Total Synthesis of the Potent Antitumor Agent Roseophilin: A Concise Approach to the Macrotricyclic Core

Alois Fürstner*,† and Holger Weintritt

Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1, D-45470 Mülheim/Ruhr, Germany

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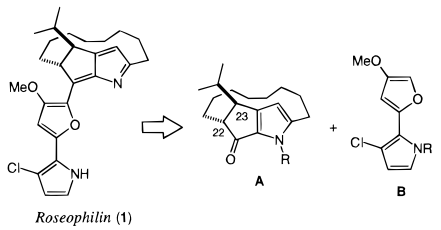
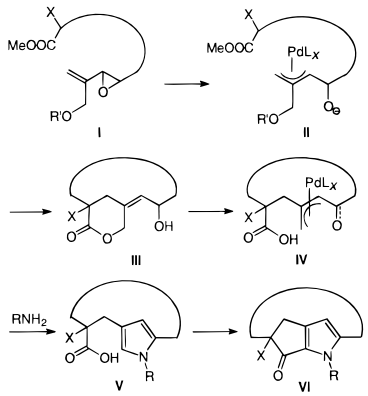
Roseophilin (**1**), a structurally unique metabolite isolated from a culture broth of *Streptomyces griseoviridis*, exhibits cytotoxicity against several human epidermoid and leukemia cell lines in the submicromolar range.[1,2] This very promising biological profile renders **1** a new lead compound in the search for antitumor agents and a rewarding target for total synthesis. Obviously, the major challenge toward this end is the preparation of segment **A**, which when condensed with the known heterocyclic ring system **B**[2a] according to literature procedures[2a,3] will afford the desired *ansa*-bridged 1-azafulvene core of the natural product (Scheme 1). As part of our endeavors in the synthesis of physiologically active compounds[4] we now disclose a concise and highly flexible approach to this intricate macrotricyclic skeleton which may easily be adapted to the synthesis of analogues as well.

Our plan is guided by the idea to effect the macrocyclization such that it also sets the stage for a convenient construction of the ketopyrrolic entity of the target. Based on the subtle differences in reactivity of various allylic precursors in palladium catalyzed substitution reactions,[5] we perceived a well-orchestrated manifold for this very purpose (Scheme 2). Driven by the release of the ring strain, the oxidative addition of Pd(0) into a difunctional substrate of the general type **I** will regioselectively occur at the vinyloxirane site,[6] provided that the allylic OR′ group is properly tuned. The alkoxide **II** thus formed deprotonates the tethered prenucleophile of the malonate type which will attack the allylpalladium complex and lead to the formation of a macrocyclic ring according to literature precedence.[7] By taking advantage of the juxtaposition of the OR′ group and the incoming ester, a simple lactonization of these entities activates the remaining allylic position. A second palladium-catalyzed reaction with an amine as the nucleophile may then not only deliver the desired pyrrole ring encoded in the 1,4-dioxygen functionality of the substrate (**III** → **IV** → **V**)[8] but also will liberate the acid for an ensuing acylation of its C-2 position (**V** → **VI**).

Scheme 1



Scheme 2



This concept was reduced to practice as shown in Scheme 3. O-Silylation of the known alcohol **2**[9] with TBDMSCl, followed by a chloride for iodide exchange and subsequent reaction of the rather unstable allylic iodide with tetrahydrothiophene in the presence of $AgBF_4$ in thoroughly dried acetone, afforded the nicely crystalline sulfonium salt **4** in good overall yield.[10] Its deprotonation with *t*-BuLi in THF at −78 °C followed by trapping of the sulfur ylide[11] formed in situ with 9-bromononanal[12] gave the desired vinyloxirane **5** in 84% isolated yield which can be alkylated with methyl (phenylsulfonyl)acetate in DMF under standard conditions at the bromide terminus without affecting the labile functionality at the other end of the chain.[7] This simple sequence provided gram amounts of compound **6** which is suitable to test the palladium-manifold outlined above as the key strategic element of our synthesis plan.

Gratifyingly, substrate **6** cyclized smoothly to the 13-membered carbocyclic ring **7** in very well reproducible 85% isolated yield when slowly added to a refluxing solution of

† Tel. Int. 208-306-2372. Fax: Int. 208-306-2980.

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(2) For synthetic studies on roseophilin segments or model compounds, see: (a) Nakatani, S.; Kirihara, M.; Yamada, K.; Terashima, S. *Tetrahedron Lett*. **1995**, *36*, 8461−8464. (b) Kim, S. H.; Fuchs, P. L. *Tetrahedron Lett.* **1996**, *37*, 2545−2548.

(3) The prodigiosin tripyrrole pigments are the closest relatives to roseophilin. Similar condensation reactions have been used for their synthesis, c.f.: (a) Wasserman, H. H.; Keith, D. D.; Nadelson, J. *J. Am. Chem. Soc.* **1969**, *91*, 1264−1265. (b) Boger, D. L.; Patel, M. *J. Org. Chem*. **1988**, *53*, 1405−1415. (c) Wasserman, H. H.; Lombardo, L. J. *Tetrahedron Lett*. **1989**, 1725−1728. (d) Rapoport, H.; Holden, K. G. *J. Am. Chem. Soc*. **1962**, *84*, 635−642. (e) D'Alessio, R.; Rossi, A. *Synlett* **1996**, 513−514 and lit. cited.

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(5) Review: Tsuji, J. *Palladium Reagents and Catalysts*; Wiley, New York, 1995.

(6) (a) Trost, B. M.; Molander, G. A. *J. Am. Chem. Soc*. **1981**, *103*, 5969−5972. (b) Tsuji, J.; Kataoka, H.; Kobayashi, Y. *Tetrahedron Lett*. **1981**, *22*, 2575−2578.

(7) See the following for leading references: (a) Trost, B. M.; Warner, R. W. *J. Am. Chem. Soc*. **1982**, *104*, 6112−6114. (b) Trost, B. M.; Warner, R. W. *J. Am. Chem. Soc*. **1983**, *105*, 5940−5942. (c) Kende, A. S.; Kaldor, I.; Aslanian, R. *J. Am. Chem. Soc*. **1988**, *110*, 6265−6266. (d) Trost, B. M.; Hane, J. T.; Metz, P. *Tetrahedron Lett*. **1986**, *27*, 5695−5698. (e) Review: Trost, B. M. *Angew. Chem*. **1989**, *101*, 1199−1219.

(8) (a) For another palladium-catalyzed pyrrole synthesis, see: Trost, B. M.; Keinan, E. *J. Org. Chem*. **1980**, *45*, 2741−2746. (b) For a timely compilation of pyrrole chemistry, see: Gossauer, A. in *Houben-Weyl, Methoden der Organischen Chemie*; Kreher, R. R., Ed.; Thieme: Stuttgart, 1994; Vol. E 6a, Part 1, pp 556−798.

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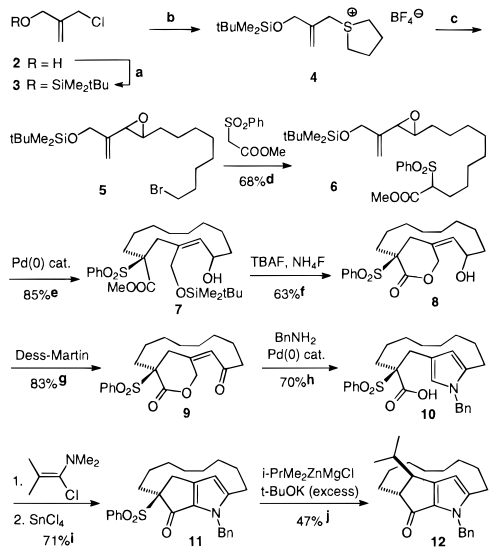
(10) Rosenberger, M.; Newkom, C., Aig, E. R. *J. Am. Chem. Soc*. **1983**, *105*, 3656−3661. Since the excess of tetrahydrothiophene can be removed *in vacuo*, this sulfide is preferred over the non-volatile PhSPh[11a] for practical reasons.

(11) (a) *t*-BuLi was recommended as the deprotonating agent of choice, c.f.: LaRochelle, R. W.; Trost, B. M.; Krepski, L. *J. Org. Chem*. **1971**, *36*, 1126−1136. (b) Review: Trost, B. M.; Melvin, L. S. *Sulfur Ylides*; Academic Press: New York, Organic Chemistry Series, 1975; Vol. 31.

(12) Obtained in 78% yield by oxidation of commercially available 9-bromo-1-nonanol with the Dess−Martin periodinane;[14] the analytical data are in accordance with those reported: Muralikrishna, C.; Dasaradhi, L.; Rao, S. J.; Bhalerao, U. T. *Ind. J. Chem*. **1989**, *28B*, 579−580.

S0002-7863(96)03795-X CCC: $14.00

Scheme 3[a]



[a] Compounds **5**−**9** have been obtained as mixtures of all possible stereoisomers.[13] [a] TBDMSCl, DBU, CH_2Cl_2, room temperature, 90%; [b] (i) NaI, acetone, 50 °C; (ii) tetrahydrothiophene, $AgBF_4$, acetone, room temperature, 73%; [c] *t*-BuLi, then 9-bromononanal, THF, −78 °C → room temperature, 84%; [d] KH, DMF, room temperature; [e] $Pd(PPh_3)_4$ (10 mol %), dppe (20 mol %), THF, reflux; [f] THF, room temperature; [g] Dess−Martin periodinane, CH_2Cl_2, room temperature; [h] $Pd(PPh_3)_4$ (15 mol %), THF, 35 °C; [i] (1) CH_2Cl_2, room temperature; (2) 1,2-dichloroethane, reflux; [j] THF, room temperature.

catalytic amounts of $Pd(PPh_3)_4$ and dppe (dppe = bis(diphenylphosphino)ethane) in THF over a period of 6 h (≈0.0014 M final concentration).[13] The observed, selective activation of the vinyloxirane group was very much in line with our anticipation. It should also be mentioned that the use of polymer-bound Pd(0) precatalysts previously recommended in order to ensure pseudohigh dilution conditions[7a,b] led to significantly lower yields in this crucial macrocyclization step. Desilylation of **7** afforded the somewhat strained lactone **8**. Best results in this pivotal step were obtained in a buffered medium with a mixture of TBAF/NH_4F as the reagents. Oxidation of the OH group with the Dess−Martin periodinane[14] followed by treatment of ketone **9** thus formed with benzylamine in the presence of catalytic amounts of $Pd(PPh_3)_4$ in THF resulted in the clean formation of the desired pyrrole carboxylic acid **10** in 70% isolated yield. The reaction is best carried out at ≈35 °C in order to avoid problems caused by premature base-induced elimination of the sulfone group and/or concomittant decarboxylation of the acid formed. Compound **10** was then converted into the acid chloride under neutral conditions using the highly convenient α-chloroenamine reagent introduced by *Ghosez* et al.[15] Subsequent treatment with $SnCl_4$ in refluxing 1,2-dichloroethane cleanly afforded the tricyclic ketone **11** in 71% yield by an intramolecular Friedel−Crafts acylation. This reaction occurs regioselectively at C-2 rather than C-4 of the pyrrole ring as can be unambiguously deduced from the observed ^nJ(C,H) correlated NMR spectra (for details see Supporting Information).

We envisaged using the sulfone moiety at C-22 (roseophilin numbering, Scheme 1) in order to introduce the missing isopropyl substituent at the adjacent position. A base-induced elimination of $PhSO_2H$ followed by a 1,4-addition of an appropriate nucleophile to the resulting enone may well effect this transformation. Since the shielding excerted by the fairly rigid *ansa*-chain not only provides effective facial guidance in the Michael addition step but also will force the protonation of the resulting enolate to occur from the same side, the proper relative configuration of the newly formed chiral centers at C-22 and C-23 is likely to ensue.

However, our initial attempts along these lines revealed that the tricyclic enone formed upon elimination of the sulfone group with *t*-BuOK in THF at ambient temperature owes a peculiar reactivity to its highly strained character.[16] Since it undergoes immediate dimerization,[17] we faced the problem to effect the crucial elimination step in the presence of an appropriate nucleophile in order to intercept the enone immediately subsequent to its formation. Cuprates turned out to be unsuitable for this purpose because of their insufficient thermal stability and their poor reactivity in the presence of excess *t*-BuOK. A viable alternative, however, was found in zincate chemistry.[18] Specifically, addition of an excess of *t*-BuOK to a solution of **11** and *i*-$PrMe_2ZnMgCl$ (formed in situ from $ZnCl_2$·TMEDA, 2MeLi, and *i*-PrMgCl) in THF at ambient temperature afforded the desired product **12** in 47% isolated yield together with some dimeric byproducts. Although this result may likely be further improved, it is respectable in view of the complexity of this specific two-step/one-pot transformation. The structural integrity of **12** was unambiguously assigned by means of extensive 2D NMR investigations. Specifically, the coupling pattern of H-23 in the ^{1}H NMR spectrum at 600 MHz (d, 2.63 ppm) as well as the observed crosspeaks in the ^nJ(C,H) correlated spectra clearly locate the isopropyl group in the cyclopentanone ring rather than in the ansa chain. This rules out that strain and/or antiaromaticity prevent the elimination of the sulfone into the five-membered ring. Moreover, a $^3J_{H22,H23}$ of ≈0 Hz matches that observed in the spectrum of roseophilin itself and pinpoints the proper relative configuration at these chiral centers (for details see Supporting Information).

In summary we have achieved the first synthesis of the intricate macrotricyclic core segment of roseophilin **1** in only 10 efficient steps. Our approach merges the potential of an established palladium-catalyzed macrocyclization reaction with a conceptually new entry into substituted ketopyrroles. Based on this, one may not only gain access to roseophilin itself but also can prepare various analogues of this promising antibiotic for the study of its structure/activity profile. Efforts along these lines as well as the completion of the total synthesis by condensation of **12** with the known heterocyclic side chain[2a] are actively pursued in our laboratory and will be reported in due course.

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Supporting Information Available: Relevant preparative procedures, listing of the spectral and analytical data, and copies of the ^{1}H, ^{13}C, and some 2D NMR spectra of all new compounds (41 pages). See any current masthead page for ordering and Internet access instructions.

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(13) Products **5**−**9** shown in Scheme 3 were obtained as mixtures of all possible diastereoisomers. Since all of them lead to the final product, no attempts were made to separate the individual compounds.

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(15) Devos, A.; Remion, J.; Frisque-Hesbain, A.-M.; Colens, A.; Ghosez, L. *J. Chem. Soc., Chem. Commun.* **1979**, 1180−1181.

(16) The use of other bases and/or lower temperatures in this elimination step were in vain.

(17) The dimeric structure of the product formed ensues from GC/MS analyses of the reaction mixtures. We did not yet investigate the structure of this dimer any further. However, there is some precedence in the recent literature that structurally related heterocyclic ketones exhibit a strong bias for dimerization, c.f.: (a) Comer, M. C.; Despinoy, X. L. M.; Gould, R. O.; McNab, H.; Parsons, S. *J. Chem. Soc., Chem. Commun.* **1996**, 1083−1084. (b) Neidlein, R.; Jeromin, G. *Chem. Ber.* **1982**, *115*, 706−713.

(18) (a) Kjonaas, R. A.; Hoffer, R. K. *J. Org. Chem.* **1988**, *53*, 4133−4135. See also: (b) Kjonaas, R. A.; Vawter, E. J. *J. Org. Chem.* **1986**, *51*, 3993−3996. (c) Morita, Y.; Suzuki, M.; Noyori, R. *J. Org. Chem.* **1989**, *54*, 1785−1787. (d) Isobe, M.; Kondo, S.; Nagasawa, N.; Goto, T. *Chem. Lett.* **1977**, 679−682. For a study on the interaction of organozinc reagents with *t*-BuOK, see: (e) Rathke, M. W.; Yu, H. *J. Org. Chem.* **1972**, *37*, 1732−1734.