

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 2,3,4,5tetrahydro-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 ${f 2}$ 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 comSCHEME 1



pound, 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 cisdisubstituted 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.

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SCHEME 2^a



^a Key: (a) TsCl, Et₃N, DMAP, CH₂Cl₂, 25 °C, 16 h; (b) allylmagnesium bromide, THF, $0 \rightarrow 25$ °C, 6 h; (c) TsCl, LHMDS, THF, -20 °C, 1 h; (d) PhNTf₂, KHMDS, THF, -78 °C, 1 h; then to 0 °C; (e) 13, 4% (Ph₃P)₂PdCl₂, 2 M Na₂CO₃, THF, 55 °C, 4 h.

SCHEME 3^a



^a Key: (a) triethyl orthoformate, NH₄NO₃, 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 conditions⁸ 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



^a Key: (a) PhNTf₂, KHMDS, THF, -78 °C, 1 h; then to 0 °C; (b) 10% Pd(OAc)₂, 20% Ph₃P, CO, DMF 10 min; then Et₃N, MeOH, 40 °C, 4 h; (c) CH₃PO(OCH₃)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.

acidic conditions (Amberlyst 15 resin in dichloromethane or 0.02 M HCl in MeOH-H₂O) 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.

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, $^{4\mathrm{b}}$ 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 conditions¹³ 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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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 systems¹⁴ 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 CF₃SO₃H solution in CH₂Cl₂. 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-hydroxymethylsubstituted 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) PhNTf₂, KHMDS, THF, -78 °C, 1 h; then to 0 °C; (b) Me₆Sn₂, 5% Pd(MeCN)₂Cl₂, Ph₃As, THF, 40 °C, 4 h; (c) 5% (Ph₃P)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-2pentenoyl 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 ¹H 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, (2R,4S)-6 was also obtained as a single diastereomer (43% yield after chromatography) whose 2,4-cis relative stereochemistry was established by NOE-SY studies (Figure 1).¹⁵ Compound 6 was finally subjected to oxidation by DDQ¹⁸ yielding our target compound (4S)-5 in 48% after chromatography.¹⁹ In total, this key

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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.

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Supporting Information Available: Full experimental details and compound characterization; copies of the ¹H 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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⁽¹⁹⁾ The 13 C NMR spectrum of (S)-5 is identical to that of the racemic material kindly provided by Prof. Fuchs.