ORGANIC LETTERS

1999
Vol. 1, No. 7
973−976

Stereocontrolled Total Synthesis of (±)-Catharanthine via Radical-Mediated Indole Formation

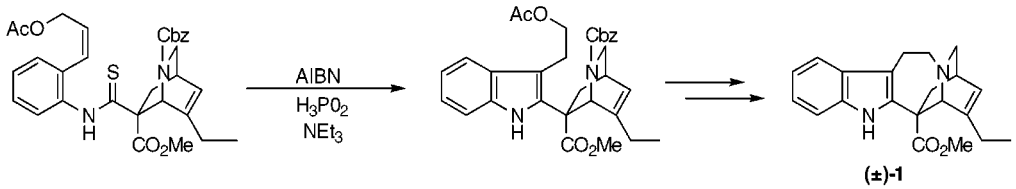
Matthew T. Reding[†] and Tohru Fukuyama*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, CREST, The Japan Science and Technology Corporation (JST), 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-0033, Japan

fukuyama@mol.f.u-tokyo.ac.jp

Received June 21, 1999

ABSTRACT



(±)-1

A stereocontrolled total synthesis of (±)-catharanthine, 1, has been completed. The key step involves the radical-mediated cyclization of a highly functionalized intermediate to furnish the corresponding indole. The cyclization utilizes a simple phosphorus-based radical-reducing agent. This synthesis provides a potential route for the production of analogues of catharanthine and is more convergent and experimentally less complex than previous syntheses of 1.

Catharanthine, **1**, is an important member of the *Iboga* class of alkaloids.[1] It is a chemical and presumed biological precursor of the antitumor alkaloids vinblastine and vincristine, two venerable yet effective anticancer agents used in the treatment of a number of human cancers.[2] The dense, pentacyclic skeleton of **1** contains a tryptamine fragment substituted at the 2-position by a quaternary sp^3 carbon, and thereby represents an attractive challenge to our recently disclosed methodology for the synthesis of 2,3-disubstituted indoles.[3] The successful completion of this synthesis demonstrates the utility of this radical-based methodology for the construction of complex indole-containing natural products.

(±)-Catharanthine has been the target of numerous successful total and formal total syntheses.[4−6] However, all of the previously reported routes to **1** have made use of preexisting indolyl frameworks,[7] and as such offer little hope for the facile construction of analogues of **1** substituted on the aromatic carbocyle. Controlled access to such compounds is essential for the rational examination of structure and activity relationships of the derived drugs. Furthermore, recent syntheses of **1** have relied on nonstereocontrolled

[†] Current Address: Department of Structural, Analytical & Medicinal Chemistry, Pharmacia & Upjohn, Kalamazoo, MI 49001.

(1) (a) Gorman, M.; Neuss, N.; Svoboda, G. H.; Barnes, A. J.; Cone, N. J. *J. Am. Pharm. Assoc. (Sci. Ed.)* **1959**, *48*, 256. (b) Svoboda, G. H.; Neuss, N.; Gorman, M. *J. Am. Pharm. Assoc. (Sci. Ed.)* **1959**, *48*, 659. (c) Neuss, N.; Gorman, M. *Tetrahedron Lett.* **1961**, 206. (d) Gorman, M.; Neuss, N.; Cone, N. J. *J. Am. Chem. Soc.* **1965**, *87*, 93. (e) Büchi, G.; Coffen, D. L.; Kocsis, K.; Sonnet, P. E.; Ziegler, F. E. *J. Am. Chem. Soc.* **1966**, *88*, 3099.

(2) *The Alkaloids. Antitumor Bisindole Alkaloids from Catharanthus roseus (L.)*; Brossi, A., Suffness, M., Eds.; Academic Press: San Diego, 1990; Vol. 37.

(3) Tokuyama, H.; Yamashita, T.; Reding, M. T.; Kaburagi, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 3791.

(4) Total syntheses: (a) Büchi, G.; Kulsa, P.; Ogasawara, K.; Rosati, R. L. *J. Am. Chem. Soc.* **1970**, *92*, 999. (b) Kutney, J. P.; Bylsma, F. *Helv. Chim. Acta* **1975**, *58*, 1672. (c) Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y. *Heterocycles* **1980**, *14*, 1457. (d) Marazano, C.; LeGoff, M.; Fourrey, J.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1981**, 389. (e) Raucher, S.; Bray, B. L. *J. Org. Chem.* **1985**, *50*, 3236. (f) Kuehne, M. E.; Bornmann, W. G.; Earley, W. G.; Marko, I. *J. Org. Chem.* **1986**, *51*, 2913. (g) Raucher, S.; Bray, B. L.; Lawrence, R. F. *J. Am. Chem. Soc.* **1987**, *109*, 442. (h) Szántay, C.; Bölcskei, H.; Gács-Baitz, E. *Tetrahedron* **1990**, *46*, 1711.

(5) Formal syntheses: (a) Trost, B. M.; Godleski, S. A.; Belletire, J. L. *J. Org. Chem.* **1979**, *44*, 2052. (b) Imanishi, T.; Shin, H.; Yagi, N.; Hanaoka, M. *Tetrahedron Lett.* **1980**, *21*, 3285. (c) Imanishi, T.; Yagi, N.; Shin, H.; Hanaoka, M. *Chem. Pharm. Bull.* **1982**, *30*, 4052.

(6) Only one account of a nonracemic synthesis of **1**, via resolution, has been published (see ref 4h).

(7) All of the syntheses listed in refs 4 and 5 utilize 2-indoleacetic acid or tryptamine as their indole source, except ref 4d, which begins with thioxindole.

10.1021/ol990749i CCC: $18.00
Published on Web 09/08/1999

methods for the formation of some of the key bonds in the desired polycyclic framework.[8]

The advent of our new indole construction methodology allowed us to envision a completely stereocontrolled route to **1** that would culminate in the intramolecular alkylation of a fully functionalized, highly preorganized molecule such as **2** (Figure 1). This precursor would be available from a

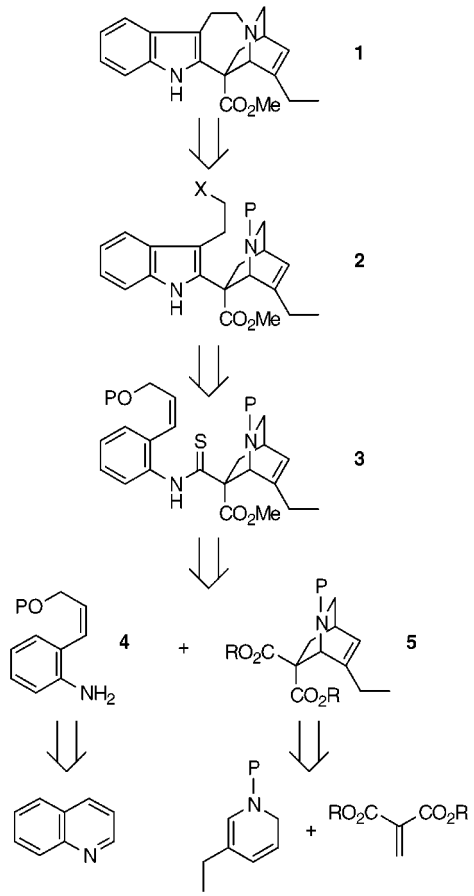
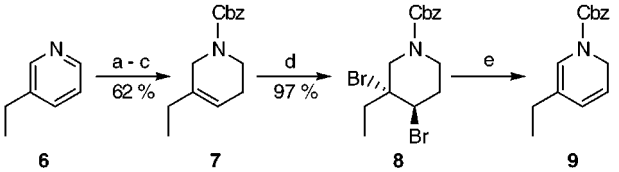


Figure 1. Retrosynthetic analysis of catharanthine.

late-stage radical-mediated indole formation reaction carried out upon a 2-alkenylthioanilide similar to **3**. The left and right halves of **3** could be joined by selective amide bond formation between fragments **4** and **5**. The *cis*-2-alkenyl aniline **4** was available in a three-step sequence from quinoline,[9] while the two carboxyl groups present in **5** could be differentiated by means of a chemoselective, reversible halolactonization reaction. The isoquinuclidine skeleton of **5** could most easily be assembled by a regioselective Diels–Alder reaction. The successful realization of this strategy is disclosed herein.

Our synthesis begins with the construction of the desired diene **9** from commercially available 3-ethylpyridine (**6**) by means of a high-yielding multistep sequence similar to one used by Szántay (Scheme 1).[10] Pyridine **6** was benzylated

Scheme 1. Diene Synthesis

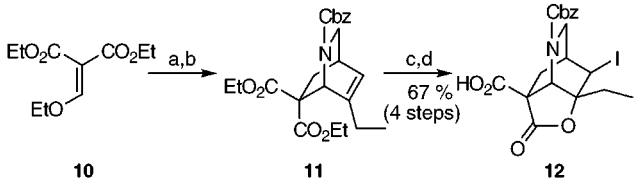


Key: (a) BnBr, 0 °C to rt, >99%; (b) $NaBH_4$, EtOH, 0 °C to rt; (c) CbzCl, benzene, reflux, 62% (2 steps); (d) Br_2, CH_2Cl_2, rt, 97%; (e) DABCO, MeCN, reflux.

in quantitative yield and then reduced to the corresponding tetrahydropyridine. The benzyl group was replaced by a benzyl carbamate to give **7** in 62% overall yield from the pyridinium salt. The trisubstituted double bond was then brominated in 97% yield to afford *trans*-dibromide **8**. This compound was treated with DABCO to afford the desired diene **9** which was predictably somewhat oxygen-sensitive.[11] Diene **9** was thus immediately carried on without further purification.

Several earlier syntheses of our target have made use of the regioselective Diels–Alder reaction of dienes such as **9** and 1,1-heterodisubstituted acrylates.[4,5] This choice has generally led to diastereomeric mixtures of cyclized products due to imperfect *exo*/*endo* selectivity. To avoid this difficulty, we chose to use a 1,1-homodisubstituted acrylate dienophile, i.e., diethyl methylenemalonate. This compound, while known, readily polymerizes even at low temperature.[12] We found that the desired dienophile could be generated in situ from diethyl ethoxymethylmalonate, easily obtained by hydrogenation of commercially available diethyl ethoxymethylenemalonate at atmospheric pressure over palladium on carbon (**10**, Scheme 2). The saturated product was quite

Scheme 2. Synthesis of the Right-Hand Side of Catharanthine



Key: (a) H_2, Pd/C, EtOAc, rt, quant.; (b) **9**, neat, 100 °C; (c) KOH, H_2O/EtOH, reflux; (d) I_2, $NaHCO_3$, H_2O, rt, 67% (4 steps from **8**).

stable at room temperature and could be stored indefinitely at −25 °C. However, reaction with **9** at 100 °C under argon

(8) For example, see refs 4e, g, and h.

(9) Aniline **4** can also be constructed by a longer (though more flexible) route involving the use of palladium-mediated coupling reactions; see ref 3 for details.

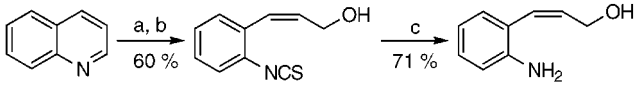
(10) See ref 4h.

(11) Compound **9** could be handled briefly (<1 h) in air and was stable to *neutral* aqueous workup. Exposure to air over longer periods resulted in decomposition.

effected elimination of ethanol followed by cycloaddition to afford the desired diester isoquinuclidine **11** with complete regioselectivity.[13] The diester was saponified, and the resulting diacid was then chemoselectively iodolactonized under kinetic conditions to give the desired *endo*-lactone **12** in 67% overall yield for the four steps from dibromide **8**.[14]

Having successfully assembled the right-hand building block of catharanthine, we moved next to the construction of the left-hand portion. A modified literature procedure for the deannulation of quinoline afforded the desired *cis*-2-alkenyl aniline **15** in 42% overall yield as a single diastereomer (Scheme 3).[15] The *cis*-olefin was selected in preference to the *trans* isomer in light of our earlier observation that *cis* olefins react more efficiently in the indole-forming reaction.[3]

Scheme 3. Synthesis of the Left-Hand 2-Alkenylaniline

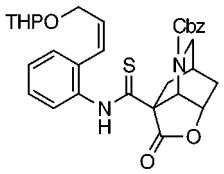


13 **14** **15**

Key: (a) thiophosgene, $BaCO_3$, CH_2Cl_2/H_2O, 0 °C; (b) $NaBH_4$, $MeOH/CH_2Cl_2$, -15 °C, 60% (2 steps); (c) KOH, H_2O/t-BuOH, reflux, 71%.

Following completion of the right- and left-hand catharanthine precursors, the two fragments were joined using standard carbodiimide coupling conditions (Scheme 4). After protection of the free primary alcohol to afford anilide iodolactone **16** in 74% yield over two steps, iodolactonization was reversed by treatment with zinc and acetic acid, followed by immediate esterification of the free carboxylic acid with diazomethane. This procedure regenerated the alkene while also supplying the requisite methyl ester, providing compound **17** in 83% yield. Anilide ester **17** was then treated with Lawesson's reagent in refluxing toluene to selectively afford the desired radical cyclization precursor, 2-alkenylthioanilide **18**, in 86% yield.

We observed in earlier work that an analogue of **18** which bore an adamantyl group in place of the isoquinuclidine cyclized only with difficulty in the presence of triethylborane and tributyltin hydride, and then in low (~30%) yield.[3] However, a model study indicated that the cyclization of compound **21** (Figure 2) could successfully be carried out



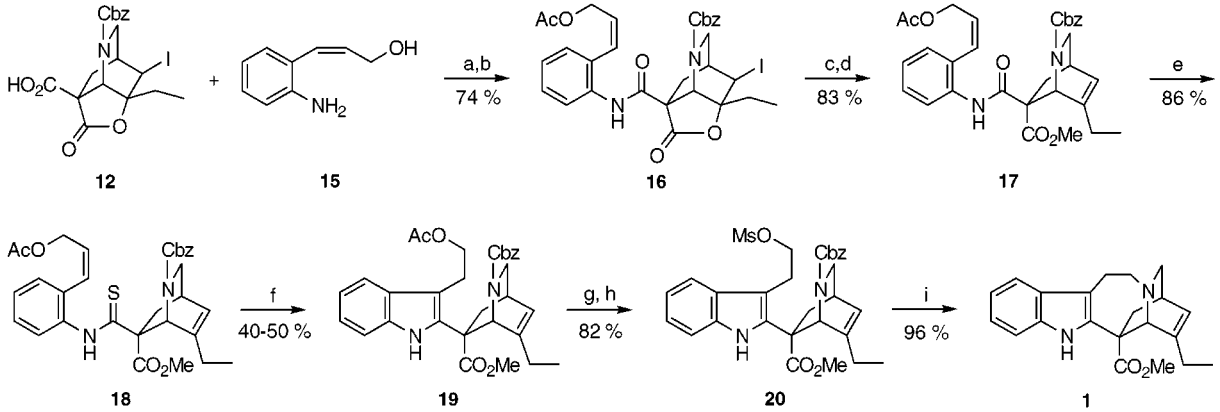
21

Figure 2. Model radical cyclization precursor.

in moderate (~55%) yield under these same conditions.[16] Unfortunately, treatment of **18** with tributyltin hydride in the presence of triethylborane afforded only low and variable yields (12−22%) of the desired indole **19**, even with slow, inverse addition of the tin reagent.

The reasons for the failure of substrate **18** to efficiently cyclize under these conditions are not well understood. The proposed mechanism of this reaction suggests that the rate of initial radical attack on the thiocarbonyl, the steric bulk of the thiocarbonyl-bearing substituent, and facile reduction of the ultimately formed secondary radical are all contributing factors.[3] We speculate that the steric requirements of the isoquinuclidine fragment in **18** are sufficiently different from those in **21** to prevent efficient cyclization under "standard" tin−hydride conditions. Especially, we note that the lacton-

Scheme 4. Total Synthesis of Catharanthine



12 **15** **16** **17**

18 **19** **20** **1**

Key: (a) Water-soluble carbodiimide, NEt_3, CH_2Cl_2, rt; (b) Ac_2O, pyridine, 74% (2 steps); (c) Zn, HOAc, CH_2Cl_2, rt; (d) CH_2N_2, Et_2O/CH_2Cl_2, rt, 83% (2 steps); (e) Lawesson's Reagent, toluene, reflux, 86%; (f) AIBN, H_3PO_2, NEt_3, 1-propanol/H_2O, 90 °C, 40-50%; (g) K_2CO_3, MeOH, rt; (h) MsCl, NEt_3, CH_2Cl_2, rt, 82% (2 steps); (i) $HSiEt_3$, $Pd(OAc)_2$, NEt_3, EtOH/EtOAc, rt, 96%.

ized ester in **21** could reasonably be expected to be sterically less encumbering than the untethered methyl ester in **18**.

An alternative set of tin−free radical cyclization conditions were noted in our initial report, which involve the use of a phosphorus-based hydrogen atom donor.[3,17] A marked improvement in yield was noted when these conditions were used with substrate **18**. Cyclization initiated with stoichiometric AIBN in the presence of excess aqueous hypophosphorous acid and triethylamine in refluxing 1-propanol reliably afforded the desired indole **19** in 40−50% yield. Further attempts to improve the yield of this reaction by altering the solvent, radical initiator, temperature, and hydrogen donor were unsuccessful. We therefore carried out the cyclization of **18** on a 0.75 mmol scale under the aforementioned conditions to obtain indole **19** in 50% yield.

Having completed the crucial indole cyclization, the final steps of the synthesis proceeded smoothly. The acetate in **19** was replaced with a mesylate to give **20** in 82% yield over two steps, and the benzyl carbamate was then removed under mild and highly selective conditions[18] to directly afford (±)-catharanthine (**1**) in 96% isolated yield.[19] As planned, the desired intramolecular S_N2 alkylation ensued efficiently from carbamate cleavage due to the highly rigid nature of the surrounding molecular framework.[20]

In summary, our newly disclosed radical-mediated cyclization reaction for the formation of indoles has been successfully applied to a completely stereocontrolled total synthesis of (±)-catharanthine. The modular, convergent nature of this methodology provides synthetic flexibility and opens the door for the controlled construction of analogues of this important drug precursor. Further application of this methodology to related indole alkaloids is under way in our laboratories and will be reported in due course.

Acknowledgment. This work was supported in part by the Japanese Ministry of Education, Sports and Culture. M.T.R. gratefully acknowledges the support of a Japan Science and Technology Corporation fellowship. We thank Professor H. Tokuyama for insightful discussions and suggestions.

Supporting Information Available: Experimental details for the synthesis of intermediates **7**−**9**, **11**, **12**, **14**−**20**, and (±)-catharanthine (**1**), as well as spectroscopic data for selected compounds. This information is available free of charge via the Internet at http://pubs.acs.org/.

OL990749I

(12) Feely, W.; Boekelheide, V. In *Organic Syntheses, Collective Volume IV*, Rabjohn, N., Ed.; Wiley: New York, 1963; p 298. The reference calls for hydrogenation over Raney nickel at 1000 psi and 45 °C. This procedure results in the formation of appreciable amounts (∼20%) of diethyl methylmalonate from in situ elimination of ethanol and subsequent hydrogenation. The milder conditions reported here afford the desired compound in greater than 90% purity (by ^{1}H NMR integration).

(13) The other possible regioisomer was not detected in the crude reaction mixture.

(14) Compound **11** typically retains a small amount of polymeric esters (derived from excess starting material) after a single chromatography, while the derived diacid is a highly viscous oil from which solvent can be completely removed only with difficulty. These compounds were carried forward as obtained to iodolactone **12**.

(15) Hull, R. *J. Chem. Soc. (C)* **1968**, 1777. We have found that Na_2CO_3 can be used in place of the barium salt used here. (Ueda, T.; Fukuyama, T. Unpublished results.)

(16) Reding, M. T.; Fukuyama, T. Unpublished results.

(17) In a report published concurrently with our previous paper, Murphy and co-workers showed that 1-ethylpiperidine hypophosphite was an effective hydrogen atom source in a radical-mediated ring-forming reaction: Graham, S. R.; Murphy, J. A.; Coates, D. *Tetrahedron Lett.* **1999**, *40*, 2415.

(18) (a) Sakaitani, M. S.; Hori, K.; Ohfune, Y. *Tetrahedron Lett.* **1988**, *29*, 2983. (b) Sakaitani, M. S.; Ohfune, Y. *J. Org. Chem.*, **1990**, *55*, 870. We noted earlier that hydrogenation of compound **12** over palladium on carbon resulted in the saturation of the olefin as well as cleavage of the Cbz group. (Reding, M. T.; Fukuyama, T. Unpublished results.)

(19) The analytical data of the material obtained by this route was in accord with that reported in the literature for (±)-catharanthine (ref 4f).

(20) Proton NMR measurements of the indole NH chemical shift in compounds **19** and **20** show the signal as a broad singlet at abnormally high values (near 10 ppm downfield from TMS), indicating possible intramolecular hydrogen bond donation to the adjacent carboxyl group. Such a bond would be expected to enhance the desired alkylation reaction by further predisposing the molecule to a favorable conformation. Interestingly, the chemical shift for the analogous proton in **1** is found near 7.7 ppm, a relatively normal value.