Pergamon

Tetrahedron Letters 42 (2001) 1911–1913

TETRAHEDRON LETTERS

Enantioselective synthesis of the ester side chain of homoharringtonine

Laurent Keller, Françoise Dumas* and Jean d'Angelo*

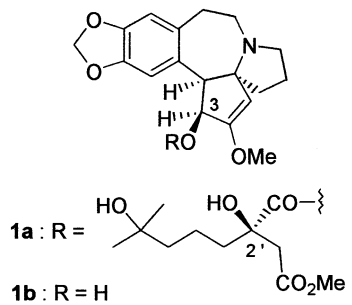
Unité Associée au CNRS, Centre d'Etudes Pharmaceutiques, Université de Paris Sud, 5, rue J.-B. Clément, 92296 Châtenay-Malabry, France

Received 3 November 2000; accepted 13 January 2001

Abstract—The Michael adduct **6** was converted in ten steps with an overall yield of 5.7% into the methyl ester derivative of the side chain of homoharringtonine, (*R*)-**17**.

Homoharringtonine (HHT, **1a**), accompanied by several congener alkaloids, was isolated from the plumyew *Cephalotaxus harringtonia* (Cephalotaxaceae, Coniferae), an evergreen tree native of the southern provinces of China.[1] Research efforts have focused on HHT, since it is the main natural ester of cephalotaxine (**1b**) in the tree, and the most potent in this family of antitumor drugs. Several teams have investigated the mechanism by which HHT and related alkaloids exert their antineoplastic effects; all have concluded that these drugs inhibit protein biosynthesis in the cell. The effects of HHT and congeners on protein synthesis are the breakdown of polyribosomes to monosomes, the release of completed globin chains, and delayed inhibition of initiation of protein synthesis without affecting chain elongation. HHT has been clinically tested in advanced breast cancer, acute myelogenous leukemia and myelodysplastic syndrome (MDS), and MDS evolving to acute myeloid leukemia.[2] This drug is now widely used in China as the front-line chemotherapy for acute myeloid leukemias, particularly in acute promyelocytic leukemia. In the US, the efficiency of HHT in the treatment of chronic myeloid leukemia is being evaluated in a large scale study.[3]

The structure–activity relationships for *Cephalotaxus* alkaloids have been defined. In this respect, it has been established that the tetracyclic alcohol cephalotaxine



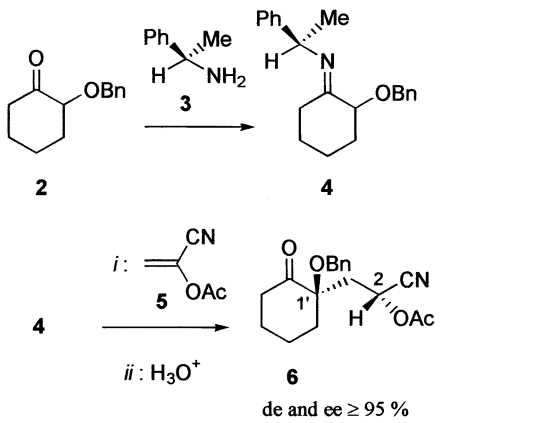
(**1b**), although more abundant in *C. harringtonia* than HHT and congener esters, per se is devoid of biological activity; thus, the presence of an ester side chain at C-3 appears to be critical to the antitumor potency of HHT (and analogs). As a result of nearly 30 years of intensive research, numerous strategies for the elaboration of the side chain of HHT, or its cyclic equivalents, have been developed.[4] However, there is a marked stereorequirement of the structure of the side chains for both their antitumor activity and toxicity; thus *epi*-HHT, which only differs from HHT in the configuration of the stereogenic center at C-2′, exhibited no significant antineoplastic activity.[1]

Reported herein is a highly stereoselective approach to the methyl ester derivative of the HHT side chain, in the natural *R* configuration, exploiting our general methodology for the enantioselective construction of quaternary carbon centers.[5] The key tactical element in this synthesis was the enantiopure Michael adduct (2*R*,1′*R*)-**6** which resulted from the addition of imine **4**, derived from *racemic* 2-benzyloxycyclohexanone (**2**) and (*R*)-1-phenylethylamine (**3**), to 2-acetoxyacrylonitrile (**5**)[6] (Scheme 1).

Keywords: antitumor compounds; asymmetric synthesis; cyanohydrins; ozonolysis; ring transformations.

* Corresponding authors. E-mail: francoise.dumas@cep.u-psud.fr; jean.dangelo@cep.u-psud.fr

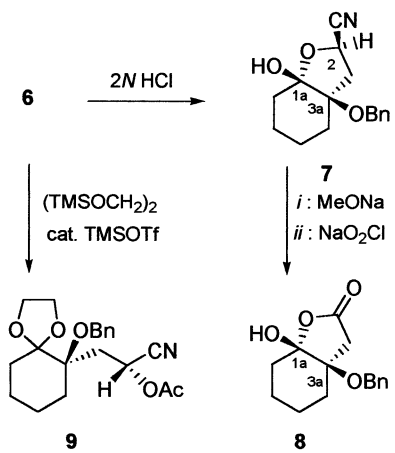
0040-4039/01/$ - see front matter
PII: S0040-4039(01)00086-7



Scheme 1.

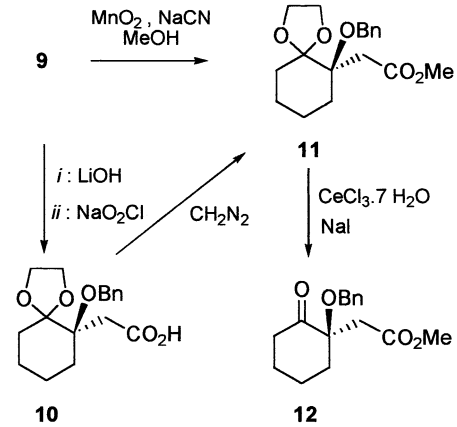
The conversion of compound **6** into the HHT side chain would require, in no particular order, three essential chemical operations, namely the transformation of the α-acetoxypropionitrile appendage into an acetate moiety, the regioselective oxidative cleavage of the cyclohexane ring at the less substituted α-side of the carbonyl function, and the introduction of two geminate methyl groups to complete the carbinol termini.

Regeneration of the masked aldehyde function at C-2 was examined first. While basic treatments of adduct **6** furnished invariably undefined compounds, the hemiacetal (2*R*,1a*S*,3a*R*)-**7** was formed under acidic conditions. The conversion of **7** into lactone (1a*S*,3a*R*)-**8** has recently been accomplished;[6] however, the overall yield for the process was found to be unsatisfactory (ca. 25%). This troublesome hemiacetalization side-reaction was circumvented by protecting first ketone **6** as the acetal **9**[7] ($TMSOCH_2CH_2OTMS$, TMSOTf, −78 to 20°C, 80% yield)[8] (Scheme 2).



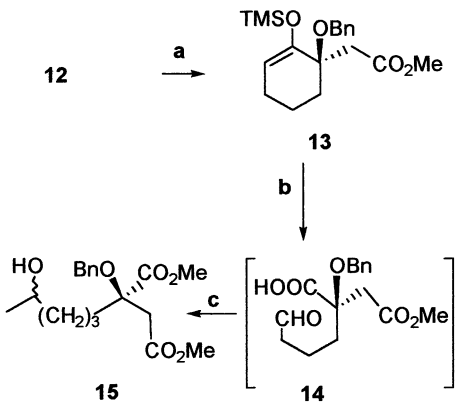
Scheme 2.

Transformation of the protected cyanohydrin moiety of acetal **9** into a carbomethoxy group now proceeded straightforwardly, either by basic treatment followed by the in situ oxidation of the intermediary aldehyde and esterification of the resulting acid **10** (**9** to **10**: i: 2.1 equiv. LiOH, THF, 1 h at 20°C; ii: NaO_2Cl, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O, 16 h at 20°C, 75% yield;[9] **10** to **11**: CH_2N_2, quantitative yield), or more directly by treating **9** with MnO_2 in MeOH in the presence of NaCN (72 h at 20°C, 60% yield).[10] Removal of the acetal protecting group ($CeCl_3 \cdot 7H_2O$, NaI, MeCN, 18 h at 80°C)[11] delivered finally the cornerstone ketone (*R*)-**12**[12] with a 85% yield (Scheme 3).



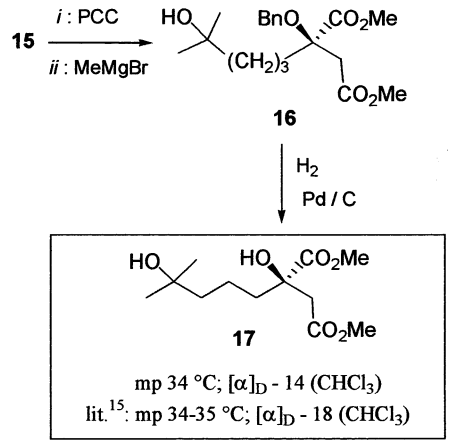
Scheme 3.

The oxidative cleavage of the cyclohexane ring of **12** was next undertaken. For this purpose, ketone **12** was first converted into silyl enol ether **13** (TMSCl, Et_3N, MeCN, 20 h at 20°C),[13] which was ozonolyzed (i: O_3, CH_2Cl_2/EtOH, −78°C; ii: Me_2S) into sensitive aldehyde **14** (not characterized). Slow addition (30 min) of methyl Grignard reagent to crude **14** (1.95 equiv. of MeMgBr, THF, −40°C), followed by esterification with CH_2N_2 afforded an equimolar mixture of epimeric alcohols **15** with an overall yield of 35%, calculated from ketone **12** (Scheme 4).



Scheme 4. (a) TMSCl, Et_3N; (b) i: O_3; ii: Me_2S; (c) i: MeMgBr; ii: H_3O^+; iii: CH_2N_2.

At this juncture, we stood ready to complete the synthesis of the methyl ester derivative of the HHT side chain. In the event, sequential exposure of alcohol **15** to pyridinium chlorochromate (CH_2Cl_2, 16 h at 20°C) and 1 equiv. of MeMgBr (slow addition at −30°C) produced with a 40% yield carbinol (*R*)-**16**, which was finally transformed by hydrogenolysis of the benzyloxy group (1 bar of H_2, Pd/C, EtOH, 24 h at 20°C, quantitative



Scheme 5.

yield) into our goal (*R*)-methyl 3-carbomethoxy-3,7-dihydroxy-7-methyloctanoate (**17**),[14] identical in all respects with the ester deriving from the methanolysis of natural HHT[15] (Scheme 5).

Thus, an highly stereoselective synthesis of the methyl ester derivative of the HHT side chain **17** in the natural *R* configuration, has been completed in 5.7% overall yield from Michael adduct **6** by a linear sequence of ten chemical operations (mean yield per step: 75%). Studies directed towards the elaboration of a sterically less hindered, cyclic form of **17**,[16] suitable for coupling with cephalotaxine (**1b**) to produce enantiopure HHT (**1a**), are currently under investigation in our laboratory.

Acknowledgements

We are grateful to Dr. Jacqueline Mahuteau for the valuable assistance with NMR studies and Mrs. Sophie Mairesse-Lebrun for performing the elemental analyses (Centre d'Etudes Pharmaceutiques, Châtenay-Malabry).

References

1. In *Chinese Drugs of Plant Origin, Chemistry, Pharmacology, and Use in Traditional and Modern Medicine*; Tang, W.; Eisenbrand, G., Eds.; *Cephalotaxus* spp. Springer: Berlin, 1992; pp. 281–306.
2. Zhou, D.-C.; Zittoun, R.; Marie, J.-P. *Bull. Cancer* **1995**, *82*, 987–995.
3. Zhou, D.-C.; Ramond, S.; Viguie, F.; Faussat, A.-M.; Zittoun, R.; Marie, J.-P. *Int. J. Cancer* **1996**, *65*, 365–371.
4. Robin, J.-P.; Dhal, R.; Dujardin, G.; Girodier, L.; Mevellec, L.; Poutot, S. *Tetrahedron Lett.* **1999**, *40*, 2931–2934 and references cited therein.
5. For recent references, see: (a) Thominiaux, C.; Roussé, S.; Desmaële, D.; d'Angelo, J.; Riche, C. *Tetrahedron: Asymmetry* **1999**, *10*, 2015–2021; (b) Nour, M.; Tan, K.; Cavé, C.; Villeneuve, D.; Desmaële, D.; d'Angelo, J.; Riche, C. *Tetrahedron: Asymmetry* **2000**, *11*, 995–1002; (c) Gassama, A.; d'Angelo, J.; Cavé, C.; Mahuteau, J.; Riche, C. *Eur. J. Org. Chem.* **2000**, 3165–3169.
6. Keller, L.; Camara, C.; Pinheiro, A.; Dumas, F.; d'Angelo, J. *Tetrahedron Lett.* **2001**, *42*, 381–383; d'Angelo, J.; Dumas, F.; Keller, L. Patent application FR 0017281.
7. **9**: colorless solid; mp 138°C (EtOH); $[\alpha]_D^{20}$ +106 ($c=2.1$, $CHCl_3$); IR (KBr): 2250, 1743 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): 1.41–1.73 (m, 6H), 1.88 (m, 1H), 1.95 (s+m, 4H), 2.16 (dd, $J=5.2$, 15.9 Hz, 1H), 2.65 (dd, $J=5.2$, 15.9 Hz, 1H), 4.01 (m, 3H), 4.18 (m, 1H), 4.49 (d, $J=11.4$ Hz, 1H), 4.55 (d, $J=11.4$ Hz, 1H), 5.72 (t, $J=5.2$ Hz, 1H), 7.34 (m, 5H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): 20.1 (CH_3), 20.4 (CH_2), 22.5 (CH_2), 29.8 (CH_2), 32.2 (CH_2), 34.8 (CH_2), 58.1 (CH), 63.7 (CH_2), 64.1 (CH_2), 64.4 (CH_2), 78.6 (C), 110.3 (C), 118.3 (C), 126.8 (2 CH), 127.2 (CH), 128.3 (2CH), 138.4 (C), 168.9 (C) ppm. Anal. calcd: C, 66.83: H, 7.01: N, 3.89. Found: C, 66.89: H, 7.14: N, 3.92.
8. Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357–1358.
9. Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175–1176.
10. Busato, S.; Scheffold, R. *Helv. Chim. Acta* **1994**, *77*, 92–99.
11. Marcantoni, E.; Nobili, F.; Bartoli, G.; Bosco, M.; Sambri, L. *J. Org. Chem* **1997**, *62*, 4183–4184.
12. **12**: colorless oil; $[\alpha]_D^{20}$ +131 ($c=0.7$, $CHCl_3$); IR (neat): 1735, 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): 1.41–2.08 (m, 5H), 2.16–2.44 (m, 2H), 2.49–2.74 (m, 2H), 2.92 (d, $J=14.9$ Hz, 1H), 3.57 (s, 3H), 4.02 (d, $J=10.8$ Hz, 1H), 4.57 (d, $J=10.8$ Hz, 1H), 7.15–7.38 (m, 5H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): 20.3 (CH_2), 27.6 (CH_2), 36.7 (CH_2), 38.2 (CH_2), 39.1 (CH_2), 51.5 (CH_3), 65.7 (CH_2), 81.2 (C), 127.4 (2 CH), 127.5 (CH), 128.3 (2 CH), 137.7 (C), 170.8 (C), 210.4 (C) ppm.
13. Cazeau, P.; Moulines, F.; Laporte, O.; Duboudin, F. *J. Organometal. Chem.* **1980**, *201*, C9–C13.
14. **17**: colorless solid; mp 34°C (pentane); $[\alpha]_D^{20}$ −14 ($c=0.7$, $CHCl_3$); IR (neat): 3501, 1733 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): 1.19 (s, 6H+OH), 1.34–1.75 (m, 6H), 2.70 (d, $J=16.3$ Hz, 1H), 2.92 (d, $J=16.3$ Hz, 1H), 3.67 (s, 3H), 3.72 (s, 1H, OH), 3.80 (s, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): 18.0 (CH_2), 29.0 (CH_3), 29.2 (CH_3), 39.5 (CH_2), 43.3 (CH_2), 43.5 (CH_2), 51.7 (CH_3), 52.8 (CH_3), 70.6 (C), 75.2 (C), 171.2 (C), 175.5 (C) ppm. Anal. calcd: C, 54.94: H, 8.45. Found: C, 54.97: H, 8.55.
15. Powell, R. G.; Weisleder, D.; Smith, Jr., C. R. *J. Pharm. Sci.* **1972**, *61*, 1227–1230.
16. Kelly, T. R.; McNutt, Jr., R. W.; Montury, M.; Tosches, N. P.; Mikolajczak, K. L.; Smith, Jr., C. R.; Weisleder, D. *J. Org. Chem.* **1979**, *44*, 63–67.