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A New Approach to Highly Substituted Cyclopentanoids from a Concise Formal Synthesis of (+)-Roseophilin

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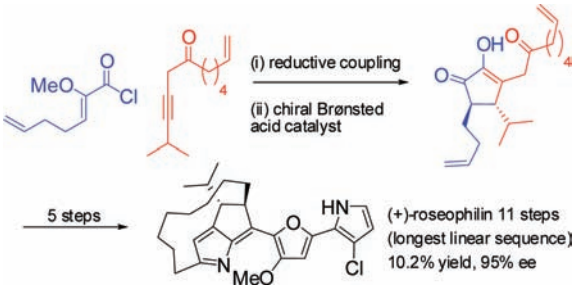
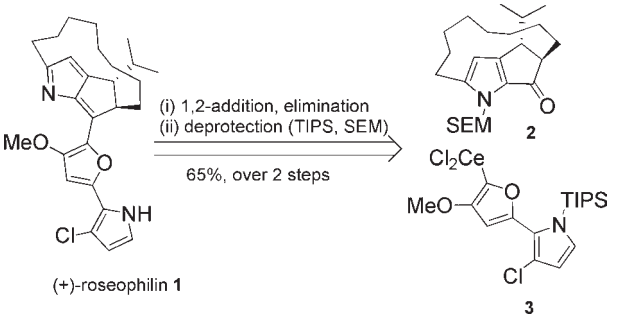
ABSTRACT



A convergent reaction sequence involving a reductive coupling and a chiral Brønsted acid catalyzed Nazarov reaction is utilized in a concise formal synthesis of (+)-roseophilin (11 steps via longest linear sequence, 10.2% yield, 95% ee).

Isolated from *Streptomyces griseoviridis* in 1992, (+)-roseophilin (**1**), is an anticancer natural product that has attracted considerable attention.[1,2] **1** has been shown to inhibit several phosphatases, including Cdc25a, VHR, and PTP1B, all of which are important to cancer cell growth and survival.[2] Interestingly, the unnatural enantiomer, *ent*-**1**, possesses higher potency than **1** against these phosphatases and against several cancer cell lines.[2,3] The unusual *ansa*-bridged, cyclopenta-fused azafulvene core of **1** has inspired a number of synthetic efforts.[4] Two landmark approaches are the first total

Scheme 1. Key Disconnect in the Synthesis of **1**



(1) Hayakawa, Y.; Kawakami, K.; Seto, H.; Furihata, K. *Tetrahedron Lett*. **1992**, *33*, 2701.

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(3) Boger, D. L.; Hong, J. *J. Am. Chem. Soc*. **2001**, *123*, 8515.

(4) For a review, see ref 2a. For asymmetric syntheses of **1**, see ref 3 and: (a) Bamford, S. J.; Luker, T.; Speckamp, W. N.; Hiemstra, H. *Org. Lett*. **2000**, *2*, 1157. (b) Trost, B. M.; Doherty, G. A. *J. Am. Chem. Soc*. **2000**, *122*, 3801. (c) Harrington, P. E.; Tius, M. A. *J. Am. Chem. Soc*. **2001**, *123*, 8509. (d) Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A. *J. Org. Chem*. **2005**, *70*, 4542. For racemic syntheses of **1**: (e) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc*. **1998**, *120*, 2817. (f) Fürstner, A.; Gastner, T.; Weintritt, H. *J. Org. Chem*. **1999**, *64*, 2361. (g) Kim, S. H.; Figueroa, I.; Fuchs, P. L. *Tetrahedron Lett*. **1997**, *38*, 2601. (h) Mochizuki, T.; Itoh, E.; Shibata, N.; Nakatani, S.; Katoh, T.; Terashima, S. *Tetrahedron Lett*. **1998**, *39*, 6911. (i) Harrington, P.; Tius, M. *Org. Lett*. **1999**, *1*, 649. (j) Robertson, J.; Hatley, R. J. D.; Watkin, D. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3389. (k) Bitar, A. Y.; Frontier, A. J. *Org. Lett*. **2009**, *11*, 49. (l) Song, C.; Liu, H.; Hong, M.; Liu, Y.; Jia, F.i; Sun, L.; Pan, Z.; Chang, J. *J. Org. Chem*. **2012**, *77*, 704. For approaches to the roseophilin core: (l) Salamone, S. G.; Dudley, G. B. *Org. Lett*. **2005**, *7*, 4443. (m) Song, C.; Knight, D. W.; Whatton, M. A. *Org. Lett*. **2006**, *8*, 163.

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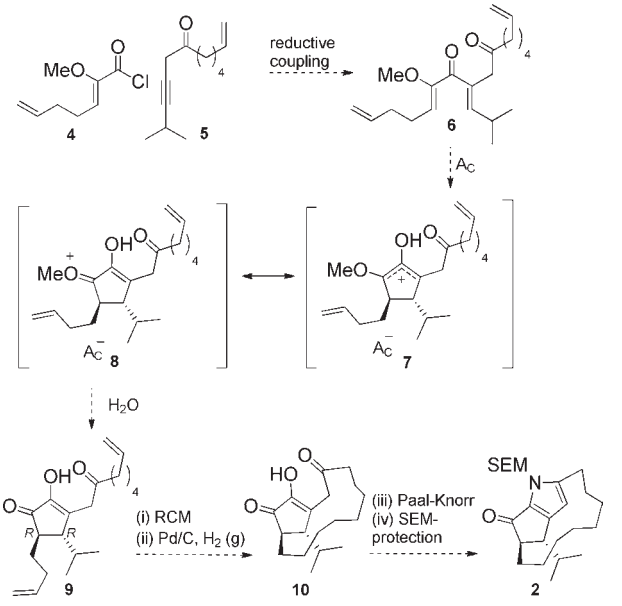
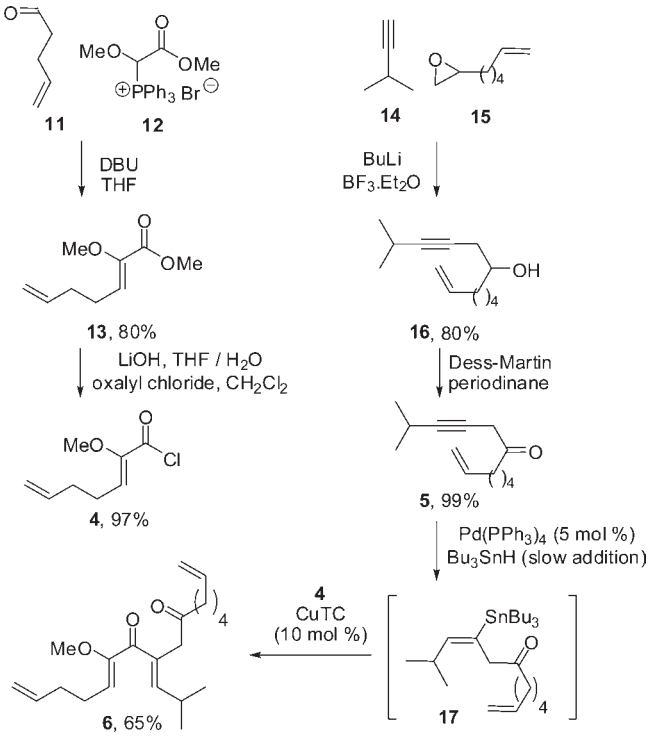
synthesis of *rac*-**1** described by Weintritt and Fürstner, which is still the most concise (13 steps), and the first enantioselective approach developed by Harrington and Tius (15 steps, 99% ee), which is also the most efficient in terms of overall yield (8%).[4c,e] Herein, we describe a nine step approach to ketopyrrole **2** (longest linear sequence), which has been previously converted to **1** by reaction with the ceriated pyrrolylfuran **3** (1,2-addition, elimination sequence), followed by deprotection (Scheme 1).[3,4c,e] A new two step protocol for the enantioselective synthesis of highly substituted cyclopentanoids has been developed in the context of this new formal synthesis of **1**.

Our planned approach to **2** is outlined in Scheme 2 and centers around the divinyl ketone **6**, which we considered accessible by reductive coupling of acid chloride **4** to alkyne **5** (see below).[5] We intended that Nazarov cyclization of **6** be accompanied by *in situ* hydrolytic trapping of the oxonium ion **7/8** to give **9** diastereospecifically.[6,7] Marocyclization of **9** to **10** by ring-closing metathesis (RCM) and hydrogenation would then be followed by Paal–Knorr and SEM-protection to give **2**.[8] Recently, divinyl ketones bearing α-alkoxy groups, as in **6**, have proven effective in chiral acid (A_C) catalyzed Nazarov reactions, offering the possibility of achieving this sequence enantioselectively.[6f,g,9]

Scheme 2. Planned Approach to **2**



Scheme 3. Synthesis of Divinyl Ketone **8**



Acid chloride **4** was prepared in two steps (Scheme 3). Wittig olefination of **11** with phosphonium reagent **12** gave ester **13** (80%), which was hydrolyzed and the crude acid treated with oxalyl chloride to give **4** (97%). Alkyne **5** was also achieved in two steps (Scheme 3). Ring opening of the epoxide **15** with alkyne **14** gave the alcohol **16** (80%), which was oxidized to give **5** (99%) (Scheme 3).

The reductive coupling of **4** and **5** to give **6** involves palladium mediated *syn*-hydrostannylation of **5** → **17**, followed by addition of the acid chloride **4** and copper(I) thiophenecarboxylate (CuTC) cocatalyst. In our previous applications of this reductive coupling protocol the alkyne has been activated to *syn*-hydrostannylation through a directly attached carbonyl.[5] In the case of **5**, the alkyne is linked to the carbonyl through a methylene. The *syn*-hydrostannylation of such remotely activated alkynes is rare and difficult to achieve.[10] In a systematic study of the

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(6) For recent reviews of the Nazarov reactions, see: (a) Tius, M. *Eur. J. Org. Chem.* **2005**, 2193. (c) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479. (f) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577. (e) Nakanishi, W.; West, F. G. *Curr. Opin. Drug Discovery Dev.* **2009**, *12*, 732. For recent reviews on asymmetric Nazarov reactions, see: (f) Vaidya, T.; Eisenberg, R.; Frontier, A. J. *ChemCatChem* **2011**, *3*, 1531. (g) Shimada, N.; Stewart, C; Tius, M. A. *Tetrahedron* **2011**, *67*, 5851.

(7) For a recent review on the interrupted Nazarov reaction, see: (a) Grant, T. N.; Rieder, C. J.; West, F. G. *Chem. Commun.* **2009**, 5676. For selected references on hydrolytic trapping, see: (b) Batson, W. A.; Sethumadhavan, D.; Tius, M. A. *Org. Lett.* **2005**, *7*, 2771–2774. (c) Bee, C.; Leclerc, E.; Tius, M. A. *Org. Lett.* **2003**, *5*, 4927–4930. (d) Kokubo, M.; Kobayashi, S. *Chem.—Asian J.* **2009**, *4*, 526–528.

(8) The conversion of **11** to **2** is similar, but nonidentical, to the synthesis of Harrington and Tius, ref 4c.

(9) (a) Liang, G.; Gradl, S. N.; Trauner, D. *Org. Lett.* **2003**, *5*, 4931. (b) Rueping, M.; Ieawsuwan, W.; Antonchick, A. P.; Nachtsheim, B. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2097. *Angew. Chem.* **2007**, *119*, 2143. (c) Cao, P.; Deng, C.; Zhou, Y.-Y.; Sun, X.-L.; Zheng, J.-C.; Xie, Z.; Tang, Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 4463. *Angew. Chem.* **2010**, *122*, 4565. (d) Rueping, M.; Ieawsuwan, W. *Chem. Commun.* **2011**, *47*, 11450.

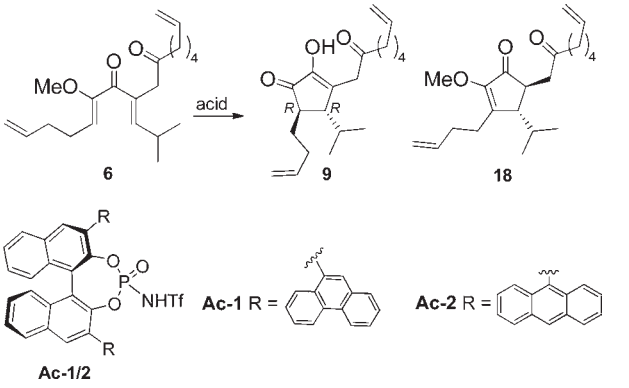
(10) Marshall, J. A.; Bourbeau, M. P. *Tetrahedron Lett.* **2003**, *44*, 1087.

reaction conditions, we discovered that *syn*-hydrostannylation of **5** → **17** could be achieved by slow addition of the tributyltin hydride to a solution of **5** and $Pd(PPh_3)_4$ (5 mol %) in dichloromethane at room temperature.[11] Slow addition avoided competitive palladium mediated disproportionation of the tributyltin hydride to hexabutylditin and hydrogen gas. When hydrostannylation of **5** was performed in the context of a reductive coupling with acid chloride **4**, **6** was obtained in good yield (65%).

We next investigated the Nazarov cyclization of **6** under various conditions (Table 1).[9a] Using the Lewis acid $AlCl_3$ (10 mol %) in dichloromethane we obtained the enol ether **18** exclusively as the *trans*-isomer in excellent yield (85%) (entry 1, Table 1). To achieve hydrolytic trapping of intermediate **8** (Scheme 2), we used the Brønsted acid $MeSO_3H$ in wet dichloromethane; this gave the desired keto enol, *rac*-**9**, in excellent yield (99%) (entry 2, Table 1). We next investigated the use of the chiral Brønsted acids.[12] In their earlier studies, Rueping and co-workers evaluated a number of binol phosphates and phosphoramides in the cyclization of pyranyl fused divinyl ketones to corresponding cyclopentenones with good induction (86−93% ee).[9b,d] They identified $\mathbf{A_C}$**-1** as the most effective catalyst and chloroform as the best solvent.[9b,13] Using just 5 mol % of $\mathbf{A_C}$**-1** in moist chloroform we were able to achieve an efficient cyclization of **6** to **9** (90%), favoring the *R,R*-isomer (60% ee) (entry 3, Table 1). By substituting the phenanthracenyl groups for anthracenyl groups ($\mathbf{A_C}$**-2**) we were able to increase the torquoselectivity giving *R,R*-**9** in 72% ee (entry 4, Table). A further increase in the torquoselectivity to 82% ee was achieved by performing the reaction in the less polar solvent, carbon tetrachloride (entry 5, Table 1). Further optimization of this reaction is ongoing.

The next two steps required to progress **9** toward **2** involved ring-closing metathesis (RCM) and palladium on charcoal hydrogenation. In our most preferred arrangement, the crude product arising from basic workup ($NaHCO_3$ aq) of the $\mathbf{A_C}$**-2** catalyzed Nazarov reaction **6** → **9** was subjected directly to RCM with Grubbs' first generation catalyst, giving the cyclic alkene **19** (72% from **6**) as a *cis*/*trans*-mixture (Scheme 4). Hydrogenation of *cis*/*trans*-**19** was quantitative, giving pure **10** (100%, 82% ee). Recrystallization of this material from diethyl ether and hexanes led to preferential crystallization of the racemate, giving enantiomerically enriched **10** (80% recovery, 95% ee) upon filtration and evaporation of the mother liquor. This material was then subject to a Paal−Knorr reaction using NH_4OAc and

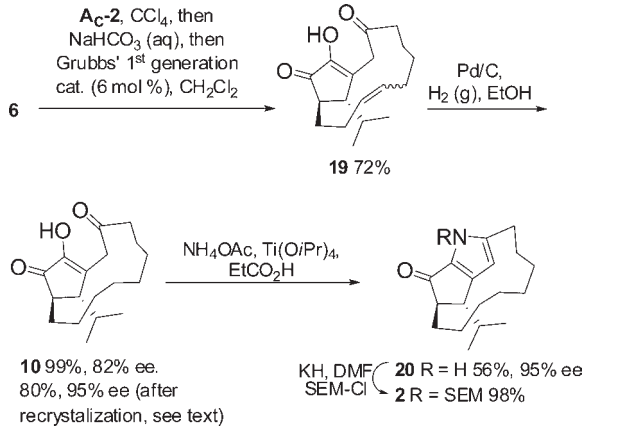
Table 1. Nazarov Cyclization of **6**



	reaction conditions			
entry	acid	solvent	product, yield %	ee
1	$AlCl_3$ (10 mol %)	CH_2Cl_2[a]	**18**, 85%	racemic
2	$MeSO_3H$ (2 equiv)	CH_2Cl_2/H_2O[b]	**9**, 99%	racemic
3	$\mathbf{A_C}$**-1** (5 mol %)	$CHCl_3$[c]	**9**, 90%	60%
4	$\mathbf{A_C}$**-2** (5 mol %)	$CHCl_3$[c]	**9**, 91%	72%
5	$\mathbf{A_C}$**-2** (5 mol %)	CCl_4[c]	**9**, 91%	82%

[a] Anhydrous solvent used. [b] Water added (2 drops) to reagent grade solvent. [c] Reagent grade solvent used; no water added.

Scheme 4. Final Steps



$Ti(OiPr)_4$ in propanoic acid to give (+)-**20** (56%). The positive rotation observed for **20** indicates that this formal synthesis provides the naturally occurring enantiomer (+)-**1**.[4a,c] SEM-protection of **20** to give **2** (98%) was performed using previously reported conditions.[4c,14]

(11) See Supporting Information.

(12) For a recent review on chiral Brønsted acid catalysis, see: Rueping, M.; Kuenkel, A.; Atodiresei, I. *Chem. Soc. Rev.* **2011**, *40*, 4539.

(13) Chiral BINOL *N*-triflyl phosphoramide catalysts were introduced by Nakashima and Yamamoto in a study on enantioselective Diels−Alder reactions: Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626.

(14) This step was conducted using racemic **20**.

In conclusion, a concise, enantioselective formal synthesis of **1** has been achieved (11 steps via longest linear sequence, 10.2% overall yield, 95% ee). Central to the attainment of this outcome has been the combination of reductive coupling and chiral Brønsted acid catalyzed Nazarov cyclization. This two step approach to highly substituted, multistereocenter containing cyclopentanoids is likely to find other valuable applications. The availability of both enantiomers of $\mathbf{A_C}$**-2** affords enantiodivergent access to **1** and its analogs. This is advantageous given that both enantiomers of **1** have activity as inhibitors of several protein phosphatases linked to cancer cell growth and survival.

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Supporting Information Available. Preparative procedures and spectroscopic data for all compounds, chiral HPLC traces for **9** and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.