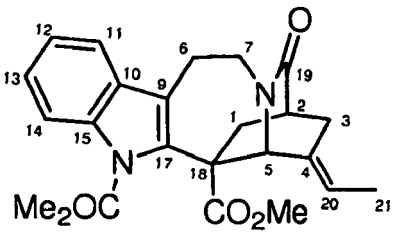
^1H NMR ($CDCl_3$) : 8.08 (d, *J* = 7.9 Hz, 1H, H-11) ; 7.48 (d, *J* = 7.3 Hz, 1H, H-14) ; 7.38-7.16 (m, 2H, H-12 and H-13) ; 5.32-5.18 (m, 1H, H-20) ; 4.06 (s, 1H, H-5) ; 3.86 (s, 3H, CO_2CH_3) ; 3.68 (m, 1H, H-7) ; 3.54 (s, 3H, CO_2CH_3) ; 3.40-3.12 (m, 2H, H-7 and H-8) ; 2.99 (m, 1H, H-19) ; 2.86 (m, 1H, H-19) ; 2.80-2.65 (m, 2H, H-8 and H-1) ; 2.44 (d, *J* = 16 Hz, 1H, H-3) ; 2.30 (d, *J* = 16 Hz, 1H, H-3) ; 2.06 (m, 1H, H-2) ; 1.76 (d, *J* = 14Hz, 1H, H-1) ; 1.56 (d, *J* = 6.7 Hz, 3H, H-21).
^{13}C NMR ($CDCl_3$): 173.4 ; 151.8 ; 138.1 ; 135.8 ; 129.5 ; 124.6; 122.7 ; 119.7 ; 118.2 ; 115.5 ; 60.6 ; 57.9 ; 54.1 ; 53.0 ; 52.0 ; 37.5 ; 29.7 ; 27.9 ; 21.8 ; 12.6.
MS (ESI TOF) : 395 [M+H$^+$](100).

HRMS (TOF MS ES+) :	
Value calculated for $C_{23}H_{27}N_2O_4$	395.1971
Value found	395.1956

$[\alpha]_D^{20}$= + 48 (c = 1.0 ; $CHCl_3$)

N_a-carbomethoxy-19-oxoisocatharanthine (12)

[0033]



[0034] To 5 mL of an aqueous solution of Na_2CO_3 (675 mg, 6.4 mmol, 9.3 equiv.) is added a solution of 11 (270 mg, 0.69 mmol, 1 equiv.) in THF (10 mL). Iodine (800 mg, 3.2 mmol, 4.6 equiv.) in solution in THF (12 mL) is added dropwise at 0°C. The reaction mixture is then brought to ambient temperature and stirred for 18 hours. Next an aqueous solution saturated in $Na_2S_2O_3$ (15 mL) is added and the reaction mixture is left under stirring for 30 minutes. The aqueous phase is then extracted with CH_2Cl_2 (3×20 mL). The organic phases are combined, dried on Na_2SO_4 and concentrated under

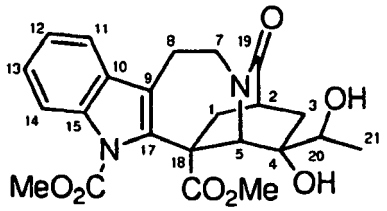
vacuum. The crude product is then purified by chromatography on silica (Eluent: CH_2Cl_2/MeOH 98/2) to give 12 (230 mg, 0.56 mmol, 82%) in the form of a white solid.

Chemical formula: $C_{23}H_{24}N_2O_5$ M = 408 g.mol^{-1}

Rf = 0.4 (CH_2Cl_2/MeOH 94/6)
F = 94°C-96°C
^{1}H NMR ($CDCl_3$) : 8.04-7.97 (m, 1H, H-11) ; 7.52-7.43 (m, 1H, H-14) ; 7.36-7.21 (m, 2H, H-12 and H-13) ; 5.53-5.41 (m, 1H, H-20) ; 4.66 (s, 1H, H-5) ; 4.32-4.17 (m, 1H, H-7) ; 3.93 (s, 3H, CO_2CH_3) ; 3.60 (s, 3H, CO_2CH_3) ; 3.28-3.15 (m, 3H, H-7 and H-8) ; 2.97 (dd, *J* = 14 Hz and *J* = 1.8 Hz, 1H, H-1) ; 2.84-2.76 (m, 1H, H-2) ; 2.56-2.48 (m, 2H, H-3) ; 2.00-1.89 (m, 1H, H-1); 1.59 (d, *J* = 6.7 Hz, 3H, H-21).
^{13}C NMR ($CDCl_3$) : 174.6 ; 172.0 ; 151.6 ; 136.4 ; 135.1 ; 132.5; 129.2 ; 124.9 ; 122.8 ; 120.9 ; 118.1 ; 117.0 ; 115.6 ; 61.5 ; 60.1 ; 58.7 ; 53.2 ; 52.1 ; 40.3 ; 38.9 ; 37.2 ; 28.5 ; 21.2 ; 20.8 ; 13.9 ; 13.1.
MS (ESI TOF) : 409 [M+H$^+$] (100); 817 [2M+H$^+$] (34) .
$[\alpha]_D^{20}$ = + 255 (c = 0.4 ; $CHCl_3$)

(4*R*, 20*R*)-N$_a$-carbomethoxy-3-hydro-4,20-dihydroxy-19-oxocatharanthine (13)

[0035]



[0036] To a solution of 12 (1.26 g, 3.08 mmol, 1 equiv.) in an acetone/water mixture (8/1) (27 mL) at 0°C are added OsO_4 in solution in *t*-BuOH (2.5%, 1.9 mL, 0.154 mmol, 0.05 equiv.), then by portion at 15 minutes NMO (0.72 g, 6.2 mmol, 2 equiv.). After 15 minutes at 0°C, the reaction mixture is left under stirring at ambient temperature for 18 h. The reaction is stopped by adding a saturated aqueous solution of $Na_2S_2O_3$ (15 mL) and water (15 mL) and left under stirring for 20 minutes. The reaction mixture is extracted with CH_2Cl_2 (4×30 mL). The organic phases are combined, dried on Na_2SO_4 and concentrated under vacuum. The crude product is then purified by chromatography on silica (Eluent: CH_2Cl_2/MeOH 97/3) to give 13 (1.16 g, 2.61 mmol, 85%) in the form of a white solid.

Chemical formula: $C_{23}H_{26}N_2O_7$ M = 442 g.mol^{-1}

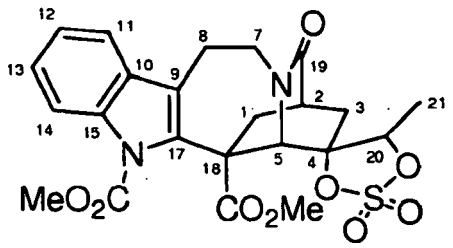
Rf = 0.5 (CH_2Cl_2/MeOH 9/1)
F = 102°C-104°C
^{1}H NMR ($CDCl_3$): 7.98 (d, *J* = 7.9 Hz, 1H, H-11) ; 7.44 (d, *J* = 7.9 Hz, 1H, H-14) ; 7.35-7.20 (m, 2H, H-12 and H-13) ; 4.77 (s, 1H, H-5) ; 4.30-4.18 (m, 1H, H-7) ; 4.05-3.93 (m, 1H, H-20) ; 3.92 (s, 3H, CO_2CH_3) ; 3.63 (s, 3H, CO_2CH_3) ; 3.34-3.08 (m, 3H, H-7 and H-8) ; 2.88 (dd, *J* = 14.0 Hz *J* = 1.8 Hz, 1H, H-1) ; 2.65-2.60 (m, 1H, H-2) ; 2.02-1.74 (m, 3H, H-1 and H-3) ; 1.16 (d, *J* = 6.1 Hz, 3H, H-21).
^{13}C NMR ($CDCl_3$) : 174.1 ; 172.5 ; 151.7 ; 135.3 ; 129.0 ; 125.1; 123.0 ; 118.2 ; 117.2 ; 115.6 ; 69.8 ; 59.2 ; 55.9 ; 53.4 ; 53.3 ; 52.9 ; 42.1 ; 38.5 ; 37.5 ; 36.7 ; 21.1 ; 17.8.
IR (tablet KBr): 3402, 2954, 1741, 1657, 1458, 760 cm^{-1}
MS (ESI TOF): 443 [M+H$^+$] (11); 465 [M+Na$^+$] (100); 907 [2M+Na$^+$] (36) .
HRMS (TOF MS ES+):

Value calculated for $C_{23}H_{26}N_2O_7Na$	465.1638
Value found	465.1631

$[\alpha]_D^{20}$ = + 97 (c = 0.5 ; $CHCl_3$)

(4R, 20R)-N_a-carbomethoxy-3-hydro-4,20-dihydroxysulphate-19-oxocatharanthine (14)

[0037]



[0038] To a solution of diol 13 (200 mg, 0.45 mmol, 1 equiv.) in CH_2Cl_2 (5 mL) at 0°C are added triethylamine (0.15 mL, 1.04 mmol, 2.3 equiv.) then, dropwise, thionyl chloride (43 μL, 0.59 mmol, 1.3 equiv.). After 30 min at 0°C, the reaction is stopped by adding a solution saturated in NaCl (5 mL) and water (5 mL). The aqueous phase is extracted with CH_2Cl_2 (3×10 mL). The organic phases are combined, dried on Na_2SO_4 and concentrated under vacuum.

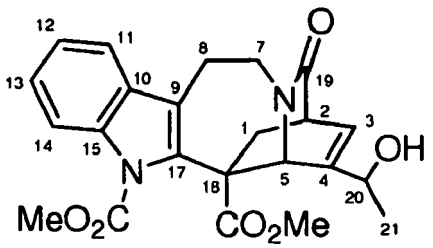
[0039] The crude product is then placed directly into a mixture of 7.5 mL CH_3CN and 6.5 mL H_2O and is stirred vigorously. $RuCl_3$ (5 mg, 0.023 mmol, 0.05 equiv.) and $NaIO_4$ (242 mg, 1.13 mmol, 2.5 equiv.) are then added successively and after 1h30 Et_2O (12 mL) is added. Agitation is prolonged for 10 min. The aqueous phase is extracted by 3×10 mL Et_2O then the combined organic phases are washed with water (30 mL), a solution saturated in $NaHCO_3$ (30 mL) and a solution saturated in NaCl (30 mL). The organic phase is then dried on Na_2SO_4 and concentrated under vacuum. Purification by chromatography on silica (eluent CH_2Cl_2/MeOH 98/2) results in 14 (137 mg, 0.27 mmol, 60%) in the form of a white solid.

Chemical formula: $C_{23}H_{24}N_2O_9S$ M = 504 g.mol^{-1}

Rf = 0.5 (CH_2Cl_2/MeOH 95/5)
F = 140°C-142°C
^{1}H NMR ($CDCl_3$) : 7.98 (d, *J* = 7.3 Hz, 1H, H-11) ; 7.44 (d, *J* = 7.3 Hz, 1H, H-14) ; 7.37-7.30 (m, 2H, H-12 and H-13) ; 5.12 (s, 1H, H-5) ; 4.75 (q, *J* = 6.7 Hz, 1H, H-20) ; 4.24-4.13 (m, 1H, H-5) ; 3.99 (s, 3H, $CO_2C\underline{H}_3$) ; 3.68 (s, 3H, $CO_2C\underline{H}_3$) ; 3.53-3.47 (m, 1H, H-7) ; 3.35-2.95 (m, 2H, H-8) ; 2.97 (dd, *J* = 14.0 Hz and *J* = 1.6 Hz, 1H, H-1) ; 2.90-2.85 (m, 1H, H-2) ; 2.45-2.38 (m, 2H, H-3) ; 2.02-1.96 (m, 1H, H-1) ; 1.64 (d, *J* = 6.7 Hz, 3H, H-21).
^{13}C NMR ($CDCl_3$): 173.2 ; 171.5 ; 152.4 ; 136.1 ; 134.8 ; 129.3; 125.6 ; 123.5 ; 118.8 ; 117.5 ; 116.0 ; 94.8 ; 84.9 ; 56.9 ; 55.1 ; 54.0 ; 53.4 ; 40.9 ; 38.4 ; 37.7 ; 32.3 ; 21.2 ; 15.8. IR (tablet KBr): 1735, 1687, 1459, 1382, 1215, 904 cm^{-1}.
MS (ESI TOF): 505 [M+H$^+$] (100); 1009 [M+Na$^+$] (13).
$[\alpha]_D^{20}$= + 165 (c = 0.3 ; $CHCl_3$)

(20*R*)-N_a-carbomethoxy-20-hydroxy-19-oxocatharanthine (15)

[0040]



[0041] To a solution of sulphate 14 (1.59, g, 3.16 mmol, 1 equiv.) in THF (25 mL) is added dropwise a solution of NBu_4F (1M in THF, 6.3 mL, 6.3 mmol, 2 equiv.). After 18h of stirring at ambient temperature, a solution of H_2SO_4 2M in

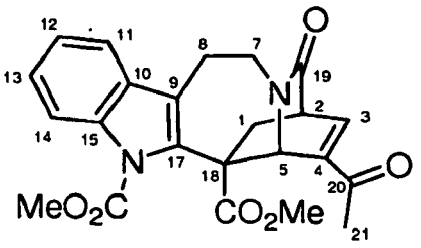
THF (37 mL) and 3.7 mL water are added. After 48h of stirring at ambient temperature, a solution saturated in $NaHCO_3$ is added (200 mL). The aqueous phase is extracted with AcOEt (4×50 mL), the organic phases are combined, dried on Na_2SO_4, filtered then concentrated under vacuum. The crude product is then purified by chromatography on silica and 15 (828 mg, 1.95 mmol, 62%) is isolated in the form of a white solid.

Chemical formula: $C_{23}H_{24}N_2O_6$ M = 424 g.mol^{-1}

Rf = 0.3 (CH_2Cl_2/MeOH 95/5)
F = 188°C-190°C
^{1}H NMR ($CDCl_3$) : 7.98 (d, *J* = 7.9 Hz, 1H, H-11) ; 7.44 (d, *J* = 7.9 Hz, 1H, H-14) ; 7.35-7.20 (m, 2H, H-12 and H-13) ; 6.43 (d, *J* = 6.3 Hz, 1H, H-3) ; 5.24 (d, *J* = 1.7Hz, 1H, H-5) ; 4.41-4.33 (m, 1H, H-20) ; 4.17-4.03 (m, 1H, H-7) ; 3.94 (s, 3H, CO_2CH_3) ; 3.57 (s, 3H, CO_2CH_3) ; 3.47-3.17 (m, 4H, H-8, H-2 and H-7) ; 2.88 (dd, *J* = 14.0 Hz and *J* = 1.8 Hz, 1H, H-1) ; 2.02 (dd, *J* = 14.0 Hz and *J* = 1.8 Hz, 1H, H-1) ; 1.33 (d, *J* = 6.1 Hz, 3H, H-21).
^{13}C NMR ($CDCl_3$) : 174.1 ; 173.8 ; 152.0 ; 145.3 ; 136.6 ; 135.3; 129.3 ; 128.5 ; 125.1 ; 123.1 ; 118.4 ; 116.7 ; 115.8 ; 67.1 ; 58.0 ; 54.3 ; 53.6 ; 52.8 ; 44.0 ; 40.7 ; 38.4 ; 21.3 ; 21.1. IR (tablet KBr): 3414, 2944, 1743, 1653, 1458, 1437, 1327, 1242, 754 cm^{-1}.
MS (ESI TOF) : 447 [M+Na$^+$] (100) ; 871 [2M+Na$^+$] (64) .
$[\alpha]_D^{20}$ = +181 (c = 0.7 ; $CHCl_3$)

N_a-carbomethoxy-19,20-dioxocatharanthine (16)

[0042]



[0043] A solution of allylic alcohol 15 (100 mg, 0.236 mmol, 1 equiv.) in 8 mL of dichloromethane is cooled to 0°C. 140 mg of activated manganese dioxide (16 mmol, 70 equiv.) are added to this at once. The black suspension obtained is stirred at 0°C for 1h30 under nitrogen atmosphere then brought to ambient temperature.

[0044] The reaction mixture is filtered on celite 545 then washed thoroughly using dichloromethane. The filtrate is concentrated under reduced pressure to give the enone 16 (85 mg, 0.201 mmol, 85%) in the form of a white solid.

Chemical formula: $C_{23}H_{22}N_2O_6$ M = 422 g.mol^{-1}

Rf = 0.4 (EtOAc)
F = 108°C-110°C

^{1}H NMR ($CDCl_3$) : 8.01 (d, *J* = 8.5 Hz, 1H, H-11) ; 7.49 (d, *J* = 7.3 Hz, 1H, H-14) ; 7.45 (d, *J* = 6.7 Hz, 1H, H-3) ; 7.37-7.23 (m, 2H, H-12 and H-13) ; 5.80 (d, *J* = 1.8 Hz, 1H, H-5) ; 4.18-4.02 (m, 1H, H-7) ; 3.91 (s, 3H, CO_2CH_3) ; 3.65 (m, 1H, H-2) ; 3.49 (s, 3H, CO_2CH_3) ; 3.48-3.34 (m, 1H, H-8) ; 3.32-3.16 (m, 2H, H-7 and H-8) ; 2.82 (dd, *J* = 12.8 Hz and *J* = 2.4 Hz, 1H, H-1) ; 2.35 (s, 3H, H-21) ; 2.07 (dd, *J* = 13.4 Hz and *J* = 3.0 Hz, 1H, H-1).
^{13}C NMR ($CDCl_3$) : 193.3 ; 172.2 ; 171.6 ; 151.9 ; 143.6 ; 142.3; 135.8 ; 135.3 ; 129.2 ; 125.2 ; 123.1 ; 118.4 ; 117.0 ; 115.8 ; 57.3 ; 53.5 ; 52.6 ; 52.5 ; 45.5 ; 41.3 ; 37.4 ; 24.6; 20.9. IR (tablet KBr): 1740, 1668, 1252, 751 cm^{-1}.
MS (ESI TOF) : 423 [M+H$^+$] (10) ; 445 [M+Na$^+$] (100) ; 867 [2M+Na$^+$] (32) .
HRMS (TOF MS ES+) :

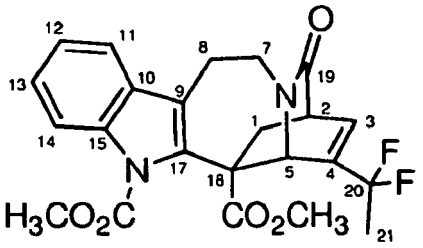
Value calculated for $C_{23}H_{22}N_2O_6Na$	445.1376
Value found	445.1357

$[\alpha]_D^{20}$ = + 183 (c = 1.8 ; $CHCl_3$)

20,20-difluoro-19-oxocatharanthine (17)

Fluorination: N_a-carbomethoxy-20,20-difluoro-19-oxocatharanthine

[0045]



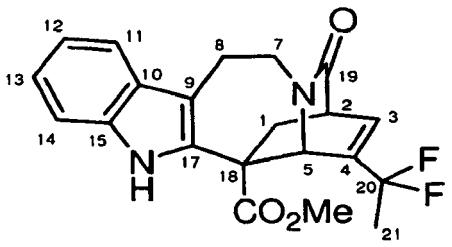
[0046] The enone 16 (300 mg, 0.71 mmol, 1 equiv.) is placed in solution in Deoxofluor™ (3 mL, 16.4 mmol, 23 equiv.). Three drops of ethanol are then added and the reaction mixture is left under stirring at 80°C for 24 h. 0.6 mL of Deoxofluor™ (3.3 mmol, 5 equiv.) and two drops of ethanol are then added and agitation is continued at this temperature for a further 48 h (the reaction is followed by ^1H NMR until the starting product disappears). The reaction medium is diluted in 200 mL of dichloromethane and 100 mL of an aqueous solution saturated in K_2CO_3 are then added. The mixture is left for 15 min under stirring at ambient temperature, then the aqueous phase is extracted by 3×50 mL of dichloromethane. The organic phases are combined, dried on Na_2SO_4 and concentrated under vacuum. The crude product is then purified by two filtrations on silica gel (CH_2Cl_2/MeOH 98/2 and C_6H_{12}/AcOEt 6/4) and the residue enters the following stage.

Chemical formula: $C_{23}H_{22}N_2O_5F_2$ M = 444 g.mol^{-1}

Rf = 0.3 (Hexane/AcOEt 40/60)
^1H NMR ($CDCl_3$): 8.01-7.99 (m, 1H, H-11) ; 7.53-7.47 (m, 1H, H-14) ; 7.38-7.28 (m, 2H, H-12 and H-13) ; 6.87-6.77 (m, 1H, H-3) ; 5.36 (d, *J* = 1.8 Hz, 1H, H-5) ; 4.20-4.03 (m, 1H, H-7) ; 3.93 (s, 3H, CO_2CH_3) ; 3.61-3.54 (m, 1H, H-2) ; 3.57 (s, 3H, CO_2CH_3) ; 3.45-3.20 (m, 3H, H-8 and H-7) ; 2.93-2.83 (m, 1H, H-1) ; 2.09-1.98 (m, 1H, H-1) ; 1.81 (dd, *J* = 18 Hz, *J* = 18 Hz, 3H, H-21).

Deprotection of indole: 20,20-difluoro-19-oxocatharanthine (17)

[0047]



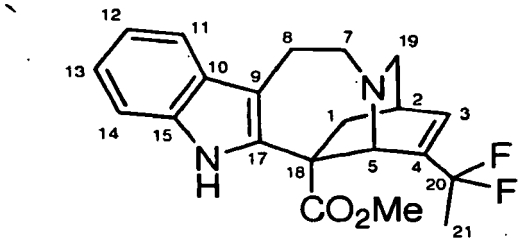
[0048] To a solution of the above protected 20,20-difluorocatharanthine in 100 mL of methanol are added in one time 2 g of potassium carbonate (14.5 mmol) and the suspension is stirred at ambient temperature for 18 h. 50 mL of water are then added to the now limpid reaction medium and the mixture is extracted by 3×50 mL dichloromethane. The combined organic phases are dried on Na_2SO_4 and concentrated under reduced pressure. The residue obtained is precipitated in a cyclohexane/ ethyl acetate mixture 7/3 to give 17 (118 mg, 0.307 mmol, 43% in two steps) in the form of a white solid.

Chemical formula: $C_{21}H_{20}F_2N_2O_3$ M = 386 g.mol^{-1}

Rf = 0.3 (CH_2Cl_2/MeOH 95/5)
^{1}H NMR ($CDCl_3$) : 7.95 (s, 1H, NH) ; 7.52 (d, *J* = Hz, 1H, H-11) ; 7.26 (d, *J* = Hz, 1H, H-14) ; 7.16-7.11 (m, 2H, H-12 and H-13) ; 6.83 (m, 1H, H-3) ; 5.55 (d, *J* = 1 Hz, 1H, H-5) ; 4.24 (m, 1H, H-7) ; 3.67 (s, 3H, CO_2CH_3) ; 3.58 (m, 1H, H-2) ; 3.36-3.24 (m, 3H, H-8 and H-7) ; 2.82 (dd, *J* = 13 Hz, *J* = 2 Hz, 1H, H-1) ; 2.27 (dd, *J* = 13 Hz, *J* = 2 Hz, 1H, H-1) ; 1.82 (dd, *J* = 18 Hz, *J* = 18 Hz, 3H, H-21).
^{13}C NMR ($CDCl_3$): 172.8 ; 171.6 ; 139.5 (t, *J* = 30 Hz) ; 135.8 ; 135.2 (t, *J* = 9 Hz) ; 133.8 ; 127.7 ; 122.4 ; 119.7 ; 119.1 (t, *J* = 233 Hz) ; 118.4 ; 110.6 ; 108.8 ; 56.3 ; 53.6 ; 53.0 ; 44.0 ; 42.8 ; 35.6 ; 22.4 (t, *J* = 28 Hz) ; 20.7.
$[\alpha]_D^{20}$ = + 155 (c = 0.4 ; $CHCl_3$) .

20,20-difluorocatharanthine (6)

[0049]



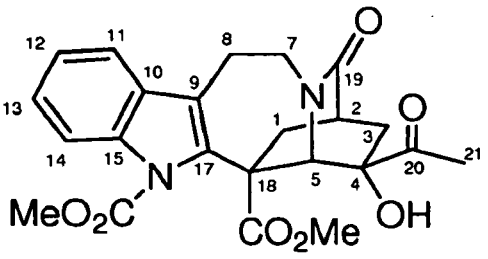
[0050] To a solution of 17 (140 mg, 0.36 mmol, 1 equiv.) in 50 mL of tetrahydrofurane are added in one time 360 mg of sodium borohydride (9.5 mmol, 26.5 equiv.). The resulting suspension is cooled to 0°C and placed under stirring and nitrogen atmosphere. 1.9 mL (14.6 mmol, 40.5 equiv.) of trifuoroborane diethylic etherate are added dropwise, then the reaction mixture is brought to ambient temperature and stirred for 3h. The solvent is evaporated under vacuum and replaced by 30 mL of methanol to which are added 6 mL of water and 4.5 mL of a solution of hydrochloric acid at 10%. The whole is stirred at ambient temperature for 15h. The methanol is evaporated and replaced by 20 mL of dichloromethane. The medium is neutralised by addition of 40 mL of an aqueous solution saturated in sodium hydrogenocarbonate then extracted by 3×20 mL of dichloromethane. The combined organic phases, dried on Na_2SO_4, are concentrated under reduced pressure. Purification of the residue by chromatography on silica (eluent: CH_2Cl_2/MeOH 98/2) produces 74 mg (0.2 mmol, 55%) of 6 in the form of a white solid.

Chemical formula: $C_{21}H_{22}F_2N_2O_2$ M = 372 g.mol^{-1}

Rf = 0.5 (CH_2Cl_2/MeOH 95/5)
^{1}H NMR ($CDCl_3$) : 7.68 (s, 1H, NH) ; 7.53 (d, *J* = 7.5 Hz, 1H, H-11) ; 7.27 (d, *J* = 7.5 Hz, 1H, H-14) ; 7.20 (td, *J* = 7.5 Hz, *J* = 1.5 Hz, 1H, H-13) ; 7.14 (td, *J* = 7.5 Hz, *J* = 1.5 Hz, 1H, H-12) ; 6.61 (m, 1H, H-3) ; 4.64 (d, *J* = 2 Hz, 1H, H-5) ; 3.72 (s, 3H, CO_2CH_3) ; 3.63 (ddd, *J* = 14 Hz, *J* = 10 Hz, *J* = 5 Hz, 1H, H-7) ; 3.43 (ddd, *J* = 14 Hz, *J* = 5 Hz, *J* = 5 Hz, 1H, H-7) ; 3.32 (ddd, *J* = 17 Hz, *J* = 10 Hz, *J* = 5 Hz, 1H, H-8) ; 3.01 (ddd, *J* = 17 Hz, *J* = 5 Hz, *J* = 5 Hz, 1H, H-8) ; 2.88 (m, 3H, H-2 and H-19) ; 2.81 (dd, *J* = 13 Hz, *J* = 2 Hz, 1H, H-1) ; 1.84 (dd, *J* = 18 Hz, *J* = 18 Hz, 3H, H-21) ; 1.81 (d, *J* = 13 Hz, 1H, H-1).
^{13}C NMR ($CDCl_3$): 173.4 ; 143.3 (t, *J* = 28 Hz) ; 136.1 ; 135.3 ; 132.1 (t, *J* = 9 Hz) ; 128.8 ; 122.1 ; 119.7 (t, *J* = 232 Hz) ; 119.4 ; 118.3 ; 110.6 ; 110.4 ; 57.0 ; 55.3 ; 52.7 ; 52.3 ; 47.0 ; 37.0 ; 30.8 ; 22.6 (t, *J* = 28 Hz) ; 21.6.
SM (ESI TOF): 353 [M-HF+H$^+$] (6) ; 373 [M+H$^+$] (100).
$[\alpha]_D^{20}$ = + 43 (c = 0.4 ; $CHCl_3$).

(4*R*)-N_a-carbomethoxy-3-hydro-4-hydroxy-19,20-dioxocatharanthine (18)

[0051]



[0052] To a solution of oxalyl chloride (0.56 mL, 6.47 mmol, 2.2 equiv.) in CH_2Cl_2 (25 mL) maintained at -65°C (internal temperature) is added dropwise DMSO (1.15 mL, 16.2 mmol, 5.5 equiv.) in solution in CH_2Cl_2 (0.850 mL). The mixture is stirred for 20 min, then a solution of diol 13 (1.3 g, 2.94 mmol, 1 equiv.) in CH_2Cl_2 (25 mL) is added dropwise as the temperature is regulated between -60°C and -65°C. After 45 min of stirring, triethylamine (3.7 mL, 26.5 mmol, 9.0 equiv.) is added, then the temperature of the mixture is brought to ambient temperature over a period of 45 min. Water (20 mL) and brine (10 mL) are added, then the reaction mixture is extracted with CH_2Cl_2 (3×50 mL). The organic phases are combined, dried on Na_2SO_4 and concentrated under vacuum. The crude product is then purified by flash chromatography on silica (Eluent: CH_2Cl_2/MeOH 97/3) to give keto-alcohol 18 (647 mg, 1.47 mmol, 50%) in the form of a white solid and 13 (520 mg, 1.17 mmol, 40%).

Chemical formula: $C_{23}H_{24}N_2O_7$ M = 440 g.mol^{-1}

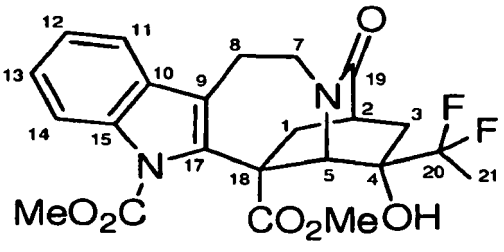
F = 123°C-125°C
Rf = 0.2 (AcOEt)
^{1}H NMR ($CDCl_3$) : 7.97 (d, *J* = 8.5 Hz, 1H, H-11) ; 7.44 (d, *J* = 7.3 Hz, 1H, H-14) ; 7.35-7.20 (m, 2H, H-12 and H-13) ; 5.16 (sl, 1H, OH) ; 5.04 (s, 1H, H-5) ; 4.23-4.04 (m, 1H, H-7) ; 3.91 (s, 3H, CO_2CH_2) ; 3.48 (s, 3H, CO_2CH_3) ; 3.41-3.35 (m, 2H, H-7 and H-8) ; 3.35-3.11 (m, 1H, H-8) ; 2.85 (dd, *J* = 14.0 Hz and *J* = 1.8 Hz, 1H, H-1) ; 2.79-2.71 (m, 1H, H-2) ; 2.59 (d, *J* = 14.0 Hz, 1H, H-3) ; 2.25 (s, 3H, H-21) ; 2.26-2.15 (m, 1H, H-3) ; 1.91-1.79 (m, 1H, H-1).
^{13}C NMR ($CDCl_3$) : 204.5 ; 174.3 ; 173.0 ; 151.9 ; 137.1 ; 135.0 ; 129.3 ; 125.1 ; 123.1 ; 118.4 ; 116.6 ; 115.8 ; 57.6 ; 54.9 ; 53.5 ; 52.7 ; 42.1 ; 38.9 ; 38.6 ; 34.9 ; 24.7 ; 21.2. IR (tablet KBr): 3270, 2953, 1732, 1652, 1461, 759.747cm^{-1}.
MS (ESI TOF): 441 [M+H$^+$] (100).

HRMS (TOF MS ES+) :	
Value calculated for $C_{23}H_{24}N_2O_7Na$	463.1481
Value found	463.1472

$[\alpha]_D^{20}$ = + 121 (c = 0.4 ; $CHCl_3$)

(4*R*)-N_a-carbomethoxy-20,20-difluoro-3-hydro-4-hydroxy-19-oxocatharanthine (19)

[0053]



[0054] To a solution of keto-alcohol 18 (44 mg, 0.1 mmol, 1 equiv.) in CH_2Cl_2 (1 mL) at -78°C is added DAST (67 µL, 0.5 mmol, 5 eq). The reaction mixture is then left under stirring at ambient temperature for 18h. Next, an aqueous solution

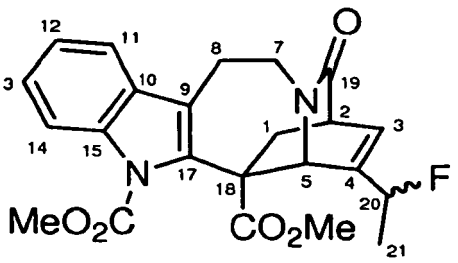
of $NaHCO_3$ at 10% (5 mL) is added dropwise at 0°C, the mixture is left for 15 min under stirring at ambient temperature, then the aqueous phase is extracted with CH_2Cl_2 (3x10 mL). The organic phases are combined, dried on Na_2SO_4 and concentrated under vacuum. The crude product is then purified by chromatography on silica (Eluent: Hexane/AcOEt 6/4) to give 19 (26 mg, 0.056 mmol, 56%).

Chemical formula: $C_{22}H_{24}F_2N_2O_6$ M = 462 g.mol^{-1}

Rf = 0.3 (EtOAc)
^{1}H NMR ($CDCl_3$): 7.98 (d, *J* = 8.5 Hz, 1H, H-11) ; 7.49 (d, *J* = 7.3 Hz, 1H, H-14) ; 7.36-7.26 (m, 2H, H-12 and H-13) ; 5.74 (s, 1H, H-5) ; 4.21-4.05 (m, 1H, H-7) ; 3.97 (s, 3H, CO_2CH_3) ; 3.66 (s, 3H, CO_2CH_3) ; 3.30-3.15 (m, 4H, H-8, H-7 and H-1) ; 2.73 (m, 1H, H-2) ; 2.62-2.52 (m, 1H, H-1) ; 2.15-2.05 (m, 1H, H-3) ; 1.83 (d, *J* = 14 Hz, 1H, H-1) ; 1.66 (dd, *J* = 19 Hz, *J* = 19 Hz, 3H, H-21).
MS (ESI TOF): 485 [M+Na$^+$] (100).

N_a-carbomethoxy-20-fluoro-19-oxocatharanthine (22)

[0055]



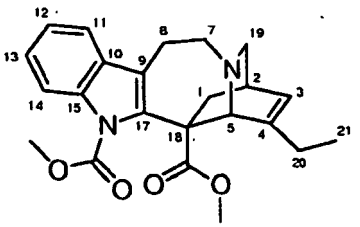
[0056] To a solution of DAST (8 µL, 0.06 mmol, 1.2 equiv.) in CH_2Cl_2 (0.1 mL) is added allylic alcohol 15 (20 mg, 0.05 mmol, 1 equiv.) in CH_2Cl_2 (0.7 mL). The reaction mixture is then left under stirring at ambient temperature for 15 min. Next, a saturated aqueous solution of K_2CO_3 (2 mL) is added dropwise at 0°C, the mixture is left for 15 min under stirring at ambient temperature, then the aqueous phase is extracted with CH_2Cl_2 (3x2 mL). The organic phases are combined, dried on Na_2SO_4 and concentrated under vacuum. The crude product is then purified on a preparative silica plate (eluent CH_2Cl_2/MeOH 98/2) to give 22 (10 mg, 0.023 mmol, 49%) in the form of two epimers A and B (white solid).

Chemical formula: $C_{23}H_{23}FN_2O_5$ M = 426 g.mol^{-1}

Rf = 0.4 (CH_2Cl_2/MeOH 95/5)
^{1}H NMR ($CDCl_3$) : 8.02 (d, *J* = 7.9 Hz, 1H, H-11) ; 7.49 (d, *J* = 7.3 Hz, 1H, H-14) ; 7.35-7.20 (m, 2H, H-12 and H-13) ; 6.53-6.48 (m, 1H, H-3) ; 5.26 (d, *J* = 1.8 Hz, 1H A, H-5) ; 5.22 (d, *J* = 1.8 Hz, 1H B, H-5) ; 4.98 (dq, *J* = 47.6Hz and *J* = 6.1 Hz, 1H, H-20) ; 4.20-4.04 (m, 1H, H-7) ; 3.93 (s, 3H, CO_2CH_3) ; 3.59 (s, 3H, CO_2CH_3) ; 3.53-3.48 (m, 1H, H-7) ; 3.43-3.19 (m, 3H, H-8 and H-2) ; 2.89-2.77 (m, 1H, H-1) ; 1.90 (d, *J* = 13.4 Hz, 1H, H-1) ; 1.51 (dd, *J* = 23.8 Hz, *J* = 6.7 Hz, 1H A, H-21) ; 1.46 (dd, *J* = 23.8 Hz, *J* = 6.7 Hz, 1H B, H-21).
^{13}C NMR ($CDCl_3$): 173.5 ; 171.8 ; 171.6 ; 151.9 ; 142.1 ; 141.9 ; 136.5 ; 136.4 ; 135.3 ; 130.0 ; 129.3 ; 125.1 ; 123.1 ; 118.3 ; 116.8 ; 115.8 ; 87.7 (d, *J* = 161 Hz) ; 87.6 (d, *J* = 161 Hz) ; 57.9 ; 57.7 ; 55.2 ; 54.7 ; 53.4 ; 53.3 ; 52.6 ; 44.3 ; 41.1 ; 40.9 ; 40.6 ; 38.7 ; 37.4 ; 29.6 ; 21.5 ; 21.1 ; 19.1 (d, *J* = 23 Hz) ; 18.4 (d, *J* = 23 Hz).
MS (ESI TOF): 465 [M + K$^+$] (100), 891 [2M + K$^+$] (33) .

N_a-Carbomethoxycatharanthine (26)

[0057]



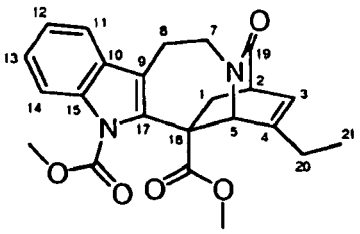
[0058] A solution of (+)-catharanthine 2 (1.0 g, 3.0 mmol, 1 equiv.) in THF (6mL) is added dropwise to a suspension of potassium hydride at 0°C (510 mg, 4.5 mmol, 1.5 equiv.) in THF (5 mL). After 1 h under stirring at 0°C, methyl chloroformate (0.35 mL, 4.5 mmol, 1.5, equiv.) is added dropwise. After 30 minutes under stirring, at 0°C, an aqueous solution of , saturated K_2CO_3 (10 mL) is added. The aqueous phase is extracted with CH_2Cl_2 (3x10 mL), the organic phases are collected, dried on Na_2SO_4 , filtered and concentrated under vacuum. The crude product is then purified by chromatography on silica (Eluent: CH_2Cl_2/MeOH 97/3) to give 26 (280 mg, 2.1 mmol, 70%) in the form of a white solid.

Chemical formula: $C_{23}H_{26}N_2O_4$ M = 394 g.mol^{-1}

^{1}H NMR ($CDCl_3$) : 8.10 (d, *J* = 7.3 Hz, 1H, H-11) ; 7.49 (d, *J* = 7.3 Hz, 1H, H-14) ; 7.33-7.24 (m, 2H, H-12 and H-13) ; 5.99 (m, 1 H, H-3) ; 4.21 (s, 1H, H-5) ; 3.87 (s, 3H, CO_2CH_3) ; 3.65 (m, 1H, H-7) ; 3.54 (s, 3H, CO_2CH_3) ; 3.23 (m, 1H, H-8) ; 3.03-2.85 (m, 3H, H-7 and H-19) ; 2.47 (m, 2H, H-2 and H-8) ; 2.48 (d, *J* = 8.5 Hz, 1H, H-1) ; 2.24 (m, 1H, H-20) ; 1.91 (m, 1H, H-20) ; 1.71 (d, *J* = 10.3 Hz, 1H, H-1) ; 1.08 (d, *J* = 7.3 Hz, 3H, H-21).
^{13}C NMR ($CDCl_3$) : 172.9 ; 151.7 ; 147.3 ; 138.6 ; 135.9 ; 129.5 ; 124.5 ; 123.3 ; 122.7 ; 119.6 ; 118.2 ; 115.4 ; 58.5 ; 55.9 ; 55.8 ; 52.9 ; 52.7 ; 52.0 ; 38.2 ; 31.5 ; 26.7 ; 21.9 ; 10.3.

N_a-carbomethoxy-9-oxocatharanthine (27)

[0059]



[0060] To 15 mL of an aqueous solution of Na_2CO_3 (2.07 g, 19.5 mmol, 9.3 equiv.) is added a solution of 26 (820 mg, 2.1 mmol, 1 equiv.) in THF (30 mL). Iodine (2.46 g, 9.7 mmol, 4.6 equiv.) in solution in THF (40 mL) is added dropwise at 0°C. The reaction mixture is then brought to ambient temperature and stirred for 18 hours. Next an aqueous solution saturated in $Na_2S_2O_3$ (30 mL) is added and the reaction mixture is left under stirring for 30 minutes. The aqueous phase is then extracted with CH_2Cl_2 (3×30 mL). The organic phases are combined, dried on Na_2SO_4, filtered and concentrated under vacuum. The crude product is then purified by chromatography on silica (Eluent: CH_2Cl_2/MeOH 98/2) to give 27 (787 mg, 1.93 mmol, 92%) in the form of a white solid.

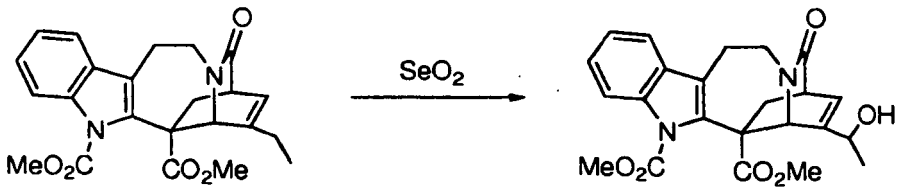
Chemical formula: $C_{23}H_{24}N_2O_5$ M = 408 g.mol^{-1}

^{1}H NMR ($CDCl_3$) : 8.06-7.98 (m, 1H, H-11) ; 7.53-7.44 (m, 1H, H-14) ; 7.36-7.22 (m, 2H, H-12 and H-13) ; 6.23-6.17 (m, 1H, H-3) ; 4.64 (d, *J* = 1.8 Hz, 1H, H-5) ; 4.19-4.03 (m, 1H, H-7) ; 3.92 (s, 3H, CO_2CH_3) ; 3.60 (s, 3H, CO_2CH_3) ; 3.47-3.37 (m, 1H, H-2) ; 3.36-3.15 (m, 3H, H-8 and H-7) ; 2.83-2.73 (m, 1H, H-1) ; 2.24-1.89 (m, 3H, H-20 and H-1) ; 1.08 (t, *J* = 7.3 Hz, 3H, H-21).
^{13}C NMR ($CDCl_3$) : 174.5 ; 171.9 ; 151.8 ; 144.1 ; 136.8 ; 135.3 ; 129.3 ; 125.6 ; 125.0 ; 123.0 ; 118.2 ; 116.8 ; 115.7 ; 59.0 ; 57.7 ; 53.9 ; 52.4 ; 44.1 ; 41.0 ; 37.8 ; 26.5 ; 21.1 ; 11.0.
IR (film) : 2996, 2959, 2881, 1739, 1681, 1461, 1443 cm^{-1}.

MS (IC) : 409 [M+H$^+$] (100).
$[\alpha]_D^{20}$ = + 141 (c = 1.9 ; $CHCl_3$)

Allylic oxidation of protected catharanthine (27) to give (20R)-N_a-carbomethoxy-20-hydroxy-19-oxocatharanthine (15)

[0061]



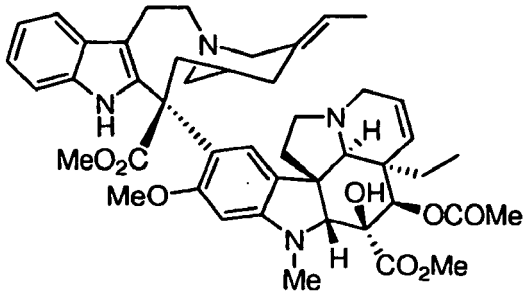
27 15

[0062] In a pressure tube of 25 mL, 50 mg of protected catharanthine 27 (0.123 mmol, 1 equiv.) is dissolved in 1.5 mL of ethanol 95%. 51 mg of selenium dioxide (0.459 mmol, 3.7 equiv.) in solution in 2.5 mL of ethanol 95% is added. The tube is hermetically sealed with a Teflon cork (equipped with a joint) and placed at 120°C (temperature of the oil bath) under magnetic stirring. After 24 hours, 40 mg (0.36 mmol, 2.9 equiv.) of SeO_2 is added in one portion (in a solid form). This operation is repeated every 24 hours during 4 days (before every addition, the tube is brought at ambient temperature to be safely uncorked). After 5 days of reaction, the starting material is completely consumed. The reaction mixture is brought at ambient temperature and diluted with Et_2O. It is washed with 20 mL of brine. The aqueous phase is extracted with Et_2O (3x20 mL). The organic phases are combined, dried on Na_2SO_4, filtered and concentrated under vacuum. The crude product is then purified by chromatography on silica (Eluent: CH_2Cl_2/MeOH 98/2 then 95/5) to give 35 mg (0.083 mmol, 67%) of a white solid corresponding to allylic alcohol 15, spectral characteristics of which are identical to those of the allylic alcohol obtained by the protocol using isocatharanthine.

[0063] Thus, 20,20-difluoro-catharanthine (6), (4*R*)-N_a-carbometoxy-20,20-difluoro-3-hydro-4-hydroxy-19-oxocatharanthine (19) after deprotections and N_a-carbometoxy-20-fluoro-19-oxocatharanthine (22) after deprotections, can be coupled, in a manner well known per se in the prior art, with vindoline, then subjected to a ring contraction reaction and if required to a reduction of the endocyclic double bond C3'-C4', so as to respectively result in vinflunine (1), 20',20'-difluorovinblastine (21) and 20'-fluorovinorelbine (25), which in turn can be subjected to an additional step of reduction of the double bond to result in the monofluorinated vinflunine analogue.

4',20'-Anhydrovinblastine (28)

[0064]



[0065] To a mixture of 60 mL of a glycine buffer and of 100 mL of a 0.1M hydrochloric acid aqueous solution is added in one time 1 g (2.98 mmol, 1 equiv.) of isocatharanthine 10. After complete dissolution, 1.36 g (1 equiv.) of vindoline, then 2.43 g (5 equiv.) of $FeCl_3$ are added. The reaction mixture, placed under nitrogen atmosphere, is stirred at ambient temperature for 15 h. The reaction is stopped by a dropwise addition of a solution of 172 mg (1.5 equiv.) of $NaBH_4$ in 15 mL of a 28% NH_3 aqueous solution. After 10 minutes of stirring at ambient temperature, 30 mL of CH_2Cl_2 and 30 mL

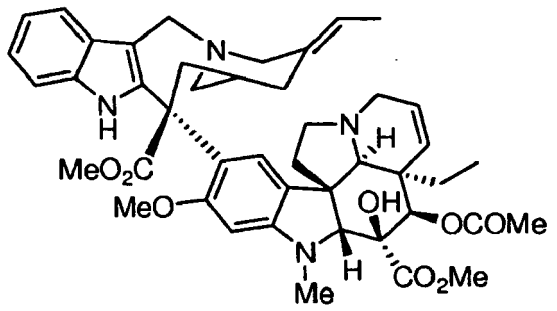
of a solution of Rochelle salt are added and the mixture is vigorously stirred for 4 h. It is then extracted with CH_2Cl_2 (4x80 mL). The organic phases are combined, dried on Na_2SO_4, filtered and concentrated under vacuum. The crude product is then purified by chromatography on silica (Eluent: CH_2Cl_2/MeOH 95/5) to give 28 (1.18 g, 1.49 mmol, 50%).

Chemical formula: $C_{46}H_{56}N_4O_8$ M = 792 g.mol^{-1}

^{1}H NMR ($CDCl_3$): 9.82 (sl, 1H) ; 7.99 (sl, 1H) ; 7.45 (d, *J* = 7.6 Hz, 1H) ; 7.20-7.05 (m, 3H) ; 6.52 (s, 1H) ; 6.10 (s, 1H) ; 5.85 (dd, *J* = 4 and 10 Hz, 1H) ; 5.57 (q, *J* = 6.4 Hz, 1H) ; 5.43 (s, 1H) ; 5.28 (d, *J* = 12 Hz, 1H) ; 3.81 (s, 3H) ; 3.78 (s, 3H) ; 3.76 (s, 1H) ; 3.61 (s, 3H) ; 3.60-3.08 (m, 10H) ; 2.91-2.79 (m, 2H) ; 2.72 (s, 3H) ; 2.65 (s, 1H) ; 2.45-2.31 (m, 3H) ; 2.16-2.05 (m, 5H) ; 1.84-1.71 (m, 2H) ; 1.67 (d, *J* = 6.4 Hz, 3H) ; 1.35-1.29 (m, 1H) ; 1.24-1.18 (m, 1H) ; 0.78 (t, *J* = 7.6 Hz, 3H).
^{13}C NMR ($CDCl_3$): 8.3 ; 12.8 ; 21.1 ; 24.6 ; 30.7 ; 31.8 ; 33.3 ; 34.7 ; 38.2 ; 42.6 ; 44.6 ; 47.5 ; 50.0 ; 50.2 ; 52.2 ; 52.4 ; 53.2 ; 55.2 ; 55.8 ; 56.9 ; 59.9 ; 65.2 ; 76.4 ; 79.7 ; 83.2 ; 94.0 ; 110.5 ; 116.8 ; 118.2 ; 119.0 ; 119.8 ; 120.6 ; 122.5 ; 122.7 ; 123.3 ; 124.6 ; 129.0 ; 129.9 ; 130.0 ; 133.1 ; 135.1 ; 152.8 ; 158.0 ; 170.9 ; 171.6 ; 174.6.
MS (ESI-TOF): 793 [M+H$^+$] (100).

nor-7'-4',20'-Anhydrovinblastine (29)

[0066]



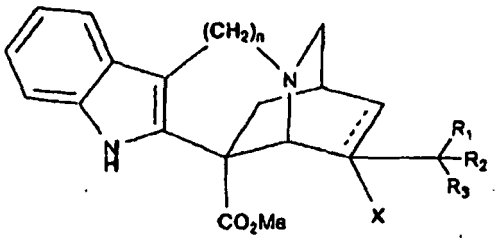
[0067] At 0 °C, a solution of 30 µL (1 equiv.) of trifluoroacetic acid in 3 mL of CH_2Cl_2 is added dropwise to a solution of 296 mg (0.374 mmol, 2 equiv.) of 4',20'-anhydrovinblastine 28 diluted in 3 mL of anhydrous CH_2Cl_2. After 10 min of stirring, the mixture is cooled at -78 °C and 67 mg (1 equiv.) of NBS in solution in 3 mL of CH_2Cl_2 are added dropwise. After 20 min at -78 °C, the cold bath is removed and after 15 min, 15 mL of a 10% aqueous solution of K_2CO_3 is added. The mixture is extracted with CH_2Cl_2 (3x15 mL). The organic phases are combined, dried on Na_2SO_4, filtered and concentrated under vacuum. The crude product is dissolved in 40 mL of a mixture THF/water 1/1 and 182 mg (2.5 equiv.) of silver tetrafluoroborate are added in one time. The mixture is brought at temperature ambient and 30 mL of a 10% aqueous solution of Na_2CO_3 are added. The mixture is extracted with Et_2O (2x30 mL), then with CH_2Cl_2 (2x30 mL). The organic phases are combined, dried on Na_2SO_4, filtered and concentrated under vacuum Purification by chromatography on silica (Eluent: CH_2Cl_2/MeOH 93/7) give 29 (58 mg, 0.075 mmol, 20%) in the form of a beige solid.

Chemical formula: $C_{45}H_{54}N_4O_8$ M = 778 g.mol^{-1}

^{1}H NMR ($CDCl_3$) : 9.81 (s, 1H) ; 8.40 (s, 1H) ; 7.81 (d, J = 8 Hz, 1H) ; 7.18-7.09 (m, 3H) ; 6.28 (s, 1H) ; 6.09 (s, 1H) ; 5.84 (dd, J = 4 and 10.4 Hz, 1H) ; 5.74 (q, J = 6.4 Hz, 1H) ; 5.38 (s, 1H) ; 5.26 (d, *J* = 10.8 Hz, 1H) ; 4.55-4.45 (m, 2H) ; 3.86 (d, J = 13.6 Hz, 1H) ; 3.82 (s, 3H) ; 3.77 (s, 3H) ; 3.71 (s, 1H) ; 3.68 (s, 3H) ; 3.50-3.21 (m, 5H) ; 2.81-2.71 (m, 6H) ; 2.63-2.45 (m, 4H) ; 2.12-2.05 (m, 4H) ; 1.83 (m, 12H) ; 1.77 (d, J = 6.4 Hz, 3H) ; 1.91 (m, 1H) ; 1.41 (m, 1H) ; 1.23 (m, 1H) ; 0.69 (t, *J* = 7.6 Hz, 3H).
^{13}C NMR ($CDCl_3$) : 8.1 ; 13.0 ; 21.0 ; 30.0 ; 30.6 ; 32.4 ; 33.5 ; 38.1 ; 42.6 ; 44.5 ; 45.4 ; 47.5 ; 49.7 ; 50.2 ; 52.1 ; 52.7 ; 53.2 ; 55.0 ; 55.7 ; 59.8 ; 65.0 ; 76.3 ; 79.6 ; 83.0 ; 93.9 ; 110.4 ; 118.9 ; 119.8 ; 120.6 ; 122.2 ; 122.9 ; 123.3 ; 124.8 ; 128.4 ; 129.7 ; 133.5 ; 134.5 ; 152.9 ; 157.9 ; 170.8 ; 171.5 ; 174.0.
MS (ESI-TOF): 779 (M+H$^+$) (100).

Claims

1. Fluorinated catharanthine derivatives responding to the general formula I:



in which:

- the dotted line expresses the possibility of the presence of a double bond when the substitution -X is absent or else of a single bond when -X designates a substitution for a group:

  • H,
  • OR,
  • NR'R",
  • SR, or
  • a halogen atom with R, R' and R" designating independently of one another a hydrogen atom or a linear or branched alkyl group in C_1 à C_6,
  • R_1, R_2 and R_3 represent independently of one another an atom of hydrogen, fluorine or a methylated group, on the condition all the same that at least one of the radicals R_1 and R_2 represents an atom of fluorine, and

- n = 1 or 2.

2. Fluorinated catharanthine derivatives according to claim 1, **characterised in that** it is chosen among:

   - 20,20-Difluorocatharanthine which corresponds to a compound of formula (I) in which the double bond in dotted lines is present, R_1 represents a methylated group, R_2, R_3 each represent an atom of fluorine, and n = 2,
   - 20-Fluorocatharanthine which corresponds to a compound of formula (I) in which the double bond in dotted lines is present, R_1, R_2 and R_3 represent respectively a hydrogen, a fluorine and a methylated group, and n = 2, and
   - 20,20-Difluoro-4-hydroxycatharanthine which corresponds to a compound of formula (I) in which the bond in dotted lines is absent, -X represents the group -OH, R_1 is the methylated group, R_2, R_3 each represent an atom of fluorine, and n = 2.

3. Use of a fluorinated derivative of catharanthine as claimed in any one of Claims 1 and 2 as a synthesis intermediate useful in the preparation of fluorinated dimeric alkaloids of *Vinca*, and in particular vinflunine, which implies optionally a coupling reaction with vindoline or else with a derivative of vindoline.

4. Use as claimed in Claim 3, **characterised in that** vinflunine is prepared by coupling vindoline with 20,20-difluorocatharanthine, resulting in 20',20'-difluoro-3',4'-anhydrovinblastine, said 20',20'-difluoro-3',4'-anhydrovinblastine being optionally subjected to a ring contraction reaction, followed by a reduction reaction of the endocyclic double bond at position $C_{3'}$-$C_{4'}$.

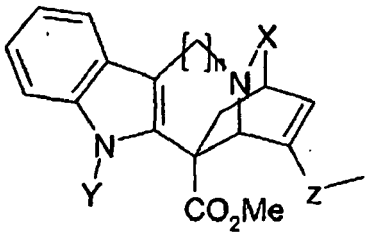
5. A process for preparation of a fluorinated derivative of catharanthine as claimed in any one of Claims 1 and 2, **characterised in that** it implies oxidation of the lateral chain of catharanthine prior to the fluorination reaction; such as an allylic oxidation of the lateral chain of catharanthine in alcohol or in ketone which is preceded by a protection of the two nitrogen atoms of catharanthine.

6. The process as claimed in Claim 5, **characterised in that** said oxidation is preceded by a stage of activation of the lateral chain by isomerisation of the endocyclic double bond to the exocyclic position by catalytic hydrogenation.

7. The process as claimed in Claim 6, **characterised in that** said exocyclic double bond is subjected to a dihydroxylation reaction, after protection of the two nitrogen atoms, resulting in the formation of a diol.

8. The process as claimed in Claim 7, **characterised in that** the diol obtained is activated in the form of a cyclic sulphate, transformed into allylic alcohol, then oxidised in the corresponding enone which is subjected to a difluorination reaction, then deprotection of the indol and reduction of the amidic group to result in 20,20-difluorocatharanthine.

9. The process as claimed in Claim 5, **characterised in that** the oxidation step is carried out in conditions leading to the formation of an oxidised catharanthine derivative responding to the general formula II:

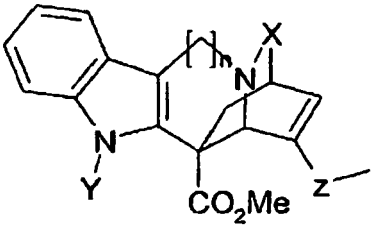


II

in which:

- n = 1 or 2,
- X designates a C=O, or C=S group,
- Y designates a CO_2R, SO_2R or COR group with R designating an aryl group or a linear or branched alkyl group in C_1 to C_4 and
- Z designates a CH-OH or C=O group.

10. Oxidised catharanthine derivative responding to the general formula II:



II

in which:

- n = 1 or 2,
- X designates a C=O, or C=S group,
- Y designates a CO_2R, SO_2R or COR group with R designating an aryl group or a linear or branched alkyl group in C_1 to C_4 and
- Z designates a CH-OH or C=O group.

11. Oxidised catharanthine derivative according to formula II as claimed in claim 10, in which

- n = 2,
- X designates a C=O group,
- Y designates a CO_2R group with R designating a linear or branched alkyl group in C_1 to C_4,
- Z designates a CH-OH or C=O group.

12. Use of an oxidised derivative of catharanthine as claimed in any one of claims 10 and 11 as a synthesis intermediate

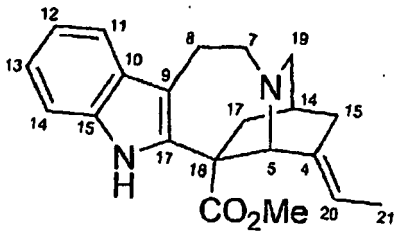
useful in the preparation of fluorinated dimeric alkaloids of *Vinca,* and in particular vinflunine.

13. Use as claimed in Claim 12, **characterised in that** the preparation of the alkaloid dimeric implies a fluorination reaction of the oxidised derivative of catharanthine, followed by deprotection of the two nitrogen atoms, resulting in a fluorinated derivative of catharanthine as claimed in any one of claims 1 to 4.

14. Use as claimed in Claim 13, **characterised in that** the preparation of the alkaloid dimeric further implied a coupling reaction between the said fluorinated derivative of catharanthine, resulting from reactions of fluorination and deprotection, and vindoline or a derivative of vindoline.

15. Use as claimed in any one of claims 12 to 14, **characterised in that** vinflunine is prepared by coupling vindoline with 20,20-difluorocatharanthine,obtained by fluorination and deprotection of the two nitrogen atoms of the oxidised derivative of catharanthine as claimed in claim 16 for which Z = C=O, resulting in 20',20'-difluoro-3',4'-anhydrovinblastine, said 20',20'-difluoro-3',4'-anhydrovinblastine being optionally subjected to a ring contraction reaction, followed by a reduction reaction of the endocyclic double bond at position $C_{3'}$-$C_{4'}$.

16. Isocatharanthine responding to the following formula (10) :



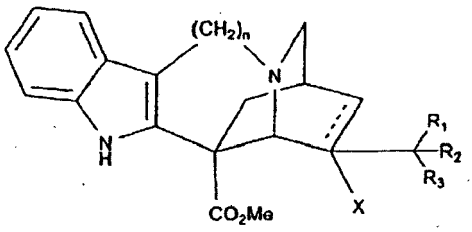
(10)

17. Use of isocatharanthine as a synthesis intermediate useful in the preparation of fluorinated dimeric alkaloids of *Vinca,* and in particular vinflunine, implying optionally a coupling reaction with vindoline or else with a derivative of vindoline.

18. Use as claimed in any one of claims 16 and 17, **characterised in that** vinflunine is prepared by coupling vindoline with isocatharanthine, resulting in 4',20'-anhydrovinblastine, said 4',20'-anhydrovinblastine being optionally subjected to a ring contraction reaction, followed by a *gem*-difluorination reaction, the order of these two steps being inversable.

Patentansprüche

1. Fluorierte Catharanthin-Derivate, die der allgemeinen Formel I entsprechen:



I

in der:

- die gepunktete Linie die Möglichkeit der Anwesenheit einer Doppelbindung ausdrückt, wenn die Substitution -X fehlt, oder andernfalls einer Einfachbindung, wenn -X die Substitution für eine Gruppe:

- H,
- OR,
- NR'R",
- SR oder
- ein Halogenatom bezeichnet, wobei R, R' und R" unabhängig voneinander ein Wasserstoffatom oder eine lineare oder verzweigte C_1-bis C_6-Alkylgruppe bezeichnen,

- R_1, R_2 und R_3 unabhängig voneinander ein Wasserstoff-, Fluoratom oder eine Methylgruppe darstellen, jedoch mit der Bedingung, dass mindestens einer der Reste R_1 und R_2 ein Fluoratom darstellt, und
- n = 1 oder 2.

2. Fluorierte Catharanthin-Derivate nach Anspruch 1, **dadurch gekennzeichnet, dass** sie ausgewählt sind aus :

- 20,20-Difluorcatharanthin, das einer Verbindung der Formel (I) entspricht, in der die Doppelbindung in der gepunkteten Linie vorliegt, R_1 eine Methylgruppe darstellt, R_2, R_3 jeweils ein Fluoratom darstellen und n = 2,
- 20-Fluorcatharanthin, das einer Verbindung der Formel (I) entspricht, in der die Doppelbindung in der gepunkteten Linie vorliegt, R_1, R_2 und R_3 einen Wasserstoff, ein Fluor und eine Methylgruppe bzw. darstellen und n = 2, und
- 20,20-Difluor-4-hydroxycatharanthin, welches einer Verbindung der Formel (I) entspricht, in der die Bindung in der gepunkteten Linie abwesend ist, -X die Gruppe -OH darstellt, R_1 die Methylgruppe ist, R_2, R_3 jeweils ein Fluoratom darstellen und n = 2.

3. Verwendung eines fluorierten Derivats von Catharanthin nach irgendeinem der Ansprüche 1 und 2 als Synthese-Zwischenprodukt, das bei der Herstellung von fluorierten dimeren Vinca-Alkaloiden und insbesondere Vinflunin nützlich ist, was gegebenenfalls eine Kupplungsreaktion mit Vindolin oder auch mit einem Derivat von Vindolin beinhaltet.

4. Verwendung nach Anspruch 3, **dadurch gekennzeichnet, dass** Vinflunin hergestellt wird durch Kupplung von Vindolin mit 20,20-Difluorcatharanthin, was 20',20'-Difluor-3',4'-anhydrovinblastin zum Ergebnis hat, wobei das 20', 20'-Difluor-3',4'-anhydrovinblastin gegebenenfalls einer Ringkontraktionsreaktion unterzogen wird, gefolgt von einer Reduktionsreaktion der endocyclischen Doppelbindung an der Position $C_{3'}$ - $C_{4'}$.

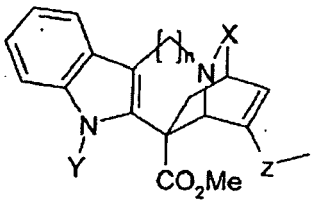
5. Verfahren zur Herstellung eins fluorierten Derivats von Catharanthin wie in irgendeinem der Ansprüche 1 und 2 beansprucht, **dadurch gekennzeichnet, dass** es die Oxidation der Seitenkette von Catharanthin vor der Fluorierungsreaktion beinhaltet; wie eine allylische Oxidation der Seitenkette von Catharanthin in Alkohol oder in Keton, der der Schutz der zwei Stickstoffatome von Catharanthin vorangeht.

6. Verfahren nach Anspruch 5, **dadurch gekennzeichnet, dass** der Oxidation eine Stufe der Aktivierung der Seitenkette durch Isomerisierung der endocyclischen Doppelbindung zur exocyclischen Position durch katalytische Hydrierung vorangeht.

7. Verfahren nach Anspruch 6, **dadurch gekennzeichnet, dass** die exocyclische Doppelbindung nach Schutz der zwei Stickstoffatome einer Dihydroxylierungsreaktion unterzogen wird, was die Bildung eines Diols zur Folge hat.

8. Verfahren nach Anspruch 7, **dadurch gekennzeichnet, dass** das erhaltene Diol in Form eines cyclischen Sulfats aktiviert, in einen allylischen Alkohol überführt wird, dann zum entsprechenden Enon oxidiert wird, welches einer Difluorierungsreaktion unterzogen wird, dann Schutzgruppenentfernung des Indols und Reduktion der amidischen Gruppe, was 20,20-Difluorcatharanthin zum Ergebnis hat.

9. Verfahren nach Anspruch 5, **dadurch gekennzeichnet, dass** der Oxidationsschritt unter Bedingungen durchgeführt wird, welche zur Bildung eines oxidierten Catharanthin-Derivats führen, welches der allgemeinen Formel II entspricht:

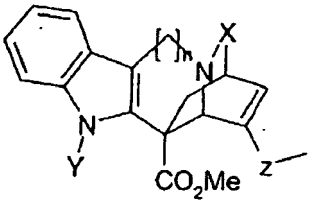


II

in der:

- n = 1 oder 2,
- X die Gruppe C=O oder C=S bezeichnet,
- Y die Gruppe CO_2R, SO_2R oder COR bezeichnet, wobei R eine Arylgruppe oder lineare oder verzweigte C_1- bis C_4-Alkylgruppe bezeichnet, und
- Z die Gruppe CH-OH oder C=O bezeichnet.

10. Oxidiertes Catharanthin-Derivat, das der allgemeinen Formel II entspricht:



II

in der:

- n = 1 oder 2,
- X die Gruppe C=O oder C=S bezeichnet,
- Y die Gruppe CO_2R, SO_2R oder COR bezeichnet, wobei R eine Arylgruppe oder eine lineare oder verzweigte C_1- bis C_4-Alkylgruppe bezeichnet, und
- Z die Gruppe CH-OH oder C=O bezeichnet.

11. Oxidiertes Catharanthin-Derivat gemäß Formel II, wie in Anspruch 10 beansprucht, in dem:

- n=2,
- X die Gruppe C=O bezeichnet,
- Y die Gruppe CO_2R bezeichnet, wobei R eine lineare oder verzweigte C_1-bis C_4- Alkylgruppe bezeichnet,
- Z die Gruppe CH-OH oder C=O bezeichnet.

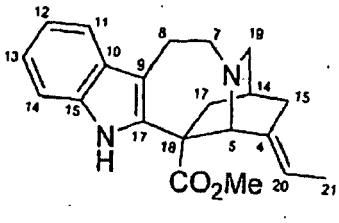
12. Verwendung eines oxidierten Derivats von Catharanthin nach irgendeinem der Ansprüche 10 und 11 als Synthese-Zwischenprodukt, das bei der Herstellung von fluorierten dimeren Vinca-Alkaloiden und insbesondere Vinflunin nützlich ist.

13. Verwendung nach Anspruch 12, **dadurch gekennzeichnet, dass** die Herstellung des dimeren Alkaloids eine Fluorierungsreaktion des oxidierten Derivats von Catharanthin beinhaltet, gefolgt vom Entschützen der zwei Stickstoffatome, was ein fluoriertes Derivat von Catharanthin, wie in irgendeinem der Ansprüche 1 bis 4 beansprucht, zum Ergebnis hat.

14. Verwendung nach Anspruch 13, **dadurch gekennzeichnet, dass** die Herstellung des dimeren Alkaloids weiter eine Kupplungsreaktion zwischen dem fluorierten Derivat von Catharanthin, welches aus Fluorierungs- und Entschützungsreaktionen resultiert, und Vindolin oder einem Derivat von Vindolin beinhaltet.

15. Verwendung nach irgendeinem einem der Ansprüche 12 bis 14, **dadurch gekennzeichnet, dass** Vinflunin durch Kupplung von Vindolin mit 20,20-Difluorcatharanthin hergestellt wird, welches durch Fluorierung und Entschützung der zwei Stickstoffatome des oxidierten Derivats von Catharanthin, wie in Anspruch 16 beansprucht, erhalten wird, bei dem Z = C=O, was 20',20'-Difluor-3',4'-anhydrovinblastin zum Ergebnis hat, wobei das 20',20'-Difluor-3',4'-anhydrovinblastin gegebenenfalls einer Ringkontraktionsreaktion unterzogen wird, gefolgt von einer Reduktionsreaktion der endocyclischen Doppelbindung an der Position C_3' - $C_{4'}$.

16. Isocatharanthin, das der folgenden Formel (10) entspricht:



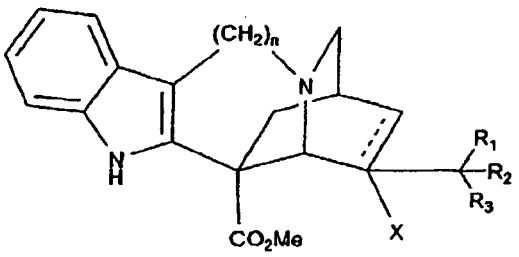
(10)

17. Verwendung von Isocatharanthin als Synthese-Zwischenprodukt, das bei der Herstellung von fluorierten dimeren Vinca-Alkaloiden und insbesondere Vinflunin nützlich ist, welche gegebenenfalls eine Kupplungsreaktion mit Vindolin oder auch mit einem Derivat von Vindolin beinhaltet.

18. Verwendung nach irgendeinem der Ansprüche 16 und 17, **dadurch gekennzeichnet, dass** Vinflunin durch Kupplung von Vindolin mit Isocatharanthin hergestellt wird, was 4',20'-Anhydrovinblastin zum Ergebnis hat, wobei das 4',20'-Anhydrovinblastin gegebenenfalls einer Ringkontraktionsreaktion unterzogen wird, gefolgt von einer *gem*-Difluorierungsreaktion, wobei die Reihenfolge dieser beiden Schritte umkehrbar ist.

Revendications

1. Dérivés fluorés de la catharanthine répondant à la formule générale I :



I

dans laquelle

- la ligne en pointillée exprime la possibilité de la présence d'une double liaison lorsque la substitution -X est absente ou sinon d'une liaison simple lorsque -X représente une substitution pour un groupe :

  • H,
  • OR,
  • NR'R",
  • SR, ou
  • un atome d'halogène, avec R, R' et R" représentant indépendamment les uns des autres un atome d'hydrogène ou un groupe alkyle en C_1-C_6 linéaire ou ramifié,

- R_1, R_2 et R_3 représentent indépendamment les uns des autres un atome d'hydrogène, un atome de fluor ou un groupe méthyle, à condition tout de même qu'au moins l'un des radicaux R_1 et R_2 représente un atome de fluor, et

- n = 1 ou 2.

2. Dérivés fluorés de la catharanthine selon la revendication 1, **caractérisés en ce qu'**il est choisi parmi :

- la 20,20-difluorocatharanthine qui correspond a un composé de formule (I) dans laquelle la double liaison représentée par la ligne en pointillée est présente, R_1 représente un groupe méthyle, R_2 et R_3 représentent chacun un atome de fluor et n = 2,
- la 20-fluorocatharanthine qui correspond à un composé de formule (I) dans laquelle la double liaison représentée par la ligne en pointillée est présente, R_1, R_2 et R_3 représentent respectivement un atome d'hydrogène, un atome de fluor et un groupe méthyle, et n = 2, et
- la 20,20-difluoro-4-hydroxycatharanthine qui correspond à un composé de formule (I) dans laquelle la liaison représentée par la ligne en pointillée est absente, -X représente un groupe -OH, R_1 est le groupe méthyle, R_2 et R_3 représentent chacun un atome de fluor et n = 2.

3. Utilisation d'un dérivé fluoré de la catharanthine selon l'une quelconque des revendications 1 et 2 en tant qu'intermédiaire de synthèse utile pour la préparation d'alcaloïdes dimériques fluorés de Vinca, et en particulier la vinflunine, qui implique éventuellement une réaction de couplage avec la vindoline ou sinon avec un dérivé de la vindoline.

4. Utilisation selon la revendication 3, **caractérisée en ce que** la vinflunine est préparée par couplage de la vindoline avec la 20,20-difluorocatharanthine, donnant la 20',20'-difluoro-3',4'-anhydrovinblastine, ladite 20',20'-difluoro-3',4'-anhydrovinblastine étant éventuellement soumise à une réaction de contraction de cycle, suivie par une réaction de réduction de la double liaison endocyclique en position $C_{3'}$-$C_{4'}$.

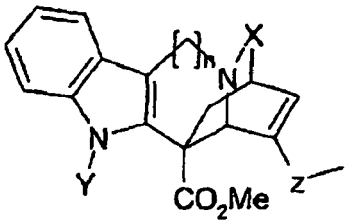
5. Procédé de préparation d'un dérivé fluoré de la catharanthine selon l'une quelconque des revendications 1 et 2, **caractérisé en ce qu'**il implique l'oxydation de la chaîne latérale de la catharanthine avant la réaction de fluoration ; telle qu'une oxydation allylique de la chaîne latérale de la catharanthine en alcool ou en cétone qui est précédée par une protection des deux atomes d'azote de la catharanthine.

6. Procédé selon la revendication 5, **caractérisé en ce que** ladite oxydation est précédée par une étape d'activation de la chaîne latérale par isomérisation de la double liaison endocyclique dans la position exocyclique par hydrogénation catalytique.

7. Procédé selon la revendication 6, **caractérisé en ce que** ladite double liaison exocyclique est soumise à une réaction de dihydroxylation, après protection des deux atomes d'azote, entraînant la formation d'un diol.

8. Procédé selon la revendication 7, **caractérisé en ce que** le diol obtenu est activé sous la forme d'un sulfate cyclique, transformé en alcool allylique, puis oxydé en l'énone correspondante qui est soumise à une réaction de difluoration suivie par la déprotection de l'indole et la réduction du groupe amidique pour donner la 20,20-difluorocatharanthine.

9. Procédé selon la revendication 5, **caractérisé en ce que** l'étape d'oxydation est réalisée dans des conditions entraînant la formation d'un dérivé oxydé de la catharanthine répondant à la formule générale II :



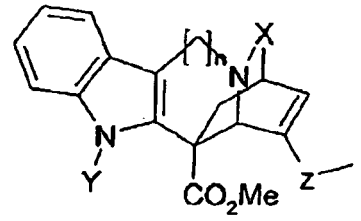
II

dans laquelle

- n = 1 ou 2,
- X représente un groupe C=O ou C=S,
- Y représente un groupe CO_2R, SO_2R ou COR, R représentant un groupe aryle ou un groupe alkyle en C_1-C_4 linéaire ou ramifié, et

- Z représente un groupe CH-OH ou C=O.

10. Dérivé oxydé de la catharanthine répondant à la formule générale II :



II

dans laquelle

- n = 1 ou 2,
- X représente un groupe C=O ou C=S,
- Y représente un groupe CO_2R, SO_2R ou COR, R représentant un groupe aryle ou un groupe alkyle en C_1-C_4 linéaire ou ramifié, et
- Z représente un groupe CH-OH ou C=O.

11. Dérivé oxydé de la catharanthine répondant à la formule générale II selon la revendication 10 dans laquelle

- n = 2,
- X représente un groupe C=O,
- Y représente un groupe CO_2R, R représentant un groupe alkyle en C_1-C_4 linéaire ou ramifié,
- Z représente un groupe CH-OH ou C=O.

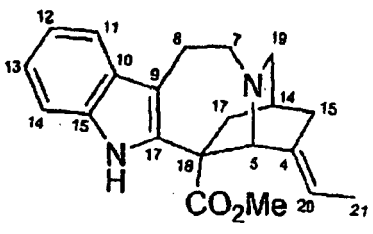
12. Utilisation d'un dérivé oxydé de la catharanthine selon l'une quelconque des revendications 10 et 11 en tant qu'intermédiaire de synthèse utile pour la préparation d'alcaloïdes dimériques fluorés de Vinca, et en particulier la vinflunine.

13. Utilisation selon la revendication 12, **caractérisée en ce que** la préparation de l'alcaloïde dimérique implique une réaction de fluoration du dérivé oxydé de la catharanthine, suivie par la déprotection des deux atomes d'azote, donnant un dérivé fluoré de la catharanthine selon l'une quelconque des revendications 1 à 4.

14. Utilisation selon la revendication 13, **caractérisée en ce que** la préparation de l'alcaloïde dimérique implique en outre une réaction de couplage entre ledit dérivé fluoré de la catharanthine, obtenu à partir des réactions de fluoration et de déprotection, et la vindoline ou un dérivé de la vindoline.

15. Utilisation selon l'une quelconque des revendications 12 à 14, **caractérisée en ce que** la vinflunine est préparée par couplage de la vindoline avec la 20,20-difluorocatharanthine, obtenue par fluoration et déprotection des deux atomes d'azote du dérivé oxydé de la catharanthine selon la revendication 16 dans lequel Z = C=O, donnant la 20', 20'-difluoro-3',4'-anhydrovinblastine, ladite 20',20'-difluoro-3',4'-anhydrovinblastine étant éventuellement soumise à une réaction de contraction de cycle, suivie par une réaction de réduction de la double liaison endocyclique en position $C_{3'}$-$C_{4'}$.

16. Isocatharanthine répondant à la formule (10) suivants :



(10)

17. Utilisation d'isocatharanthine en tant qu'intermédiaire de synthèse utile pour la préparation d'alcaloïdes dimériques fluorés de Vinca, et en particulier la vinflunine, impliquant éventuellement une réaction de couplage avec la vindoline ou sinon avec un dérivé de la vindoline.

18. Utilisation selon l'une quelconque des revendications 16 et 17, **caractérisée en ce que** la vinflunine est préparée par le couplage de la vindoline avec de l'isocatharanthine, donnant la 4',20'-anhydrovinblastine, ladite 4',20'-anhydrovinblastine étant éventuellement soumise à une réaction de contraction de cycle, suivie par une réaction de *gem*-difluoration, l'ordre de ces deux étapes étant inversable.

REFERENCES CITED IN THE DESCRIPTION

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Non-patent literature cited in the description

- **J.-C. Jacquesy et al.** *Journal of Fluorine Chemistry,* 2002, vol. 114, 139 **[0024]**
- **Andriamialisoa, R.Z. ; Langlois, N. ; Langlois Y. ; Potier P.** *Tetrahedron,* 1980, vol. 36, 3053-3060 **[0027]**