Stereoselective Synthesis

A Stereodivergent Synthesis of Virantmycin by an Enzyme-Mediated Diester Desymmetrization and a Highly Hindered Aryl Amination**

Thomas G. Back and Jeremy E. Wulff*

(−)-Virantmycin (**1**) is an unusual chlorinated tetrahydroquinoline that was isolated from a strain of *Streptomyces nitrosporeus* in 1980.[1] It was found to possess both strong inhibitory activity against RNA and DNA viruses, and antifungal activity.[2] The initial structure elucidation of virantmycin was reported in the 1980s,[2,3] but not until 1990 was the correct stereochemistry established by NMR methods,[4] and later confirmed by synthesis.[5] To date, racemic syntheses of **1** have been completed by Hill and Raphael,[6] Morimoto, Shirahama et al.,[5,7] and by Steinhagen and Corey.[8] The preparation of the (+)-antipode of the naturally occurring antibiotic has also been reported.[9] Very recently, Kogen et al. achieved the first enantioselective synthesis of (−)-**1** from (*S*)-indoline-2-carboxylic acid.[10] The latter report prompted us to disclose our own efforts in this area, which have resulted in a stereodivergent route to both (+)-**1** and (−)-**1**.

The principal challenge in the synthesis of virantmycin involves the stereoselective construction of the two contiguous stereocenters, which include the quaternary carbon atom at C2. Our plan was to construct the latter center by the desymmetrization of a key intermediate diester **2** by an enzyme-mediated partial hydrolysis. After appending the aryl moiety by a Claisen-like condensation, we envisaged the stereoselective introduction of the amino group to the highly hindered stereocenter by a Curtius rearrangement and ring-closure to complete the tetrahydroquinoline skeleton by an intramolecular aryl amination reaction (Scheme 1).

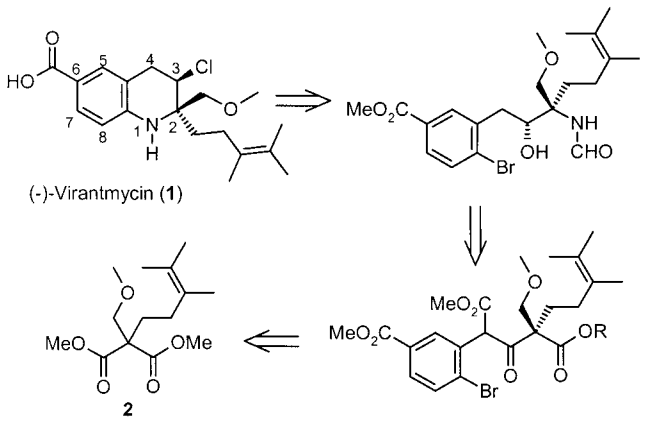
Diester **2** was readily obtained by sequential alkylation of the enolate derived from dimethyl malonate by using NaH with 5-iodo-2,3-dimethyl-2-pentene[11] and methoxymethyl chloride. Scheme 2 illustrates the desymmetrization of **2**, which was achieved by partial hydrolysis with porcine liver esterase (PLE)[12] to afford the half-ester **3** in 89% yield and 95% *ee*, as determined by integration of the NMR spectrum of the salt formed from **3** and (*S*)-(−)-α-methylbenzylamine.

[*] Prof. Dr. T. G. Back, J. E. Wulff
Department of Chemistry
University of Calgary
Calgary, AB, T2N 1N4 (Canada)
Fax: (+1) 403-289-9488
E-mail: tgback@ucalgary.ca

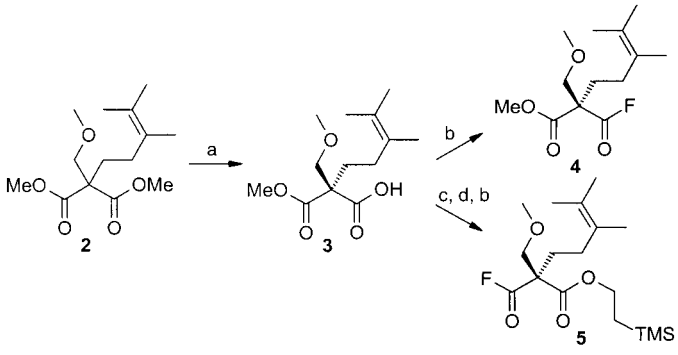
[**] We thank the Natural Sciences and Engineering Research Council of Canada (NSERC) for financial support. J.E.W. thanks, the NSERC, the Alberta Heritage Foundation for Medical Research, and the Izaak Walton Killam Foundation for Postgraduate Scholarships. We thank Dr. B. A. Keay for helpful discussions and a generous gift of BINAPFu.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

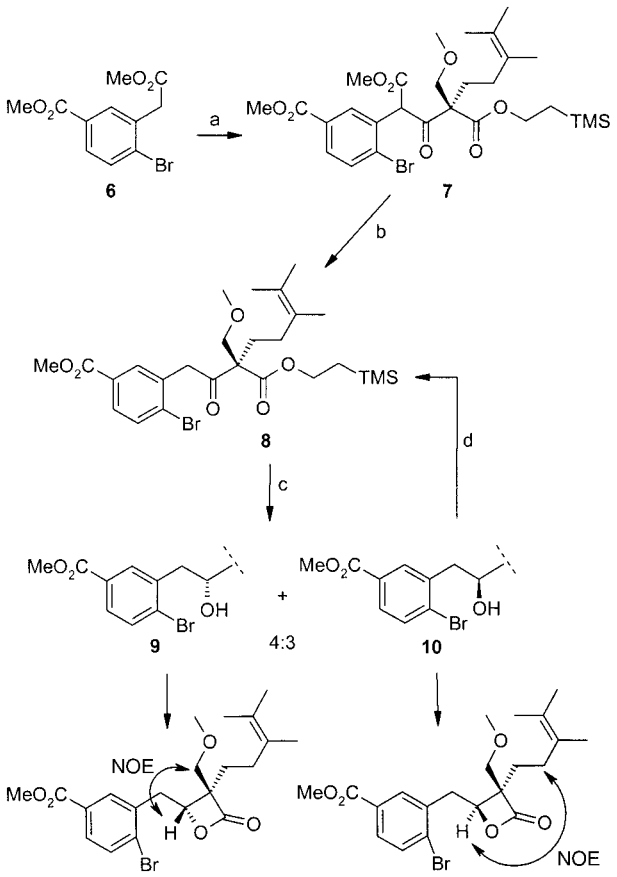
 DOI: 10.1002/ange.200461327



Scheme 1. Retrosynthesis of (−)-virantmycin (**1**).



Scheme 2. Desymmetrization of diester **2** to generate chiral intermediates **4** and **5**: a) porcine liver esterase (PLE), DMSO-pH 8.0 phosphate buffer (1:4), 7 days, RT, 89%, 95% *ee*; b) cyanuric fluoride, pyridine, dichloromethane, 1 h, 0°C, 71% for **4** and 75% for **5**; c) 2-(trimethylsilyl)ethanol, 1,3-dicyclohexylcarbodiimide (DCC), *N*,*N*-dimethylaminopyridine (DMAP), dichloromethane, 3 days, RT, 77%; d) 10% aqueous KOH, methanol, 15 h, 45°C, 88% (based on 20% of recovered **3**.

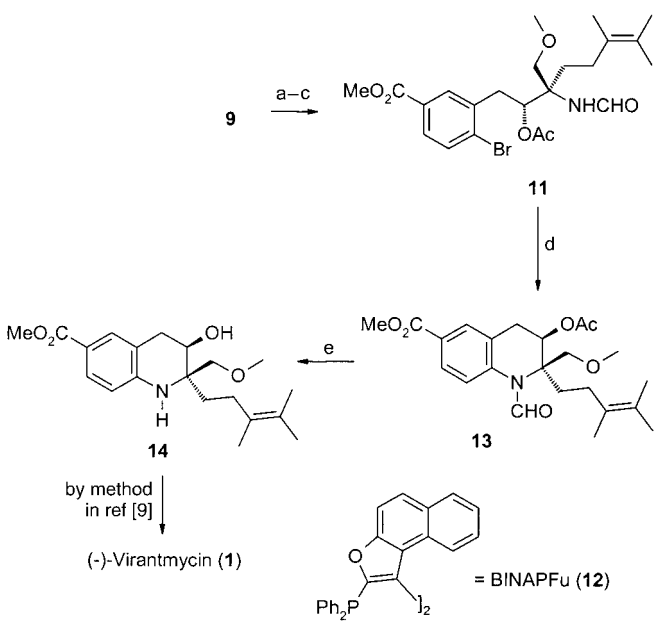


Scheme 3. Coupling of diester **6** with chiral intermediate **5**: a) lithium hexamethyldisilazide (LiHMDS), Et_2O, 0°C, 10 min; then **5**, Et_2O, 1 h at 0°C→20 h at RT, 63%; b) 10% aqueous NaCl, DMSO, 20 h, 125°C, 78%; c) $NaBH_4$, methanol, 2.5 h, 0°C, 83%; d) pyridinium chlorochromate (PCC), dichloromethane, 3 days, RT, 77%.

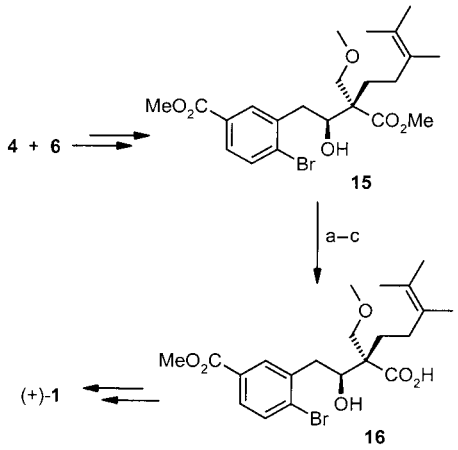
The absolute configuration of **3** was assumed to be (*S*) on the basis of earlier studies[12b,c] of PLE-mediated hydrolyses of other β-diesters, and this assignment was confirmed unequivocally by the ultimate conversion of **3** to essentially pure enantiomers of the final products. Thus, half-ester **3** was converted separately into each of the pseudo-enantiomeric acyl fluorides **4** and **5** (Scheme 2),[13] which in turn served as respective precursors of (+)-**1** and (−)-**1**. Acylation of the enolate of diester **6**[14] with **5** afforded triester **7** (Scheme 3), which was subjected to selective Krapcho decarboxylation[15] of the less hindered β-keto ester moiety to furnish **8**. The reduction of the ketone group of **8**, which was required to introduce a hydroxy group to serve as the chlorination site for the final product, resulted in poor stereoselectivity under a variety of conditions. However, the undesired epimer **10** was easily separated from **9** and recycled back to ketone **8** with PCC. The configurations of epimers **9** and **10** were assigned on the basis of NOE experiments conducted on the corresponding β-lactones (Scheme 3).

Alcohol **9** was acetylated and the trimethylsilylethyl ester was selectively removed with fluoride ion. The resulting carboxylic acid was subjected to a Curtius rearrangement mediated by diphenylphosphoryl azide (DPPA),[16] followed by workup with sodium borohydride, to afford formamide **11** (Scheme 4). The crucial intramolecular Buchwald–Hartwig aryl amination[17] step was then attempted under a variety of conditions, with generally unsatisfactory results. However, we were pleased to discover that the treatment of formamide **11** with $[Pd_2(dba)_3]$ in the presence of the Keay ligand BINAPFu (**12**)[18] under the conditions shown in Scheme 4 resulted in quantitative cyclization to **13**.

The selection of BINAPFu as the Pd ligand of choice was based on model studies of the aryl aminations of other α-quaternary amines (1-adamantylamine and methyl α,α-dimethylglycinate) with methyl 4-bromo-3-methylbenzoate. Other ligands, such as BINAP,[19a] DPPF,[19b] PCy_3,[19c] *o*-biphenyl-PCy_2,[19d] *o*-biphenyl-P*t*Bu_2,[19d] DPEphos,[19e] MAP,[19f] and IMES hydrochloride[19g] failed to effect coupling or produced very low yields of the corresponding aryl amines under a wide variety of conditions. The successful intramolecular aryl amination of formamide **11** using the BINAPFu ligand is particularly noteworthy because very few examples of aryl aminations of aliphatic amines containing α-quaternary centers are known.[20] BINAPFu is a less strongly donating ligand than other commonly employed bidentate phosphines such as BINAP.[18] Moreover, the reductive elimination steps



Scheme 4. Synthesis of (−)-virantmycin (1) from intermediate **9**: a) *N*,*N*-dimethylaminopyridine (DMAP), pyridine, acetic anhydride, 3 days, RT; b) 1.0 M tetrabutylammonium fluoride in tetrahydrofuran, 1 h, RT; c) diphenylphosphoryl azide (DPPA), *N*,*N*-dimethylaminopyridine (DMAP), triethylamine, toluene, 2.25 h, reflux; then $NaBH_4$, tetrahydrofuran, 12.5 h, RT, 84% overall yield for steps a–c; d) $[Pd_2(dba)_3]$, **12**, Cs_2CO_3, toluene, 6.5 h, 90 °C, 100%; e) 0.13 M NaOH in methanol, 24 h, RT, 84%.



Scheme 5. Synthesis of (+)-virantmycin from acyl fluoride **4**: a) 10% aqueous KOH, methanol, 20 h, RT; b) NaH, *n*PrSH, HMPA, 4.75 h, RT; c) $SOCl_2$, methanol, 1 h at −10 °C→3 h at reflux, 46% overall yield for steps a–c.

of aryl aminations and related Pd-catalyzed coupling reactions are enhanced by weakly coordinating phosphine ligands.[21] It is therefore possible that reductive elimination is the rate-determining step in the present case because of the high degree of steric hindrance associated with coupling an *ortho*-substituted aryl bromide with an α-quaternary amine derivative. The particular efficacy of BINAPFu may be attributed to its ability to facilitate this step.

Deacetylation and concomitant deformylation of tetrahydroquinoline **13** provided the free alcohol **14**, which was converted into (−)-**1** by the same method used previously by Morimoto and Shirahama[9] in their synthesis of (+)-**1** (Scheme 4). The product displayed NMR spectra consistent with the literature[4,6,9] and gave a specific rotation $[\alpha]_D^{20} = -11°$ ($c = 0.13$, chloroform) that compared favorably with that reported for the natural product: $[\alpha]_D^{24} = -11.1°$ ($c = 0.175$, chloroform).[9]

Finally, acyl fluoride **4** was converted into the unnatural antipode (+)-**1** by a similar process (Scheme 5), except that the aromatic and aliphatic ester moieties of **15** were converted to the free carboxylic acids in **16** by saponification of the former and dealkylation with sodium propanethiolate of the latter, followed by selective reesterification of the aromatic carboxylic acid and Curtius rearrangement of the remaining aliphatic acid (Scheme 5). Completion of the synthesis was achieved as in the case of (−)-**1**. The NMR spectra of the product were identical to those of (−)-**1** and the optical rotation data $[\alpha]_D^{20} = +13°$ ($c = 0.14$, chloroform), compared favourably with the literature value $[\alpha]_D^{24} = +11.2°$ ($c = 0.125$, chloroform).[9]

In conclusion, the present method provides a new route to both enantiomers of the antiviral agent virantmycin (**1**). It employs as key steps a highly enantioselective enzyme-mediated desymmetrization and a remarkably effective intramolecular aryl amination of a hindered α-quaternary aliphatic amine. The procedure is also potentially amenable to the preparation of analogues for the purpose of structure–activity studies.

Received: July 16, 2004

Keywords: aryl amination · enzyme catalysis · esterases · natural products · total synthesis

[1] S. Ōmura, A. Nakagawa, H. Hashimoto, R. Oiwa, Y. Iwai, A. Hirano, N. Shibukawa, Y. Kojima, *J. Antibiot.* **1980**, *33*, 1395.
[2] A. Nakagawa, Y. Iwai, H. Hashimoto, N. Miyazaki, R. Oiwa, Y. Takahashi, A. Hirano, N. Shibukawa, Y. Kojima, S. Ōmura, *J. Antibiot.* **1981**, *34*, 1408.
[3] Y. Morimoto, K. Oda, H. Shirahama, T. Matsumoto, S. Ōmura, *Chem. Lett.* **1988**, 909.
[4] C. M. Pearce, J. K. M. Sanders, *J. Chem. Soc. Perkin Trans. 1* **1990**, 409.
[5] Y. Morimoto, F. Matsuda, H. Shirahama, *Synlett* **1991**, 202.
[6] a) M. L. Hill, R. A. Raphael, *Tetrahedron Lett.* **1986**, *27*, 1293; b) M. L. Hill, R. A. Raphael, *Tetrahedron* **1990**, *46*, 4587.
[7] Y. Morimoto, F. Matsuda, H. Shirahama, *Tetrahedron* **1996**, *52*, 10609.
[8] H. Steinhagen, E. J. Corey, *Org. Lett.* **1999**, *1*, 823.
[9] Y. Morimoto, H. Shirahama, *Tetrahedron* **1996**, *52*, 10631.
[10] M. Ori, N. Toda, K. Takami, K. Tago, H. Kogen, *Angew. Chem.* **2003**, *115*, 2644; *Angew. Chem. Int. Ed.* **2003**, *42*, 2540.
[11] a) T. G. Back, R. J. Bethell, M. Parvez, D. Wehrli, *J. Org. Chem.* **1998**, *63*, 7908; b) A. N. De Silva, C. L. Francis, A. D. Ward, *Aust. J. Chem.* **1993**, *46*, 1657.
[12] a) For a general review, see: H. G. Davies, R. H. Green, D. R. Kelly, S. M. Roberts, *Biotransformations in Preparative Organic Chemistry*, Academic Press, London, **1989**, chap. 2; b) F. Björk-

ling, J. Boutelje, S. Gatenbeck, K. Hult, T. Norin, P. Szmulik, *Tetrahedron* **1985**, *41*, 1347; c) E. J. Toone, M. J. Werth, J. B. Jones, *J. Am. Chem. Soc.* **1990**, *112*, 4946.

[13] The acyl fluorides were prepared by the general method of: S. Groβ, S. Laabs, A. Scherrmann, A. Sudau, N. Zhang, U. Nubbemeyer, *J. Prakt. Chem.* **2000**, *342*, 711.

[14] Diester **6** was prepared by treatment of methyl 4-bromo-3-bromomethylbenzoate with NaCN, followed by alkaline hydrolysis of the corresponding benzyl nitrile and Fischer esterification with methanol.

[15] A. P. Krapcho, A. J. Lovey, *Tetrahedron Lett.* **1973**, 957.

[16] T. Shioiri, K. Ninomiya, S. Yamada, *J. Am. Chem. Soc.* **1972**, *94*, 6203.

[17] For selected reviews, see: a) J. P. Wolfe, S. Wagaw, J.-F. Marcoux, S. L. Buchwald, *Acc. Chem. Res.* **1998**, *31*, 805; b) J. F. Hartwig, *Acc. Chem. Res.* **1998**, *31*, 852; c) J. F. Hartwig in *Handbook of Organopalladium Chemistry for Organic Synthesis*, *Vol. 1* (Ed.: E. Negishi), Wiley, Hoboken, NJ, **2002**, pp. 1051 – 1096.

[18] a) N. G. Andersen, M. Parvez, R. McDonald, B. A. Keay, *Can. J. Chem.* **2004**, *82*, 145; b) for a review of 2-furylphosphine ligands in transition-metal-mediated reactions, see: N. G. Andersen, B. A. Keay, *Chem. Rev.* **2001**, *101*, 997.

[19] a) BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl: J. P. Wolfe, S. Wagaw, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 7215; b) DPPF = 1,1′-bis(diphenylphosphanyl)ferrocene: M. S. Driver, J. F. Hartwig, *J. Am. Chem. Soc.* **1996**, *118*, 7217; c) PCy_3: N. P. Reddy, M. Tanaka, *Tetrahedron Lett.* **1997**, *38*, 4807; d) *o*-biphenylPCy_2 and *o*-biphenyl$PtBu_2$: J. P. Wolfe, H. Tomori, J. P. Sadighi, J. Yin, S. L. Buchwald, *J. Org. Chem.* **2000**, *65*, 1158; e) DPEphos = 2,2′-bis(diphenylphosphanyl)-1,1′-diphenyl ether: J. P. Sadighi, M. C. Harris, S. L. Buchwald, *Tetrahedron Lett.* **1998**, *39*, 5327; f) MAP = 2′-dimethylamino-2-(diphenylphosphanyl)-1,1′-binaphthalene: S. Vyskočil, M. Smrčina, P. Kočovský, *Tetrahedron Lett.* **1998**, *39*, 9289; g) IMES hydrochloride = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene hydrochloride: G. A. Grasa, M. S. Viciu, J. Huang, S. P. Nolan, *J. Org. Chem.* **2001**, *66*, 7729.

[20] For an aryl amination with *tert*-butylamine, see: a) H. Siebeneicher, I. Bytschkov, S. Doye, *Angew. Chem.* **2003**, *115*, 3151; *Angew. Chem. Int. Ed.* **2003**, *42*, 3042; b) I. Bytschkov, H. Siebeneicher, S. Doye, *Eur. J. Org. Chem.* **2003**, 2888; for an aryl amination with *N-tert*-butylaniline, see: c) M. Prashad, X. Y. Mak, Y. Liu, O. Repič, *J. Org. Chem.* **2003**, *68*, 1163.

[21] G. Mann, Q. Shelby, A. H. Roy, J. F. Hartwig, *Organometallics* **2003**, *22*, 2775.

