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Remote Stereocontrol in the Nazarov Reaction: A New Approach to the Core of Roseophilin

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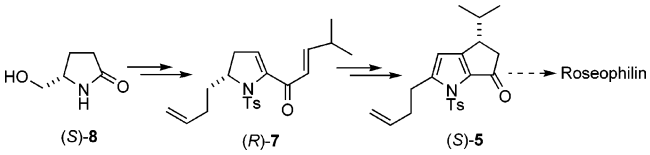
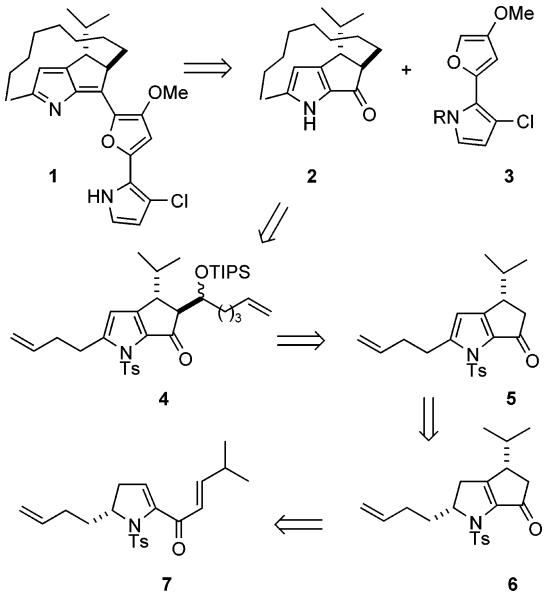


Three different procedures are compared to obtain properly substituted divinyl ketones in which one of the double bonds is embedded in a five-membered heterocyclic structure and therefore suitable to produce cyclopenta-fused pyrrole derivatives by the acid-catalyzed Nazarov reaction. These, on treatment with TFA, afforded 2,4-cis-disubstituted 2,3,4,5-tetrahydro-1*H*-cyclopenta[*b*]pyrrol-6-ones with high stereocontrol. One of these Nazarov products was oxidized to the corresponding 4,5-dihydro-1*H*-cyclopenta[*b*]pyrrol-6-one derivative, thus obtaining an enantiopure key intermediate in the total synthesis of roseophilin.

Roseophilin (**1**, Scheme 1) is a macrocyclic pigment isolated from *Streptomyces griseoviridis* that exhibits potent cytotoxicity against human cancer cell lines.[1] This, and the unique ansa-bridged cyclopenta[*b*]pyrrole structural core of roseophilin, have stimulated the interest of several groups in the partial or total synthesis of this heterocycle.[2] As pointed out by Fürstner in his exhaustive review on the chemistry and biology of roseophilin,[3] all synthetic approaches toward **1** are based on the same disconnection that includes the condensation of the macrotricyclic cyclopenta-fused pyrrole **2** with the heterocyclic portion **3**. The procedures by which intermediate **2** has been synthesized can in turn be grouped in two general strategies. The most employed relies on the construction of the ansa bridge moiety which anchors suitable functionalities to eventually assembly the 1-azafulvene moiety by diverse cyclization reactions.[2c−f,h−j,l−o] Alternatively, the isopropyl-substituted ketopyrrole **4** (Scheme 1), or a closely related compound, can be prepared in an earlier phase which is followed by the RCM of the terminal double bonds present on the two chains at C2 and C5.[2a,b,g,k] This sequence has been first used by Fuchs in his synthesis of **2**, which required, however, 13 steps to prepare key intermediate **5** in racemic form.[2b] The stimulus to revisit Fuchs' formal synthesis of roseophilin came from our recent finding that the Nazarov reaction of divinyl ketones in which one of the double bonds is embedded in a properly substituted N-heterocyclic structure proceeds in highly stereocontrolled fashion to give cis-disubstituted cyclopenta-fused heterocycles.[4] On these grounds, we envisioned a faster route to obtain bicyclic ketopyrrole **5** in enantiopure form by electrocyclization of pyrroline **7** (Scheme 1) in which the correctly oriented buten-3-yl chain on the heterocycle serves the purpose of controlling the absolute stereochemistry of the C4 atom bearing the isopropyl group in the Nazarov product **6** while being already set for the RCM following Fuchs' strategy from **5**.

SCHEME 1



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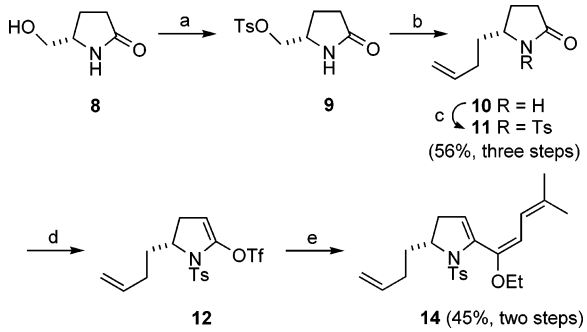
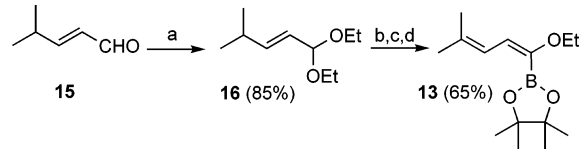
SCHEME 2[a]



[a] Key: (a) TsCl, Et_3N, DMAP, CH_2Cl_2, 25 °C, 16 h; (b) allylmagnesium bromide, THF, 0 → 25 °C, 6 h; (c) TsCl, LHMDS, THF, −20 °C, 1 h; (d) $PhNTf_2$, KHMDS, THF, −78 °C, 1 h; then to 0 °C; (e) **13**, 4% $(Ph_3P)_2PdCl_2$, 2 M Na_2CO_3, THF, 55 °C, 4 h.

SCHEME 3[a]

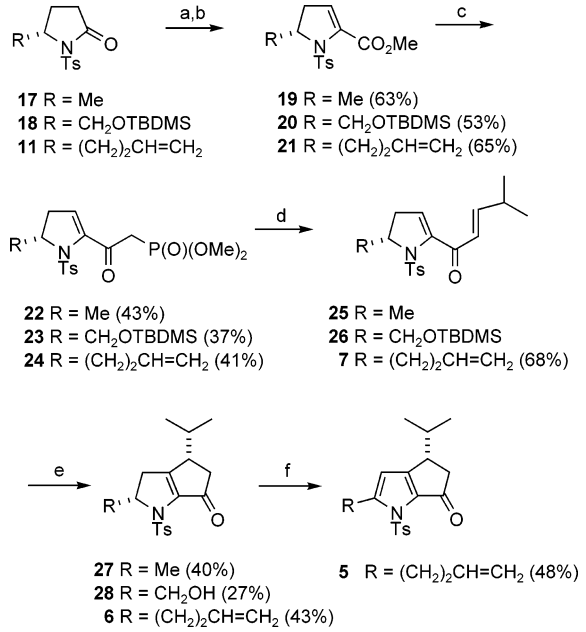


[a] Key: (a) triethyl orthoformate, NH_4NO_3, EtOH; (b) *t*-BuOK, *n*-BuLi, THF, −95 °C, 2 h; (c) triisopropylborate, 25 °C; (d) pinacol, toluene, 25 °C.

Following our earlier studies,[4a,b] we initially relied, for the preparation of **7**, on the hydrolysis of ethoxytriene **14** (Scheme 2) obtained by Pd-catalyzed coupling of vinyl triflate **12** with α-ethoxydienylboronate **13**, this in turn prepared from the corresponding aldehyde **15** as depicted in Scheme 3.[5]

Reaction of allylmagnesium bromide (5 equiv) with enantiopure (*S*)-**9**,[6] under refluxing conditions in THF,[7] furnished **10** (61% yield after chromatography) which was N tosylated (*n*-BuLi, TsCl) to give **11** (59%). Attempts at improving the yield of allylation by carrying out the reaction in the presence of Cu(I) salts (CuI, CuCN) under various conditions[8] were not successful. A better yield of **11** was obtained when the allylation on crude **9** was carried out at room temperature (6 h) with 2 equiv of the Grignard reagent and the next tosylation performed directly on crude **10** by using LHMDS as a base (56% over three steps). After N-tosylation, lactam **11** was converted into vinyl triflate **12** which was directly coupled with **13** without prior purification.[9] The Pd-catalyzed coupling[4,10] proceeded smoothly providing **14** in 45% yield (over two steps) after chromatography. Unfortunately, the hydrolysis of the ethoxydiene moiety of **14** to furnish the corresponding vinyl ketone **7** did not occur under mild acidic conditions (Amberlyst 15 resin in dichloromethane or 0.02 M HCl in MeOH−H_2O) as in other cases.[4,10c] Later, we found that the hydrolysis of this robust ethoxydiene moiety requires harsh conditions (heating at 80 °C with 20% H_2SO_4) to occur,[11] not compatible with the presence of both the delicate heterocycle moiety of **14** and the terminal olefin, and this convergent approach to **7** was abandoned.

SCHEME 4[a]



[a] Key: (a) $PhNTf_2$, KHMDS, THF, −78 °C, 1 h; then to 0 °C; (b) 10% $Pd(OAc)_2$, 20% Ph_3P, CO, DMF 10 min; then Et_3N, MeOH, 40 °C, 4 h; (c) $CH_3PO(OCH_3)_2$, *n*-BuLi, THF, −78 °C, 30 min; then **19**−**21**, 25 °C, 4 h; (d) 2-methylpropanal, DIPEA, LiCl, MeCN, 25 °C, 24 h; (e) TFA, 25 °C, 20 h; (f) DDQ, toluene, reflux, 5 h.

Two alternative routes were envisioned to prepare **7**. Initially, we started a linear sequence (Scheme 4) from enantiopure (*R*)-pyrrolidinone **17**—with R = Me, to assess the procedure—and enantiopure *O*-TBDMS-protected (*S*)-hydroxymethyl pyrrolidinone **18**.

The latter substrate was chosen in anticipation of the need to incorporate the buten-3-yl chain in a later stage of the synthesis. After transformation into the known vinyl triflates,[4b] both substrates were carbonylated (10% $Pd(OAc)_2$, Ph_3P, Et_3N, CO)[12] in the presence of MeOH to give **19** and **20** in 63% and 53% yield, respectively. Different carbonylation conditions[13] provided the methyl esters in comparable yields. We tried also the 2-methyl pyrrolidinone-derived vinyl phosphate,[12] instead of the triflate, as the substrate for the carbonylation, but it underwent hydrolysis during the reaction giving back the

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(8) (a) 43% yield in the presence of CuI. Hori, K.; Hikage, N.; Inagaki, A.; Mori, S.; Keiichi, N.; Yoshii, E. *J. Org. Chem.* **1992**, *57*, 2888−2902. (b) 19% yield in the presence of CuCN. Yoda, H.; Katoh, H.; Ujihara, Y.; Takabe, K. *Tetrahedron Lett*. **2001**, *42*, 2509−2512.

(9) Five-membered lactam-derived vinyl triflates are prone to rapid decomposition on standing. For a review on the chemistry of lactam-derived vinyl triflates, see: Occhiato, E. G. *Mini-Rev. Org. Chem*. **2004**, *1*, 149−162.

(10) (a) Occhiato, E. G.; Trabocchi, A.; Guarna, A. *Org. Lett.* **2000**, *2*, 1241−1242. (b) Occhiato, E. G.; Trabocchi, A.; Guarna, A. *J. Org. Chem.* **2001**, *66*, 2459−2465. (c) Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A.; Deagostino, A.; Venturello, P. *J. Org. Chem*. **2002**, *67*, 7144−7146.

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(12) Nicolaou, K. C.; Shi, G.-Q.; Namoto, K.; Bernal, F. *Chem. Commun*. **1998**, 1757−1758.

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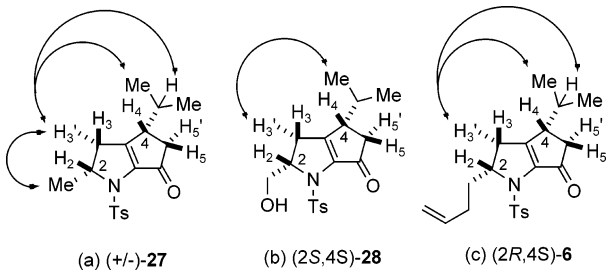
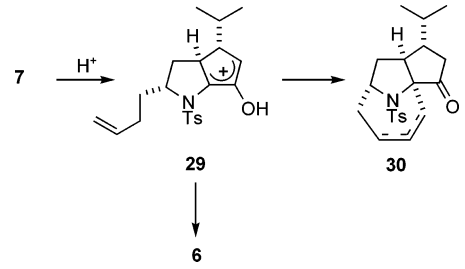


FIGURE 1. Diagnostic NOE relationships in compounds **27**, **28**, and **6**.

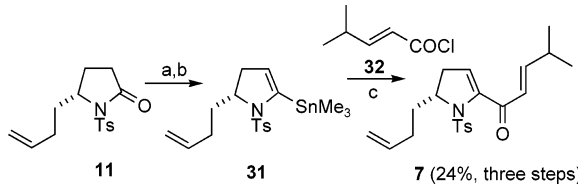
lactam. These esters were then transformed into the corresponding Horner−Emmons−Wadsworth reagents **22** (43%) and **23** (37%) according to the procedure described by Chiu for related carbacyclic systems[14] but, despite several efforts to improve the reaction conditions, never with the same excellent yields reported for those. Olefination of isobutyric aldehyde with **22** and **23** proceeded smoothly to give the required dienones **25** and **26** which were directly used without purification in the next step. The coupling constant values of the olefinic protons (15.4 Hz in **25** and 16.1 Hz in **26**) are in accordance with the expected trans stereochemistry of the newly formed double bond. The electrocyclization reaction of these divinyl ketones was carried out by dissolving the substrates in cold TFA and then allowing the mixture to sit at room temperature.[4] The reactions were complete in 20 h and furnished cyclopenta-fused systems **27** and **28** in 40% and 27% yield, respectively, after chromatography. Similar results in terms of yields were obtained by carrying out the reaction on **25** in a 0.2 M CF_3SO_3H solution in CH_2Cl_2. We were pleased to find that the methyl-substituted ketopyrroline **27** was obtained, albeit in low yield, as a single cis diastereomer (stereochemical assignment based on NOESY 1D and 2D studies, Figure 1),[15] whereas **28** was obtained as a 7:1 mixture of inseparable cis (major) and trans (minor) diastereomers.[15] These results are in accordance with those previously reported: the reaction proceeds via a clockwise conrotation which involves the less hindered face of the endocyclic double bond, i.e., that opposite to the axially oriented 2-alkyl group on the heterocycle.[4b] The substituent on the external double bond (in this case the isopropyl group) seems to have only a small influence on the choice of the sense of conrotation in the Nazarov reaction.

The low yield and the formation of a mixture of diastereomers in the cyclization of 2-hydroxymethyl-substituted dienone **26** persuaded us to insert the requisite homoallyl chain in an earlier stage of the synthesis of **5**. Although this could be an apparently obvious strategy, a potential problem arises from this choice: the terminal double bond could trap the [3.3.0] bicylic oxyallyl

SCHEME 5



SCHEME 6[a]



[a] Key: (a) $PhNTf_2$, KHMDS, THF, −78 °C, 1 h; then to 0 °C; (b) Me_6Sn_2, 5% $Pd(MeCN)_2Cl_2$, Ph_3As, THF, 40 °C, 4 h; (c) 5% $(Ph_3P)_4Pd$, toluene, reflux.

cation **29**, formed during the electrocyclization reaction, thus leading to an undesired tricyclic product **30** (Scheme 5).[16]

Compound **7** was prepared from enantiopure pyrrolidinone **11** by applying the above sequence (Scheme 4), but once again, low yields (41%) were obtained in the formation of the corresponding phosphonate **24**. Therefore we experimented with a more convergent procedure for the preparation of **7** as depicted in Scheme 6. We first converted triflate **12** into the corresponding stannane **31** by Pd-catalyzed coupling reaction with Me_6Sn_2,[17] and then crude stannane **31** was coupled with 4-methyl-2-pentenoyl chloride (**32**) in the presence of $(Ph_3P)_4Pd$ as a catalyst in refluxing toluene. To our knowledge, the Stille coupling of lactam-derived vinyl stannanes with acyl chlorides has never been reported so far, and in the present case it provided pure **7** in 24% over three steps.

To complete the synthesis, compound **7** was treated with pure TFA and the electrocyclization was complete in 20 h (by TLC). It was a relief to find, by ^{1}H NMR analysis, that the crude reaction mixture contained compound **6** as the major component in an approximately 4:1 ratio with a second compound. The presence in the spectrum of olefinic signals at 5.62, 5.50, and 5.34 ppm could actually be accounted for by the formation of **30** as the minor product; however, we were unable to isolate this byproduct in order to unequivocally assign the structure. As in the case of 2-methyl-substituted compound **27**, (2*R*,4*S*)-**6** was also obtained as a single diastereomer (43% yield after chromatography) whose 2,4-cis relative stereochemistry was established by NOESY studies (Figure 1).[15] Compound **6** was finally subjected to oxidation by DDQ[18] yielding our target compound (4*S*)-**5** in 48% after chromatography.[19] In total, this key

(14) Chiu, P.; Li, S. *Org. Lett.* **2004**, *6*, 613−616.

(15) Proton H3′, which is cis to the 2-alkyl chain on the heterocycle, consistently resonates at about 2.1 ppm (as a doublet of doublets) in all Nazarov compounds. NOE cross-peaks between the isopropyl protons and H3′ are diagnostic of the cis relative stereochemistry. In the ^{1}H NMR of **28** the signals of two rotamers in a 3:1 ratio are also present, as demonstrated by recording ^{1}H NMR spectra at different temperatures.

(16) This corresponds to an "interrupted" Nazarov reaction. See, for example: (a) Bender, J. A.; Blize, A. E.; Browder, C. C.; Giese, S.; West, F. G. *J. Org. Chem.* **1998**, *63*, 2430−2431. (b) Bender, J. A.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 7443−7444.

(17) Luker, T.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 8131−8140.

intermediate in the synthesis of roseophilin was obtained in eight step from known compound **9** (3% overall yield).

In conclusion, in this work we have experimented with and compared three different procedures to obtain properly substituted divinyl ketones in which one of the double bonds is embedded in a five-membered heterocyclic structure, suitable to produce cyclopenta-fused pyrrole derivatives by the acid-catalyzed Nazarov reaction. Despite the inherent difficulties in working with pyrrolidinone-derived vinyl triflates, in one case a convergent procedure based on the umpolung to a vinylstannane gave acceptable yields of the requisite divinyl ketone. The successive Nazarov reaction of these compounds on treatment with pure TFA afforded 2,4-cis-disubstituted 2,3,4,5-tetrahydro-1*H*-cyclopenta[*b*]pyrrolones with high stereocontrol. One of these was oxidized to the corresponding 4,5-dihydro-1*H*-cyclopenta[*b*]pyrrol-6-one, thus obtaining an enantiopure key intermediate in the total synthesis of roseophilin.

Acknowledgment. We thank MIUR and University of Florence for financial support. Mr. Maurizio Passaponti and Mrs. Brunella Innocenti are acknowledged for their technical support. Prof. P. L. Fuchs is acknowledged for providing the conditions for the *N*-iodosuccinimide oxidation. Ente Cassa di Risparmio di Firenze is acknowledged for granting a 400 MHz NMR spectrometer.

Supporting Information Available: Full experimental details and compound characterization; copies of the ^{1}H NMR spectra of compounds **27**, **28**, **10**−**12**, **21**, **24**, **7**, **6**, **5**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Shim, Y. K.; Youn, J. I.; Chun, J. S.; Park, T. H.; Kim, M. H.; Kim, W. J. *Synthesis* **1990**, 753−754. Oxidation by NIS in CCl_4 (ref 2a) provided **5** in lower yield.

(19) The ^{13}C NMR spectrum of (*S*)-**5** is identical to that of the racemic material kindly provided by Prof. Fuchs.