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The First Semi-synthesis of Enantiopure Homoharringtonine *via* Anhydrohomoharringtonine from a Preformed Chiral Acyl Moiety[#,†]

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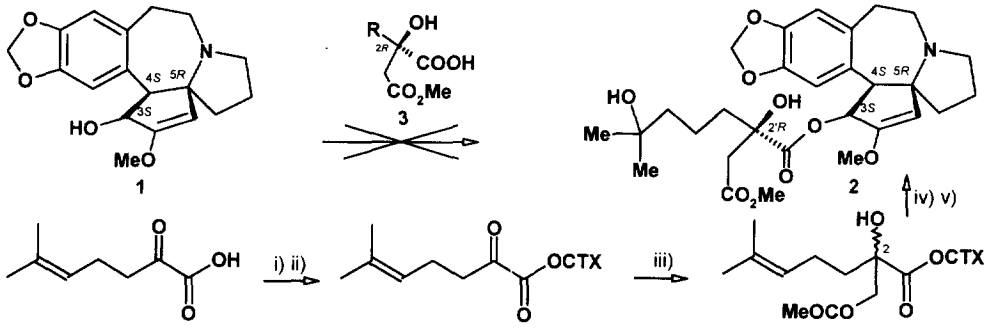
Abstract: (2'*R*,3*S*,4*S*,5*R*)-(-)-Homoharringtonine **2** was synthesized by direct esterification of cephalotaxine, using the activated forms of suitably substituted tetrahydropyrancarboxylic acids as sterically compact chiral side-chain precursors, followed by selective ring opening of the resulting (2'*R*,3*S*,4*S*,5*R*)-(-)-anhydrohomoharringtonine **6**. Both enantiomers of the anhydro acyl moiety were prepared either by asymmetric α-hydroxyalkylation of the suitably substituted ethylenic α-ketoester **7** followed by acidic cyclisation, or by resolving the corresponding racemic mixture *via* formation of diastereomers with (-)-quinine. Racemic cephalotaxine, as well as both its enantiomers, were prepared from natural —partially racemized— (-)-cephalotaxine **1**.

Homoharringtonine **2** has recently been demonstrated as the only investigational product capable of inducing a high rate of complete hematologic remission in patients with chronic myelogenous leukemia resistant to all existing chemotherapies including interferon-α.[1] Since the use of large quantities of unrenewable parts (barks and roots) of *Cephalotaxus* sp — a rare and endangered exclusively Asiatic Cephalotaxaceae —[2a], for the production of this antileukemic drug substance is going to lead to a significant environmental issue and to fast depletion of the natural source, semi-synthesis of **2** from its abundant biosynthetic precursor cephalotaxine **1** has become an urgent concern.[2b,2c]

Due to the steric hindrance of both the C-3 position of **1** and the neopentylic character of the carboxylic group of **3**, attempts to carry out esterification failed consistently.[3] For this reason, all the semi-syntheses of **2** and its congeners described since 26 years involved α-hydroxyalkylation of substituted α-ketoacylcephalotaxine,[4,5] in Reformatsky-type conditions (Scheme 1).



i) $(COCl)_2$; ii) cephalotaxine **1** (HO-CTX); iii) Br CH_2CO_2Me, Zn cr Li; iv) $Hg(CF_3CO_2)_2$; v) $NaBH_4$.

Scheme 1

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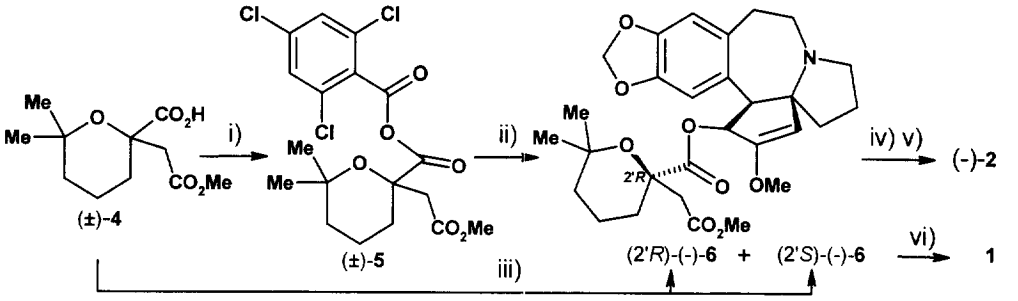
We anticipated that the acyl moiety of **2** should be introduced *via* a cyclic form. Thus esterification of natural (3*S*,4*S*,5*R*)-(-)-cephalotaxine **1** with (±)-**4** (Scheme 2), using either the dicyclohexylcarbodiimide (DCC) method or a mixed anhydride intermediate such as **5**, gave high yields of a 60/40 mixture of anhydrohomoharringtonine(2'*R*)-(-)-**6** and its epimer (2'*S*)-(-)-**6**, the later being easily removed by preparative chromatography.[6]

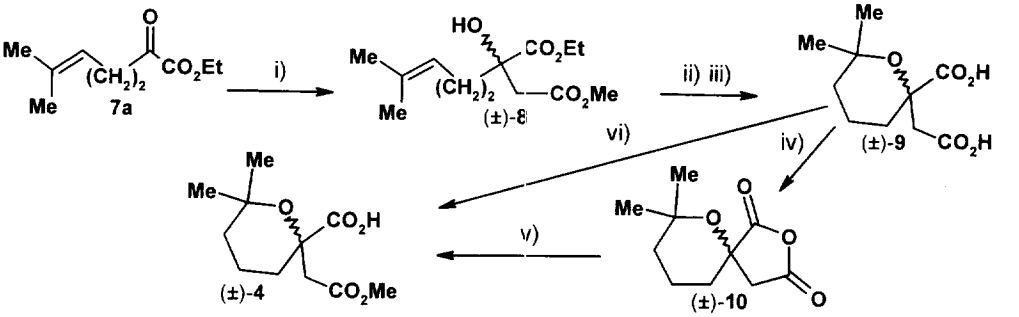
Ring opening of the tetrahydropyran ring of (-)-**6** in mild conditions[7a] gave (2'*R*)-(-)-6'-bromo-6'-deoxyhomoharringtonine, which was quantitatively hydrolyzed into enantiomerically pure homoharringtonine (2'*R*,3*S*,4*S*,5*R*)-(-)-**2** as a white crystalline solid, mp = 143-145 °C[7b] and $[\alpha]_D^{20}$ -125 (*c* 0.24; $CHCl_3$), litt. -119 (*c* 0.45; $CHCl_3$).[7c]



i) 2,4,6-trichlorobenzoyl chloride (TCBC), Et_3N, toluene, 25°C, 1h; ii) (-)-cephalotaxine **1**, DMAP, 25°, 16 h; iii) DCC, DMAP, toluene, **1**, 40°C, 6h; iv) HBr, CH_2Cl_2 -10 °, 3h; v) $NaHCO_3$, MeOH, 3h; vi) KOH, MeOH-H_2O; Overall yield ranges from **4** to **2** = 64 % according to a 1.5-fold excess of **1** / **4**.

Scheme 2

The tetrahydropyran (±)-**4** was obtained in a four-step sequence (Scheme 3). Thus, α-hydroxyalkylation of the ethylenic ketoester **7a**, with the lithium anion of methyl acetate at -70°C, gave the ethylenic diester (±)-**8**, which on complete saponification, followed by cyclisation in formic acid medium, gave the substituted tetrahydropyran dicarboxylic acid (±)-**9** . The less hindered carboxylic group of the latter was selectively esterified with boron trifluoride-methanol to give (±)-**4**. Alternatively, methanolysis of (±)-**10** which is the cyclic anhydride of (±)- **9**, led to the less hindered ester (±)- **4**.

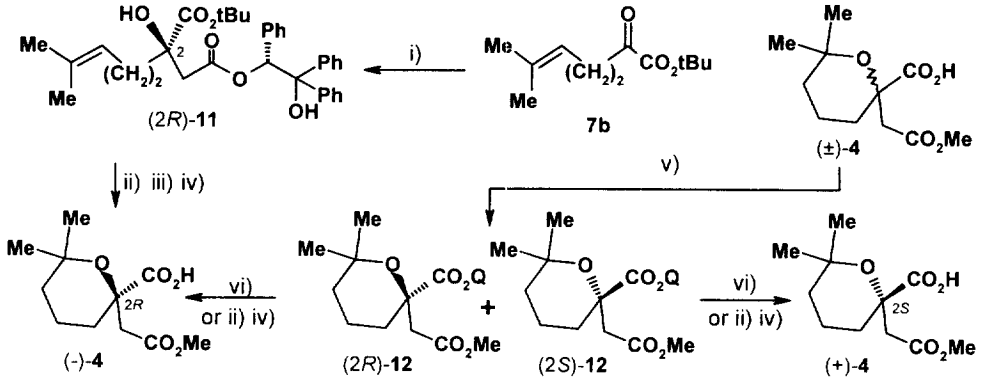


i) AcOMe, LiHMDS 2 equiv., THF, -70°C, 1 h, 70%; ii) KOH, H_2O,MeOH, Reflux 3h, 90%; iii) HCO_2H, 12 h, reflux, CH_2Cl_2, 100%; iv) AcOAc, DMAP, 12 h, 84%; v) MeOH, pyridine, CH_2Cl_2, reflux; vi) BF_3-MeOH, 25°C, 69%.

Scheme 3

Since the above method is raw material-consuming and since it was confirmed that cephalotaxine is present

in most of our *Cephalotaxus* extracts, in partially racemized form,[8] two different pathways were developed for obtaining (-)-**4** and (+)-**4**, (see scheme 4). The first one used an asymmetric induction *via* hydroxyalkylation of the hindered *tert*-butyl ketoester **7b** with chiral lithium anion of (+)-Hytra,[9a] inducing a moderate diastereoselection (65/35).[9b] However, chromatography of the diastereomeric mixture followed by crystallization, gave the expected diester (2*R*)-**11** in 30% yield, as a white crystalline solid.[9c] Above described sequence (scheme 3) applied to (2*R*)-**11** led to the substituted tetrahydropyran carboxylic acid (-)-**4**, as the free acidic form of the natural side-chain of (2'*R*)-anhydrohomoharringtonine (-)-**6**, in 65% overall yield.



i) (+)-Hytra, LiHMDS 2 eq., THF, -70°C, 1 h, 30%; ii) KOH, H_2O,MeOH, reflux 3h, 90%; iii) HCO_2H, reflux 12 h, CH_2Cl_2, 100%; iv) BF_3-MeOH, 25°C, 69%; v) TCBC, Et_3N, toluene, then Q-OH, 84%); vi) H_2, AcOEt, Pd-C, 25°C, 6 h, 50%.

Scheme 4

The second strategy involved esterification of (-)-quinine (Q-OH), acting both as resolving agent and protecting group, with (±)-**4**, followed by separation of the resulting diastereomeric mixture of (2*R*)-**12** and (2*S*)-**12**, using reverse phase HPLC (octadecyl silane).[10] Selective removal of quinine by hydrogenolysis, or complete saponification of (2*R*)-**12**, followed by the above described selective methylation gave the expected chiral acid (2*R*)-(-)-**4**, $[\alpha]_D^{20}$ -11.4 (*c* 0.2; $CHCl_3$).

O-Acylation of a sample of natural (3*S*,4*S*,5*R*)-(-)-cephalotaxine **1** containing 10% of its antipode (3*R*,4*R*,5*S*)-(+)-**1**,[8] with activated form of the acid (-)-**4** led to a 90/10 mixture of anhydrohomoharringtonine (2'*R*,3*S*,4*S*,5*R*)-(-)-**6** and the antipode of its 2'-epimer (2'*R*,3*R*,4*R*,5*S*)-(+)-**6**. Both diastereomers were completely separated by large scale HPLC, then opened as described above, thus giving homoharringtonine (2'*R*,3*S*,4*S*,5*R*)-(-)-**2**, $[\alpha]_D^{20}$ -126 (*c* 0.24; $CHCl_3$) and the antipode of its epimer (2'*R*,3*R*,4*R*,5*S*)-(+)-**2**, respectively.[11]

Finally an expeditious large scale preparation of semi-synthetic homoharringtonine was carried out in acylating native —5% racemized— cephalotaxine with the activated form of racemic **4**.[12] Two cycles only of crystallization of crude homoharringtonine gave a compound exhibiting 99.8% *ee*.[13]

References and notes

#. Dedicated to Prof. Dr. Pierre Potier on the occasion of his award: "Médaille d'or du C.N.R.S" for his work on natural substances in medicinal chemistry including his discovery of vinorelbine (Navelbine®) and docetaxel (Taxotère®), as well as the first semi-synthesis of paclitaxel (Taxol®) from its biosynthetic precursor.

†. Patent application FR 98 03492 in part.

1 (a) Kantarjian, H.M. personal communication. (b) Kantarjian, H.M.; Giles, F.J.; O'Brien, S.M.; Talpaz, M. *Hematol. Oncol. Clin. North Am.* **1998**, *12*, 31-80. (c) Kantarjian, H.M.; Talpaz, M. in *Medical Management of Chronic Myelogenous Leukemia* (Marcel Dekker, National Cancer Institute, Bethesda, Md) **1998**, *15*, 79-81 (d) O'Brien, S.; Kantarjian, H.M.; Keating, M.; Beran, M.; Koller, C.; Robertson, Hester, J.; Rios, M.; Andreeff, M.; Talpaz, M. *Blood* **1995**, *86*, 3322-3326. Ernst, T.; Shuman L.; Grossbard M. *Blood*, **1995**, *86(suppl 1)*, 529.

2 (a) Li-kuo, F. *in* China Plant Red Data Book —Rare and Endangered Plants— (Science Press, Beijing, New-York) **1992**, *1*. (b) Perdue Jr, R.E.; Spetzman, L.A.; Powell R.G.; Smith, J.R. *Amer. Hort. Mag.* **1970**,19. (c) Refer to the recent issue regarding destroying the Californian Yew Tree, *Taxus brevilolia*, to produce Taxol® drug substance —another anticancer drug.

3 Mikolajczak, K.L.; Powell R.G.; Smith, J.R. *Tetrahedron* **1972**, *28*, 1995-2001 and references cited herein.

4 Including the Reformasky and lithium anion approaches, see the recent exhaustive review, Miah, M.A.; Hudlicky, T.; Reed, J.W. in *The Alkaloids*: Cephalotaxus alkaloids (Academic Press) **1998**, *51*, 199-269, and references cited therein.

5 This situation resulted in two major disadvantages: i) This expensive intermediate was obtained with low yield and ii) the chiral center at C-2 was not stereospecifically created, giving a mixture of 4 diastereomers (since cephalotaxine is a rare case of a natural product partially racemized: Huang, W. et al. *Scientia Sinica*, **1980**,vol XXIII, 835-846).

6. Our strategy was based on our experience of the esterification of the more sterically hindered C-13 taxane hydroxyl with cyclic side-chain (in our hands, esterification of cephalotaxine with pivalic acid was easy whereas that of baccatin was impossible), Robin, J.P. et. al. Patent application FR 95 12739, FR 9515557, WO 97 15562.

7 (a) Including protonic and Lewis acids; (b) Homoharringtonine was described as an amorphous solid; Powell, R.G.; Weisleder, D.; Smith, C.R. *J. Pharm. Sci.* **1972**, 1227-1230; (c) **(-)-2**: NMR ^{1}H 400 MHz ($CDCl_3$) (δ ppm, J Hz): 6.63 (1H, s, H-17*); 6.55 (1H, s, H-14*); 6.01 (1H, d, $J_{3,4}$ = 9.8, H-3); 5.87 (2H, m, OCH_2O); 5.05 (1H, s, H-1); 3.78 (1H, d, $J_{4,3}$ = 9.8, H-4); 3.68 (3H, s, OCH_3); 3.58 (3H, s, OCH_3); 3.54 (1H, s, 2'-OH); 3.10 (2H, m, H-11β + H-8α); 2.95 (1H, m, H-10α); 2.59 (2H, m, H-8β + H-10β); 2.38 (1H, dd, J_{AB} = 14.0, J = 6.7, H-11α); 2.27 and 1.90 (2H, 2d, J_{AB} = 16.5, $\underline{CH_2}CO_2$); 2.02 (1H, m, H-6_A); 1.90 (1H, m, H-6_B); 1.76 (2H, m, CH_2-7); 1.5 - 1.15 (6H, m, 3×CH_2); 1.30 (1H, s, 6'-OH); 1.19 (6H, 2s, 2×CH_3). The resulting compound was purified until constant melting range and optical rotation. Since several total syntheses of (±)- and (-)-cephalotaxine were described in the literature, the present semi-synthesis is a formal total synthesis of homoharringtonine.

8 (+)-Cephalotaxine content was confirmed by ^{1}H NMR studies using chiral Europium complex.

9 (a) (*R*)-(+)-Hytra = (*R*)-2-hydroxy-1,2,2-triphenylethyl acetate; Braun, M.; Gräf, S. *Org. Synth.* **1995**, *72*, 38. (b) Attemps to promote asymmetric hydroxyalkylation of **7b** with chiral acetate deriving of (-)-menthol or chiral acetamide deriving from (*R*)-4-isopropyl-2-oxazolidinone gave less satisfactory results. (c) (2*R*)-**11**: NMR ^{1}H 400 MHz ($CDCl_3$)(δ ppm, J Hz): 7.53 (2H, d, J = 7.4, o-Ph); 7.36 (2H, t, J = 7.6, m-Ph); 7.28 (1H, t, J = 7.3, p-Ph); 7.2-7.0 (10H, m, Ph); 6.66 (1H, s, H-1''); 5.0 (1H, m, H-3'); 3.50 (1H, s, 2-OH); 2.94 (1H, s, 2''-OH); 2.76 and 2.61 (2H, 2d, J_{AB} = 16.3, CH_2-3); 2.06 and 1.78 (2H, 2m, CH_2); 1.65 (3H, s, CH_3); 1.55 (3H, s, CH_3) and (2H, m, CH_2); 1.23 (9H, s, O-*tert*-Bu).

10 Due to the large difference of retention times (100%) of both diastereomeric esters, (-)-quinine was chosen among a large set of hindered chiral alcohols including, for example, mandelic acid, ephedrine and menthol. **12**: NMR ^{1}H 400 MHz ($CDCl_3$) (δ ppm, J Hz) <u>(2'*R*)-diastereomer:</u> 8.73 (1H, d, J = 4.4, H-2_{qn}), 8.0 (1H, d, J = 9.2, H-8_{qn}); 7.50 (1H, broad s); 7.39 (1H, d, J = 4.5, H-3_{qn}); 7.36 (1H, dd, H-7_{qn}); 6.39 (1H, broad s); 5.88 (1H, m, =CH_{qn}); 5.03 (2H, m, =CH_{2qn}); 3.97 (3H, s, OCH_3); 3.31 (3H, broad s, OCH_3); 3.5 - 1.2 (m, 10H); 2.86 and 2.64 (2H, 2d, J_{AB} = 15.0, $\underline{CH_2}CO_2$); 1.17 (3H, s, CH_3); 0.99 (3H, s, CH_3); <u>(2'*S*)-diastereomer:</u> 8.74 (1H, d, J = 4.4, H-2_{qn}), 7.99 (1H, d, J = 9.2, H-8_{qn}); 7.65 (1H, broad s, H-3_{qn}); 7.44 (1H, s broad, H-5_{qn}); 7.36 (1H, dd, J = 9.2 and 2.7, H-7_{qn}); 6.55 (1H, broad s); 5.89 (1H, m, =CH_{qn}); 5.05 (2H, m,=CH_{2qn}); 3.99 (3H, s, OCH_3); 3.54 (3H, s, OCH_3); 3.1 - 1.0 (m, 7×CH_2 + 3×CH); 2.91 and 2.67 (2H, 2d, J_{AB} = 15.0, $\underline{CH_2}CO_2$); 1.03 (3H, broad s, CH_3); 0.44 (3H, broad s, CH_3).

11 A sample of the latter was saponified to regenerate (+)-cephalotaxine. The same acylation performed with <u>enantiomerically pure</u> (2*S*)-(+)-**4** gave a reverse rate (10/90) of (2'*S*,3*R*,4*R*,5*S*)-(+)-**6** / (2'*S*,3*S*,4*S*,5*R*)-(-)-**6** corresponding to the antipode of anhydro-homoharringtonine and the 2'-epimer of the latter, respectively. Same —but quantitatively symmetrical— preparative HPLC separation, following by side-chain ring opening yielded (+)-homoharringtonine and 2'-*epi*-homoharringtonine.

12 Large scale production, according to Good Manufacturing Practices, of highly pure drug substance for clinical use was optimized by using purified cephalotaxine prepared in high yield (2 kg / ton of dry leaves) from the crude alkaloid extract. Cephalotaxine was regenerated from unused (2'*S*)-(-)-**6**, then purified and recycled in the process.

13 By optical rotation. HPLC purity was higher than 99.9%.