HETEROCYCLES, Vol. 66, 2005, pp. 31 – 37. © The Japan Institute of Heterocyclic Chemistry
Received, 13th April, 2005, Accepted, 9th June, 2005, Published online, 10th June, 2005. COM-05-S(K)3

ENANTIOSELECTIVE SYNTHESIS OF (*R*)-1-AZASPIRO-[4.4]NONANE-2,6-DIONE ETHYLENE KETAL, KEY CHIRAL INTERMEDIATE IN THE ELABORATION OF (-)-CEPHALOTAXINE

Mathieu Pizzonero, Françoise Dumas,* and Jean d'Angelo*

Department of Organic Chemistry, BioCIS, UMR 8076 CNRS, School of Pharmacy, Paris XI University, 5, rue J.-B. Clément, F-92296 Châtenay-Malabry, France. francoise.dumas@cep.u-psud, jean.dangelo@cep.u-psud.fr

Abstract – An enantioselective synthesis of (*R*)-1-azaspiro[4.4]nonane-2,6-dione ethylene ketal (**4**), chiral relay in the elaboration of (-)-cephalotaxine (**1b**), starting from (*R*)-1-(2-methoxycarbonylethyl)-2-oxo-cyclopentanecarboxylic acid methyl ester ((*R*)-**10**) (8 chemical operations, 26% overall yield, ee ≥ 95%) is described. The Curtius rearrangement of acyl azide (**12**) was used as the key strategic element to install with a perfect stereochemical fidelity and a high efficiency an α-nitrogen substituent at the quaternary carbon center in **10**.

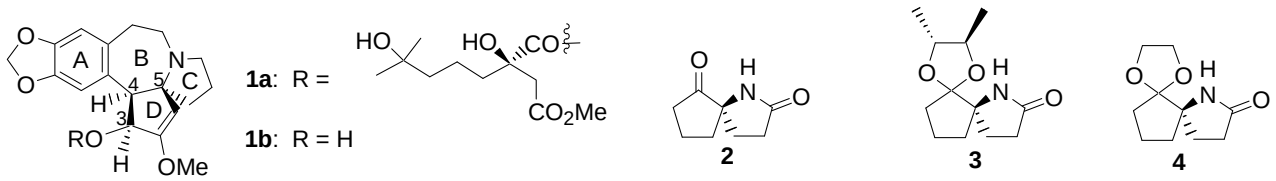
INTRODUCTION

Besides highly promising antileukemic properties exhibited by several naturally occurring esters exemplified by homoharringtonine, HHT, **1a**,[1] (-)-cephalotaxine (**1b**) has become an attractive target for the development of new synthetic methodology because of its unique backbone architecture, consisting of a 1-azaspiro[4.4]nonane unit fused to a benzazepine nucleus.[2] As a result of more than 30 years of intensive research, numerous approaches to (±)-**1b** have been developed.[3] However, structure-activity relationships of esters of cephalotaxine have demonstrated the stringent stereospecificity requirements for their antitumor potency. Regarding the cephalotaxine moiety, it has been established that esters of "unnatural" (+)-cephalotaxine (*ent*-**1b**) are devoid of antileukemic activity,[4] a factor that has stimulated interest in the enantioselective synthesis of **1b**.[5] One of the most efficient strategies in the area has featured the use of derivatives of (*R*)-1-azaspiro[4.4]nonane-2,6-dione (**2**) harboring the future stereogenic center C-5 of **1b**. Since the correct stereochemistry at the two further stereogenic centers C-3 and C-4 in **1b** has been readily secured during the completion of the synthesis,[6] the elaboration of CD subunit (*R*)-**2** constitutes an enantio-

This paper is dedicated to the memory of the Emeritus Professor Kenji Koga of Tokyo University

and diastereoselective approach to (-)-cephalotaxine in a formal sense. However, as the implementation of the synthesis requires the coupling of a *N*-metallated derivative of **2** with an arylethyl tosylate (installation of ring A together with two carbon atoms of future ring B), the very reactive cyclopentanone carbonyl of **2** needs to be protected. For that reason, the two strategies already reported for the synthesis of (*R*)-**2** have both focused on its ketal derivatives: ketal (**3**) was elaborated *via* HPLC separation of diastereomeric ketals of racemic ketone (**2**),[5b] and ketal ((*R*)-**4**) was synthesized according to a semipinacolic rearrangement-based enantioselective approach, employing (*S*)-1-(1-naphthyl)ethylamine as the chiral inducer[5e] (Chart 1).

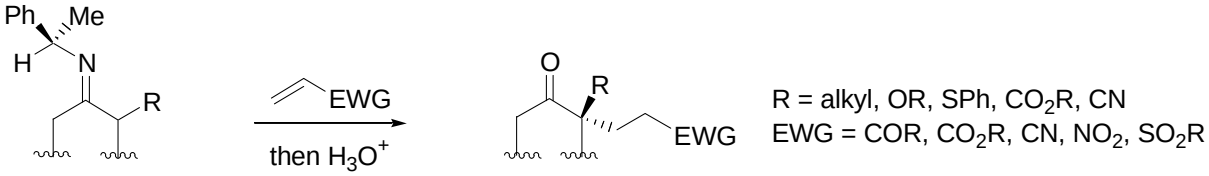
Chart 1. Structures of homoharringtonine (**1a**), cephalotaxine (**1b**) and key chiral spiro subunits **2-4**.



RESULTS AND DISCUSSION

In this paper, we report an efficient enantioselective synthesis of cornerstone ketal ((*R*)-**4**), founded on the asymmetric Michael reaction involving chiral imines/secondary enamines derived from enantiopure 1-phenylethylamine. This methodology, outlined in Scheme 1, has played a paramount role in asymmetric synthesis, particularly for the enantioselective elaboration of quaternary carbon centers.[7]

Scheme 1. Asymmetric Michael reaction involving chiral imines/ secondary enamines.



However, while this reaction tolerates the presence of α-alkoxy[8] or α-phenylthio[9] substituents in starting imine (**5**), all efforts devoted to the synthesis of adducts of type (**6**) bearing an α-nitrogen linkage at the quaternary carbon center, utilizing either a variety of α-nitrogen substituents in imine (**5**) or DEAD as the Michael acceptor, were fruitless.[7a,b] In light of this vexing outcome, we turned to an alternative "indirect" route based on the Curtius rearrangement of an acyl azide.[10]

The starting material in the present approach, keto diester ((*R*)-**10**), was elaborated in 85% yield and an ee ≥ 95% through Michael addition of enamino ester ((*R*)-**9**) to methyl acrylate.[11] Our initial synthetic efforts

were focused on the key Curtius rearrangement. However, since the planned rearrangement sequence necessarily proceeds *via* the intermediacy of a carboxylic acid linked to the quaternary carbon center, two critical problems should first be resolved: the discrimination between the two carbomethoxy groups of **10** and the masking of its carbonyl group to circumvent the generation of a β-keto acid species, of notorious thermal instability.

These two prerequisites were simultaneously satisfied through subjection of **10** to sequential reduction ($NaBH_4$, $CeCl_3.7H_2O$ in MeOH, -78 °C)[12] and saponification (LiOH in $MeOH/H_2O$, followed by acidic treatment) to provide an intermediary hydroxy diacid, the spontaneous lactonization of which furnished in 75% yield *diastereomerically pure* lactone acid (**11**), a stereochemical homogeneity revealed by the presence of a single set of nine resonance peaks in its proton-decoupled ^{13}C NMR spectrum. It should be pointed out that the above lactonization process achieved the concomitant "internal protection" of the secondary hydroxyl function and propanoic carboxyl group of the transient hydroxy diacid, hence implicitly ensuring a clear-cut chemoselective discrimination between the ester groups of adduct (**10**).

Although the configuration of the newly created stereogenic center in bicyclic lactone (**11**) could not be ascertained spectroscopically, the depicted *cis* ring junction may be reasonably assigned, assuming that the reduction step involves a transition state structure based on a cerium^{III}-coordinated β-keto ester complex, in which the incoming hydride ion is delivered on the less hindered π-face of the carbonyl group, *anti* to the vicinal propanoate appendage.[13] The unusually facile cyclization of the hydroxy diacid precursor of lactone (**11**), which occurred at 20 °C, furnishes an additional argument in favor of the *cis* ring junction assignment. Several compelling reports in the field have indeed established that the ease of formation of fused bicyclic lactones of type (**11**) from parent hydroxy acids is strongly dependent on the stereochemistry of their ring junction. By way of illustration, the hydroxy acid progenitor of *cis*-fused dihydronepetalactone cyclized at 25 °C, while elaboration of the related *trans*-isomer required prolonged heating in refluxing xylene.[14]

At this juncture, we stood ready to perform the critical Curtius rearrangement sequence. In the event, acid (**11**) was first converted into acyl azide (**12**) [$(PhO)_2PON_3$, Na_2CO_3, cat. DMAP][15] which was directly rearranged into benzyl carbamate (**13**) (BnOH in refluxing toluene, 75% yield from **11**). Conversion of fused bicyclic lactone (**13**) into a derivative possessing the requisite 1-azaspiro[4.4]nonane core was examined next.

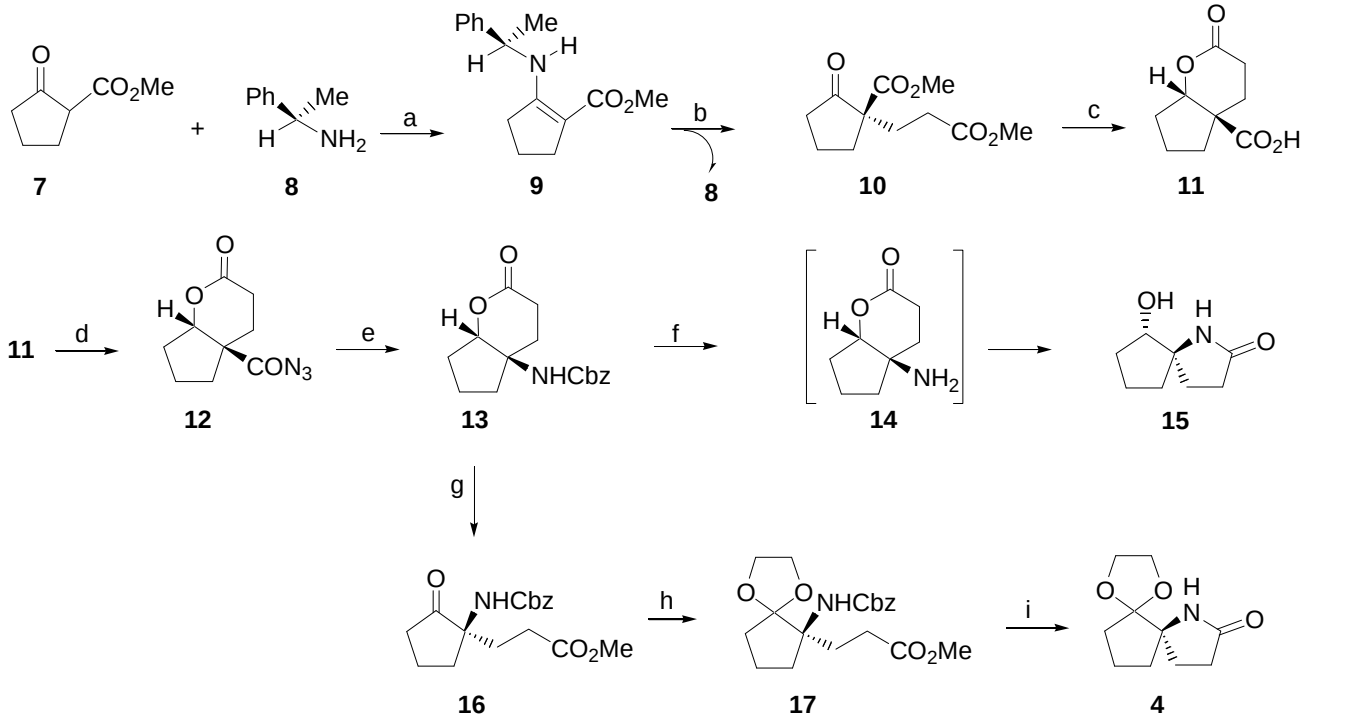
It was our original hope that amine (**14**), issuing from the hydrogenolysis of **13**, might undergo an intramolecular nucleophilic rearrangement to provide spiro lactam (**15**). However, hydrogenolysis of **13** (5 bar of H_2, 10% Pd/C, MeOH) produced **15** in only meager yield (<10%), along with high molecular weight material. Although there was no firm evidence that self-condensation of transient amine (**14**), leading to polyamides, competes with the formation of spiro lactam (**15**), the low efficiency of conversion

[**13** → **15**] may be reasonably interpreted on this basis, invoking that the expected transannular lactamization process [**14** → **15**] suffers from unfavorable steric factor, on account of a severely constrained transition state structure, in which the angle of attack of the amino group with respect to the plane of the lactone carbonyl (*ca*. 90 °)[16] markedly differs from "ideal" Bürgi-Dunitz trajectory (109 °).[17]

In view of the above result, an alternative plan was devised, in which the order of reactions was inverted, so that the lactone ring of **13** would be opened prior to the hydrogenolysis of the benzyl carbamate moiety. To achieve this aim, **13** was subjected to sequential oxidation (1 equiv. of aqueous NaOH/cat. $RuO_2/NaIO_4$, followed by acidic work-up)[18] and esterification (CH_2N_2) to afford keto ester ((*R*)-**16**) (70% yield from **13**). This was then converted into ketal ((*R*)-**17**) upon reaction with $(TMSOCH_2)_2$ in the presence of a catalytic amount of TMSOTf (THF, -78 °C → 20 °C).[19]

Finally, hydrogenolysis of crude **17** (5 bar of H_2, $Pd(OH)_2$, MeOH, 50 °C) delivered our goal (*R*)-**4** (65% yield from **16**): mp 79-80 °C, $[\alpha]_D$ -48.6 (c 1.4, $CHCl_3$); lit.,[5e]: mp 75-76 °C, $[\alpha]_D$ -49.4 (c 1.0, $CHCl_3$) (Scheme 2).

Scheme 2. Synthesis of spiro lactam (**4**).



Reagents and conditions: (a) cyclohexane, 80 °C, 12 h, 90%. (b) (i) 1.05 equiv. $MgBr_2$ (0.5 M in Et_2O), 1.5 equiv. methyl acrylate, THF, 20 °C, 24 h; (ii) 20% aq. AcOH, THF, 40 °C, 24 h (85%, ee >95%). (c) (i) $CeCl_3.7H_2O$, MeOH 20 °C, then $NaBH_4$ -78 °C; (ii) 6 M HCl, 20 °C; (iii) LiOH, H_2O, 50 °C; (iv) 6 M HCl (75 % for four steps). (d) Na_2CO_3, cat. DMAP, $(PhO)_2PON_3$, CH_2Cl_2, 20 °C (crude **12** was used in the next step). (e) BnOH, refluxing toluene (75% for steps d and e). (f) 5 bar of H_2, 10% Pd/C, MeOH, 20 °C (<10%). (g) (i) 1 equiv. 0.5 M NaOH, 50 °C; (ii) cat. RuO_2, $NaIO_4$, 20 °C; (iii) 6 M HCl; (iv) CH_2N_2 (70% for four steps). (h) $(TMSOCH_2)_2$, cat. TMSOTf, CH_2Cl_2, -78 °C → 20 °C (crude **17** was used in the next step). (i) 5 bar of H_2, $Pd(OH)_2$, MeOH, 50 °C (65% for steps h and i).

To conclude, the synthesis of ketal ((*R*)-**4**), crucial relay in the elaboration of natural (-)-cephalotaxine (**1b**), has been completed in 26% overall yield and with an ee ≥ 95% from Michael adduct ((*R*)-**10**) by a linear sequence of eight chemical operations (mean yield per step: 85%). Critical to the success of this endeavor was the demonstration of the viability of the Curtius rearrangement as the key tactical element to install with a perfect stereochemical fidelity and a high efficiency an α-nitrogen substituent at the quaternary carbon center in Michael adducts of type (**6**). Also of major significance was the use of readily available and inexpensive (*R*)-1-phenylethylamine (**8**) as the chiral auxiliary,[20] which was easily and nearly quantitatively recovered without any alteration of its stereochemical integrity. Regarding the economical viewpoint, it should be emphasized that the present synthesis takes precedence over the previously published approaches to CD subunits (**3**) and (**4**),[21] thereby offering a decisive advantage for a potential development of therapeutically important esters of (-)-cephalotaxine and analogs.

ACKOWLEGMENTS

This work was supported by a fellowship (BDI) to M.P. from the Centre National de la Recherche Scientifique. We thank Dr J.-P. Robin (Oncopharm SA) for fruitful discussions. We also thank Dr M. Ourevitch for NMR assistance and Mrs S. Mairesse-Lebrun for performing elemental analyses.

REFERENCES and NOTES

1. (a) M. A. Miah Jal, T. Hudlicky, and J. W. Reed, In *The Alkaloids*, ed. by F. M. Manske, Academic Press, New York, 1998, Vol. 51, pp. 199-269. For an hemisynthesis of enantiopure homoharringtonine, see: (b) J.-P. Robin, R. Dhal, G. Dujardin, L. Girodier, L. Mevellec, and S. Poutot, *Tetrahedron Lett.*, 1999, **40**, 2931. For an enantioselective synthesis of the ester side-chain of homoharringtonine, see: (c) L. Keller, F. Dumas, and J. d'Angelo, *Eur. J. Org. Chem.*, 2003, 2488.
2. For a recent contribution in this area, see: M. Pizzonero, L. Keller, F. Dumas, M. Ourevitch, G. Morgant, A. Spasojević-de Biré, G. Bogdanović, N. E. Ghermani, and J. d'Angelo, *J. Org. Chem.*, 2004, **69**, 4336.
3. Total syntheses of (±)-cephalotaxine: W.-D. Z. Li and Y.-Q. Wang, *Org. Lett.*, 2003, **5**, 2931 and references cited. (b) Recent formal synthesis of (±)-cephalotaxine: W.-D. Z. Li and B.-C. Ma, *J. Org. Chem.,* 2005; **70**, 3277.
4. (a) K. L. Mikolajczak, C. R. Smith Jr., and D. Weisleder, *J. Med. Chem.*, 1977, **20**, 328. (b) J.-P. Robin, R. Dhal, F. Drouye, J.-P. Marie, N. Radosevic, J. Robin, K. Souchaud, and P. Bataille, U.S. Patent 6 579 869, 2003 (*Chem. Abstr*., 2004, **140**, 94179).
5. (a) N. Isono and M. Mori, *J. Org. Chem.,* 1995, **60**, 115. (b) T. Nagasaka, H. Sato, and S.-i. Saeki, *Tetrahedron : Asymmetry*, 1997, **8**, 191. (c) L. F. Tietze and H. Schirok, *J. Am. Chem. Soc.*, 1999,

121, 10264. (d) M. Ikeda, S. A. A. El Bialy, K-i. Hirose, M. Kotake, T. Sato, S. M. M. Bayomi, I. A. Shehata, A. M. Abdelal, L. M. Gad, and T. Yakura, *Chem. Pharm. Bull.*, 1999, **47**, 983. (e) L. Planas, J. Pérard-Viret, and J. Royer, *J. Org. Chem.*, 2004, **69**, 3087.

6. M. E. Kuehne, W. G. Bornmann, W. H. Parsons, T. D. Spitzer, J. F. Blount, and J. Zubieta, *J. Org. Chem.*, 1988, **53,** 3439.
7. Reviews: (a) J. d'Angelo, D. Desmaële, F. Dumas, and A. Guingant, *Tetrahedron: Asymmetry*, 1992, **3**, 459. (b) J. d'Angelo, C. Cavé, D. Desmaële, and F. Dumas, In *Trends in Organic Synthesis*; ed. by S. G. Pandalai, Trivandrum, India, 1993, Vol. 4, pp. 555-615. For recent developments, see: (c) I. Jabin, G. Révial, M. Pfau, and P. Netchitaïlo, *Tetrahedron: Asymmetry*, 2002, **13***,* 563 (d) C. Camara, D. Joseph, F. Dumas, J. d'Angelo, and A. Chiaroni, *Tetrahedron Lett.*, 2002, **43**, 1445. (e) C. Thominiaux, A. Chiaroni, and D. Desmaële, *Tetrahedron Lett*., 2002, **43**, 4107. (f) J. Christoffers and H. Scharl, *Eur. J. Org. Chem.,* 2002**,** 1505. (g) Ref. 1c of the present paper. (h) C. Camara, L. Keller, and F. Dumas, *Tetrahedron: Asymmetry*, 2003, **14**, 3263. (i) C. Camara, L. Keller, K. Jean-Charles, D. Joseph, and F. Dumas, *Int. J. High Press. Res.*, 2004, **24**, 149. (j) M. Danet, M. Normand-Bayle, J. Mahuteau, J. d'Angelo, G. Morgant, and D. Desmaële, *Eur. J. Org. Chem.*, 2004, 1911. (k) F. Hendra, M. Nour, I. Baglin, G. Morgant, and C. Cavé, *Tetrahedron: Asymmetry*, 2004, **15**, 1027. (l) D. Desmaële, S. Delarue-Cochin, C. Cavé, J. d'Angelo, and G. Morgant, *Org. Lett.*, 2004, **6**, 2421.
8. D. Desmaële and J. d'Angelo, *Tetrahedron Lett*., 1989, **30**, 345.
9. M. Nour, K. Tan, C. Cavé, D. Villeneuve, D. Desmaële, J. d'Angelo, and C. Riche, *Tetrahedron : Asymmetry*, 2000, **11**, 2015.
10. See in relation: (a) M. Martín-Vilà, E. Muray, G. P. Aguado, A. Alvarez-Larena, V. Branchadell, C. Minguillón, E. Giralt, and R. M. Ortuño, *Tetrahedron: Asymmetry*, 2000, **11**, 3569. (b) A. Salgado, T. Huybrechts, A. Eeckhaut, J. Van der Eycken, Z. Szakonyi, F. Fülöp, A. Tkachev, and N. De Kimpe, *Tetrahedron*, 2001, **57**, 2781.
11. Ee of **10** was determined using ^{1}H NMR in the presence of Eu(hfc)$_3$. (a) A. Guingant and H. Hammami, *Tetrahedron: Asymmetry*, 1991, **2**, 411. For a further investigation of this reaction, see: (b) K. Tan, R. Alvarez, M. Nour, C. Cavé, A. Chiaroni, C. Riche, and J. d'Angelo, *Tetrahedron Lett*., 2001, **42**, 5021.
12. A. L. Gemal and J. L. Luche, *J. Am. Chem. Soc.,* 1981, **103**, 5454. However, when the reduction of **10** was performed at 20 °C, a complex mixture of products was obtained.
13. *Réduction par les alumino- et borohydrures en synthèse organique* ; ed. by J. Seyden-Penne, Technique et Documentation-Lavoisier, Paris, 1988, pp. 61-64.
14. J. Ficini and J. d'Angelo, *Tetrahedron Lett.*, 1976, **9**, 687.

15. C. Zhang, S. A. Lomenzo, C. J. Ballay II, and M. L. Trudell, *J. Org. Chem.*, 1997, **62**, 7888.
16. Value estimated on molecular model.
17. *Stereoselective Synthesis.* In *Stereochemistry of Organic Compounds*; ed. by E. L. Eliel and S. H. Wilen, Wiley, New York, 1994, pp. 835-890.
18. P. E. Eaton, Y. S. Or, and S. J. Branca, *J. Am. Chem. Soc.*, 1981, **103**, 2134.
19. T. Tsunoda, M. Suzuki, and R. Noyori, *Tetrahedron Lett.,* 1980, **21**, 1357.
20. (*R*)-**8** (99% ee) is commercially available at low cost: 73.7 € per 100 g (0.825 mole) [Supplier: Acrós Organics, 2005].
21. (a) Preparation of **3** according to ref. 5b required tedious separation of diastereomers by HPLC. (b) (*S*)-1-(1-naphthyl)ethylamine, the chiral inducer required for the synthesis of (*S*)-**4** according to ref. 5e, is a very expensive chemical: 43.9 € per 1 g (0.0058 mole) [Supplier: Acrós Organics, 2005]. Furthermore, this inducer cannot be recovered, since further immolated through hydrogenolysis.