Synthesis and Absolute Stereochemistry of Roseophilin

Paul E. Harrington and Marcus A. Tius*

Contribution from the Department of Chemistry, 2545 The Mall, University of Hawaii, Honolulu, Hawaii 96822

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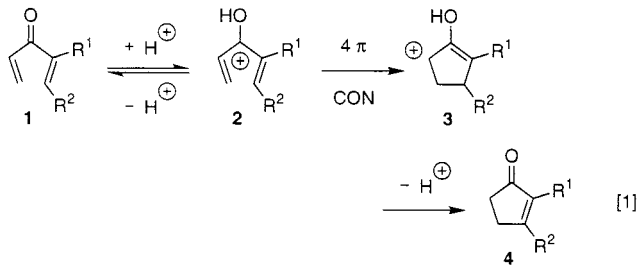
Abstract: The enantiospecific total synthesis of natural roseophilin has been completed in 7.0% overall yield over 15 steps by means of an asymmetric cyclopentannelation. This establishes the absolute configuration of the natural product as 22*R*,23*R*. Cyclopentenone (+)-**12** was prepared in 78% yield and 86% ee in the key step.

Introduction

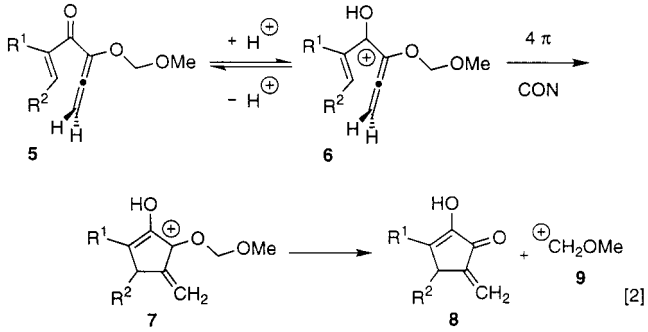
Several related variants of the classical Nazarov reaction have been an area of research focus in our group for a number of years.[1] The classical Nazarov reaction can be thought of as proceeding through the series of steps which are summarized in eq 1. Divinyl ketone **1** is typically treated with strong Lewis



[1]

or protic acid to generate pentadienyl cation **2** reversibly. This step is followed by thermally allowed 4 π conrotation which produces allylic carbocation **3**. Loss of a proton from **3** leads to cyclopentenone **4**. The more highly substituted enone is the reaction product.[2]

The variant of the Nazarov reaction which was used in the key step of the roseophilin synthesis to be described in what follows is summarized in eq 2. Allenyl ketone **5** is the precursor of pentadienyl carbocation **6** which undergoes conrotation to **7**. Loss of methoxymethyl cation **9** from **7** leads to cross-conjugated cyclopentenone **8**. We have described several variants of this reaction and have applied the methodology as the key step in a number of syntheses of simple, naturally occuring cyclopentanoids. What sets the variant of eq 2 apart from related processes is the mildness of the reaction conditions for the cyclization, which can even take place during exposure



[2]

to aqueous NaH_2PO_4 in certain cases. Allenyl ketones **5** have not been isolated as intermediates but have always undergone cyclization to **8** during acidic workup. The low activation barrier for this reaction is likely a consequence of the ease of approach of allenic sp and vinyl sp^2 carbon atoms, with partial release of the strain energy of the allene during the rate-limiting transition state. The (methoxy)methoxy allene substituent in **5** is essential for the success of the cyclization. In particular, the distal oxygen atom appears to play a role in the overall process.

Results and Discussion

Roseophilin was isolated in 1992 by Seto and co-workers from the fermentation broth of *Streptomyces griseoviridis*.[3] The compound has some activity in vitro against K562 human erythroid leukemia cells (IC_{50}, 0.34 μM) and also against KB cells, a human nasopharyngeal carcinoma cell line (IC_{50}, 0.88 μM). The unusual structure, which incorporates an azafulvene

(1) For example, see: (a) Tius, M. A.; Chu, C. C.; Nieves-Colberg, R. *Tetrahedron Lett.* **2001**, *42*, 2419−2422. (b) Tius, M. A.; Hu, H.; Kawakami, J. K.; Busch-Petersen, J. *J. Org. Chem.* **1998**, *63*, 5971−5976. (c) Tius, M. A.; Busch-Petersen, J.; Yamashita, M. *Tetrahedron Lett.* **1998**, *39*, 4219−4222. (d) Tius, M. A.; Drake, D. J. *Tetrahedron* **1996**, *52*, 14651−14660. For other work involving the Nazarov reaction, see: (e) Bender, J. A.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 7443−7444. (f) Hashmi, A. S. K.; Bats, J. W.; Choi, J.-H.; Schwarz, L. *Tetrahedron Lett.* **1998**, *39*, 7491−7494. (g) Denmark, S. E.; Wallace, M. A.; Walker, C. B., Jr. *J. Org. Chem.* **1990**, *55*, 5543−5545. (h) Jacobi, P. A.; Armacost, L. M.; Kravitz, J. I.; Martinelli, M. J.; Selnick, H. G. *Tetrahedron Lett.* **1988**, *29*, 6865−6868, et seq.

(2) For a review, see: Dolbier, W. R. Jr.; Koroniak, H.; Houk, K. N.; Sheu, C. *Acc. Chem. Res.* **1996**, *29*, 471−477.

(3) Hayakawa, Y.; Kawakami, K.; Seto, H.; Furihata, K. *Tetrahedron Lett.* **1992**, *33*, 2701−2704.

(4) Harrington, P. E.; Tius, M. A. *Org. Lett.* **1999**, *1*, 649−651.

(5) (a) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817−2825. For other synthetic studies, see: (b) Nakatani, S.; Kirihara, M.; Yamada, K.; Terashima, S. *Tetrahedron Lett.* **1995**, *36*, 8461−8464. (c) Kim, S. H.; Fuchs, P. L. *Tetrahedron Lett.* **1996**, *37*, 2545−2548. (d) Kim, S. H.; Figueroa, I.; Fuchs, P. L. *Tetrahedron Lett.* **1997**, *38*, 2601−2604. (e) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1997**, *119*, 2944−2945. (f) Luker, T.; Koot, W.-J.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1998**, *63*, 220−221. (g) Mochizuki, T.; Itoh, E.; Shibata, N.; Nakatani, S.; Katoh, T.; Terashima, S. *Tetrahedron Lett.* **1998**, *39*, 6911−6914. (h) Fürstner, A.; Gastner, T.; Weintritt, H. *J. Org. Chem.* **1999**, *64*, 2361−2366. (i) Robertson, J.; Hatley, R. J. D. *J. Chem. Soc., Chem. Commun.* **1999**, 1455−1456. (j) Fagan, M. A.; Knight, D. W. *Tetrahedron Lett.* **1999**, *40*, 6117−6120. (k) Bamford, S. J.; Luker, T.; Speckamp, W. N.; Hiemstra, H. *Org. Lett.* **2000**, *2*, 1157−1160. (l) Trost, B. M.; Doherty, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 3801−3810. (m) Robertson, J.; Hatley, R. J. D.; Watkin, D. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3389−3396.

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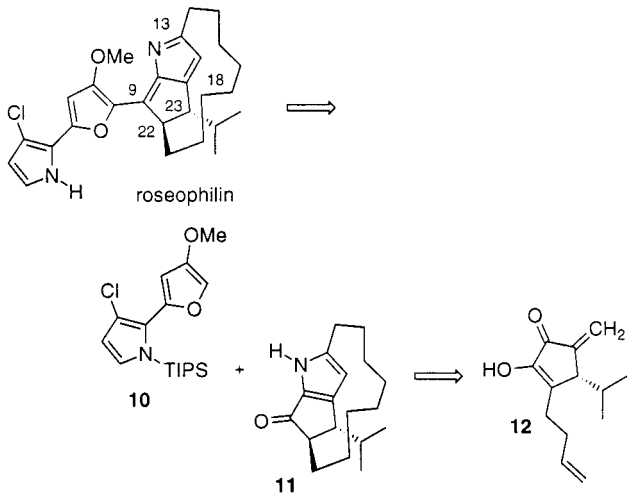


Figure 1. Retrosynthesis of roseophilin.

which is congugated to a pyrrolylfuran and an ansa macrocycle, made this an attractive and challenging target for total synthesis.[4,5] The first obvious retrosynthetic step (Figure 1) leads to pyrrolylfuran **10** and ketopyrrole **11**. Ketopyrrole **11**, in turn, can be prepared from cyclopentenone **12**. To date, a single total synthesis of racemic roseophilin has been described by Fürstner.[5a] Formal total syntheses, terminating in ketopyrrole **11** or some protected form of **11**, have been published by Fuchs,[5c,d] Terashima,[5g] Hiemstra,[5k] Trost,[5l] Robertson,[5i,m] and our group.[4] This paper and the accompanying one by Boger and Hong[16] describe the first efficient enantiospecific total syntheses of roseophilin.

In two Communications we have described the synthesis of racemic **11**[4] (Scheme 1) and the synthesis of each of the enantiomers of **12** in good yield but in modest ee.[6] 5-Hexenal **13** was chosen as the starting material for the synthesis. Conversion to the *tert*-butylimine **14** was accomplished in 94% yield. The conversion of **14** to enal **15** was carried out conventionally, by deprotonating **14** with LDA, and trapping the lithio aldimine with trimethylchlorosilane. The silyl aldimine was isolated, deprotonated once again, and intercepted with isobutyraldehyde to give **15** in 71% yield following hydrolytic cleavage of the imine by aqueous oxalic acid.[7] Oxidation of enal **15** with sodium chlorite, in the presence of 2-methyl-2-butene and phosphate buffer,[8] led to the corresponding carboxylic acid which was converted to α,β-unsaturated amide **16** in 88% overall yield for the two steps.[9] From this point on, the synthesis of Scheme 1 diverges from our earlier reported work.

The key step in this synthesis is the asymmetric cyclopentannelation reaction which leads to **12**. We have demonstrated two distinct approaches to this problem. One approach makes use of an axially chiral, nonracemic allene ether to transfer asymmetry to the tetrahedral ring carbon of the product.[10] The alternative approach involves the use of a chiral auxiliary on the allene, and it was this strategy which proved to be successful for the roseophilin synthesis.[6] Lithioallene **17** was prepared from commercially available (+)-camphoric acid in five steps.[11] Deprotonation of the allene ether took place with *n*-butyllithium at −78 °C. Addition of amide **16** was followed by warming to −30 °C over 1 h to ensure that the addition was complete. Cooling the solution to −78 °C was followed by addition to a 1/1 (v/v) solution of HCl in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) and 2,2,2-trifluoroethanol (TFE) at −78 °C. In our earlier work we had determined that HFIP was essential for ensuring high enantiomeric excesses of cyclization products; however, the high melting point (−4 °C) of HFIP made it necessary to use a mixed solvent system in order to conduct the reaction at −78 °C, the optimal temperature for the cyclization. Under these conditions **12** was isolated in 78% yield and in 86% ee. This result represents a significant improvement over our earlier efforts. Protection of the enolic hydroxyl group in **12** as the benzoate led to **18** in 90% yield. The conversion of **18** to 1,4-diketone **20** formally represents an acyl carbanion addition to the exocyclic alkene of **18**. The transformation was accomplished very conveniently through the Stetter reaction of **18** with 6-heptenal **19**.[12] Heating a dioxane solution of **18** with 2 equiv of aldehyde **19** in the presence of triethylamine and 3-benzyl-5-(hydroxyethyl)-4-methylthiazolium chloride gave **20** in 77% yield. A small amount of the *cis* diastereomer was also isolated from the reaction mixture and was separated by flash column chromatography. Ring-closing metathesis using the commercially available Grubbs catalyst[13,14] led to an *E/Z* mixture of macrocyclic alkenes **21** in 91% yield. Selective saturation of the disubstituted alkene group in **21** took place under 1 atm of hydrogen gas in the presence of palladium on carbon as the catalyst. Diketone **22** was isolated in 89% yield and 86% ee. The racemate of **22** was highly crystalline, and ether solutions of this material precipitated as large cubes during solvent evaporation. The optically enriched material showed a much diminished tendency to crystallize; however, crystallization of the racemate of **22**, followed by filtration of the crystals, led to material which was essentially a single enantiomer (99% ee) in 77% yield from **21**. The optically pure material also crystallized from a mixture of methanol and dichloromethane as delicate

(6) Harrington, P. E.; Tius, M. A. *Org. Lett*. **2000**, *2*, 2447−2450.

(7) (a) Kang, S. H.; Jun, H.-S.; Youn, J.-H. *Synlett* **1998**, 1045−1046. (b) Schlessinger, R. H.; Poss, M. A.; Richardson, S.; Lin, P. *Tetrahedron Lett.* **1985**, *26*, 2391−2394. (c) Corey, E. J.; Enders, D.; Bock, M. G. *Tetrahedron Lett*. **1976**, *27*, 7−10.

(8) (a) Kraus, G. A.; Taschner, M. J. *J. Org. Chem*. **1980**, *45*, 1175−1176. (b) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888−890.

(9) Einhorn, J.; Einhorn, C.; Luche, J.-L. *Synth. Commun.* **1990**, *20*, 1105−1112.

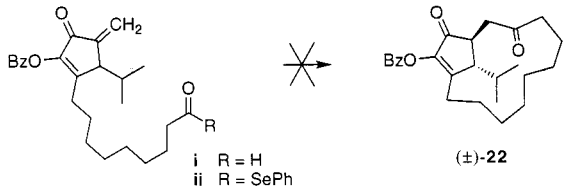
(10) Hu, H.; Smith, D.; Cramer, R. E.; Tius, M. A. *J. Am. Chem. Soc*. **1999**, *121*, 9895−9896.

(11) See Supporting Information for details of the synthesis of **17-H**. The relative stereochemistry of **17-H** was determined through NOE experiments.

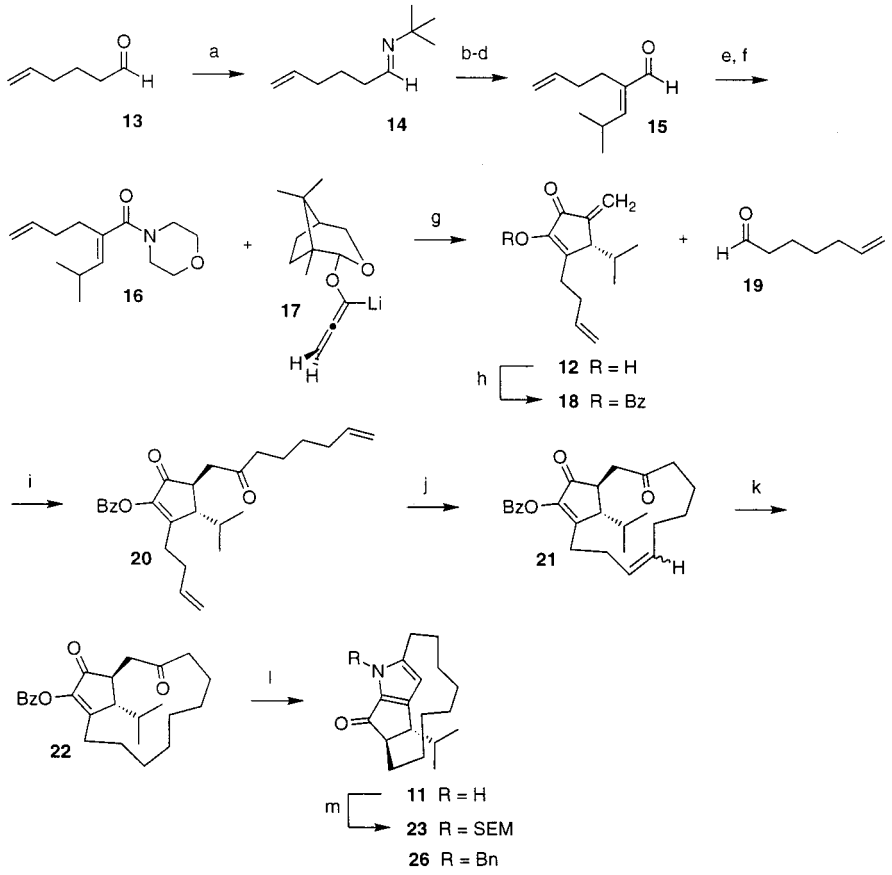
(12) Stetter, H.; Haese, W. *Chem. Ber*. **1984**, *117*, 682−693. For a review of the Stetter reaction, see: Stetter, H.; Kuhlmann, H. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1991; Vol. 40, pp 407−496.

(13) Bis(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride. For a review of olefin metathesis chemistry, see: Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043.

(14) It is noteworthy that we were unable to form (±)-**22** through the intramolecular Stetter reaction of **i** nor through the intramolecular acyl radical cyclization of **ii**. The failure of **ii** to cyclize, either with *n*-Bu_3SnH or with $(TMS)_3SiH$ as the hydrogen atom donor, is understandable, since the lifetime of the reactive intermediate could be much shorter than the half-life for macrocyclization. We cannot offer an explanation for the failure of the intramolecular Stetter reaction of **i**, which proceeds through an intermediate which is generated reversibly. For an example of an intramolecular Stetter reaction, see: Trost, B. M.; Shuey, C. D.; DiNinno, F., Jr.; McElvain, S. S. *J. Am. Chem. Soc*. **1979**, *101*, 1284−1285. For examples of the intramolecular acyl radical cyclization, see: (a) Boger, D. L.; Mathvink, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 4008−4011. (b) Astley, M. P.; Pattenden, G. *Synlett* **1991**, 335−336.



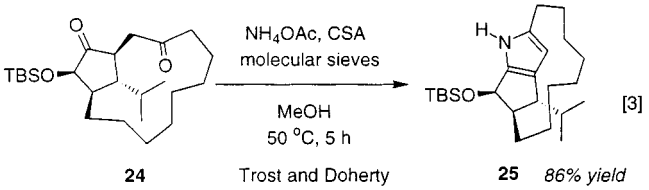
Scheme 1[a]



[a] (a) *t*-$BuNH_2$, rt, 94%; (b) LDA, TMSCl, THF, −78 to 10 °C; (c) LDA, *i*-PrCHO, −78 to 10 °C; (d) $(COOH)_2$, THF, H_2O, 71% (three steps); (e) $NaClO_2$, KH_2PO_4, 2-methyl-2-butene; (f) CBr_4, PPh_3, morpholine, 88% (two steps); (g) i. *n*-BuLi, THF, −78 °C; ii. −78 to −30 °C, 1 h **16**; iii. HCl, HFIP/TFE (1:1), −78 °C; 78%, 86% ee; (h) Bz_2O, Et_3N, DMAP, CH_2Cl_2, 90%; (i) 3-benzyl-5-(hydroxyethyl)-4-methylthiazolium chloride (10 mol %), Et_3N (0.6 equiv), 1,4-dioxane, **19** (2 equiv), 70 °C, 23 h, 77%; (j) Grubbs' catalyst (30 mol %), CH_2Cl_2, 0.0005 M, 40 °C, 30 h, 91%; (k) H_2, 10% Pd/C, THF, 89%; one crystallization from MeOH/CH_2Cl_2, 99% ee, 87% recovery; (l) NH_4OAc (50 equiv), Ti(O*i*-Pr)$_4$ (2 equiv), 140 °C, 6 h, 54%; (m) KH, SEMCl, DMF, rt, 30 min, 89%.

needles; however, recrystallization to improve the optical purity was not necessary.

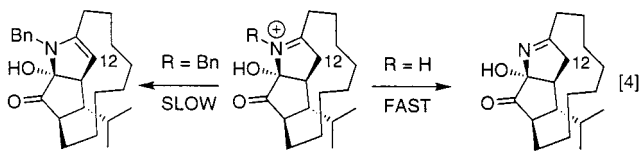
Ketopyrrole **11** was prepared from **22** in 54% yield following heating for 6 h in propanoic acid in the presence of excess ammonium acetate and 2 equiv of titanium isopropoxide. The Knorr reaction remains the low-yielding step in the synthesis and has resisted all our attempts to improve the yield. We have shown that the first step in the conversion of **22** to **11** is cleavage of the benzoate protecting group. Presumably, loss of water (or ammonia) from one of the protonated intermediate products of the Knorr reaction is inhibited by the electron-withdrawing C9 ketone carbonyl group, leading to an attrition in the yield. Support for this hypothesis comes from Trost's roseophilin work,[5l] in which the Knorr cyclization of **24** (eq 3) took place



24 **25** *86% yield*

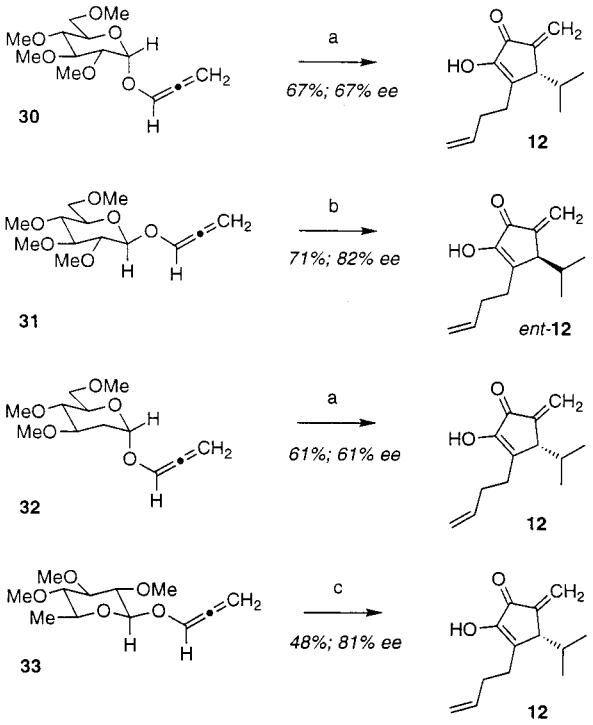
in 86% yield to give **25** under much milder conditions than for **22**. The synthesis of the ketopyrrole fragment was completed by protecting the N−H function of **11** as the SEM derivative, leading to **23** in 89% yield.

Quite a bit of effort went into optimizing the Knorr reaction leading to **11**. One of the experiments in this series deserves mention. Treatment of (±)-**22** with benzylamine in propanoic acid at 200 °C for 10 d produced *N*-benzylpyrrole **26**, an intermediate in Fürstner's synthesis of (±)-roseophilin, but in only 34% yield. The reaction mixture contained ca. 5% of (±)-**22**. The harsh conditions and the long reaction time in the case of **26** contrast starkly with the reaction conditions for the preparation of **11**. The likely reason for this large difference in reactivity is outlined in eq 4. Intermediate iminium ions **27a** or **27b** probably represent minor species which are in equilibrium with protonated ketoimines. In the case of **27a** (R = H), loss of the proton from the nitrogen atom leads to imine **28** in a fast reaction, whereas in the case of **27b** (R = Bn) a much slower loss of a proton from C12 (roseophilin numbering) leads to enamine **29**. This analysis is likely to be correct if formation of the five-membered heterocycle is rate-limiting for the Knorr reaction.



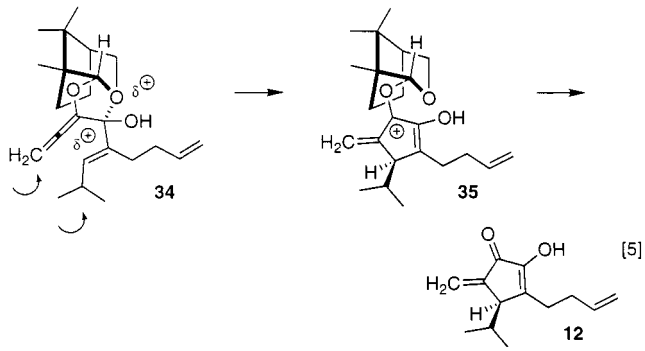
29 **27a** R = H **27b** R = Bn **28**

Scheme 2[a]



[a] (a) i. *n*-BuLi, LiCl, THF, −78 °C; ii. −78 °C, 1 h **16**; iii. HCl, EtOH, −78 °C; (b) i. *n*-BuLi, LiCl, THF, −78 °C; ii. −78 °C, 1 h **16**; warm to −40 °C; cool to −78 °C; iii. HCl, HFIP, 0 °C; (c) i. *n*-BuLi, LiCl, THF, −78 °C; ii. −78 to −45 °C, 1 h **16**; cool to −78 °C; iii. HCl, HFIP, 0 °C.

The origins of the enantioselectivity of the cyclopentannelation reaction are not known to us with certainty. Some observations which have allowed us to form a working hypothesis are summarized in Scheme 2, which shows the reactions of four sugar-derived chiral auxiliaries with **16**. Comparison of the results from α-D-glucose-derived auxiliary **30** and α-D-2-deoxyglucose-derived auxiliary **32** reveals only a small attrition in yield and enantiomeric excess (61% ee vs 67% ee) upon deletion of the methoxy group from C2 of **32**. This shows that the C2 methoxy group in **30** exerts only a small influence on the optical purity of the cyclic product. Auxiliaries **31** and **33** are derived from β-anomers of D-glucose in the case of **31** and L-6-deoxyglucose in the case of **33**. Auxiliary **33** leads again to **12**, whereas **31** gives the enantiomer, *ent*-**12**. Enantiomeric excesses of **12** and *ent*-**12** from the two reactions were essentially identical (81% ee vs 82% ee, respectively), whereas the yield of product from **33** was significantly lower than in any of the other cases. The results from **31** and **33** show that the methoxy group at C6 of **31** exerts no influence on the optical purity of the product. Consequently, neither of the two methoxy groups on the auxiliary which are closest to the allene function, the ones at C2 and C6, and which would have been expected to exert the dominant influence on the stereochemical course of the cyclization, have much effect on the optical purity of the product. The results of Scheme 2 reveal something else, that the absolute stereochemistry of the product correlates with the absolute stereochemistry of the anomeric carbon atom, regardless of whether the allene is α or β. Putting all this together, one is led to the conclusion that the critical interaction which influences the absolute stereochemistry of the product in each case involves the pyran oxygen atom of the auxiliary. This is consistent with the observation, mentioned in the introductory paragraph, that good yields for the cyclization of compounds such as **5** require a (1-alkoxy)alkoxy substituent on the allene. This indicates that the distal oxygen atom on the auxiliary must participate in the product-determining transition state. Equation 5 indicates the form that such an interaction may take in the case of the camphor-derived auxiliary **17**. Upon treatment with

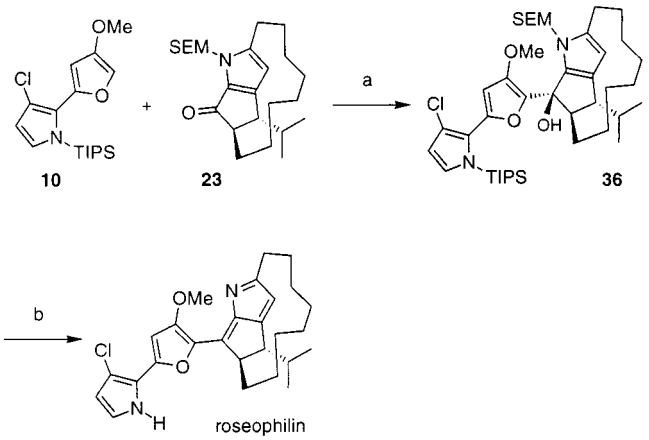


acid, the adduct of **17** and morpholino amide **16** fragments to an allenyl ketone which is rapidly protonated on the carbonyl oxygen atom. This generates the pentadienyl carbocation in the same way that **5** led to **6**. As structure **34** (eq 5) indicates, the pentadienyl cation is stabilized by donation of the axial electron pair of the pyran oxygen atom, a process which limits the conformational mobility of **34**. This interaction also has the effect of placing the ethylene bridge of the auxiliary in closer proximity to the pentadienyl cation in such a way as to block the α face of the cation. As a result, conrotation is favored to occur in the indicated counterclockwise direction so as to move isopropyl and butenyl groups away from the ethylene bridge of the auxiliary. Oxo cation **35**, which is the intermediate product of the cyclization event, undergoes fragmentation to **12**. Equation 5 is a working hypothesis which can be tested by designing and preparing the next generation of chiral auxiliaries.

The next generation of chiral auxiliaries are probably not going to be sugars. Although the β-anomers of the sugar-derived auxiliaries proved themselves to be capable of providing products in good enantiomeric excesses, the nucleophilicity of the allenyl anions was attenuated relative to **17**. Whereas it was necessary to add several equivalents of anhydrous LiCl to solutions of sugar-derived allenyllithiums in order for addition to morpholino amides to take place, no such additions were required in the case of **17**. The chemistry leading to **11** through **12** is robust: more than 1 g of **22** (>99% ee) has been prepared. This prompted us to complete an enantiospecific synthesis of the natural product.

Fürstner and Terashima had independently reported syntheses of the pyrrolylfuran fragment of roseophilin.[5a,b] We prepared **10** according to Fürstner's detailed procedure and attempted the coupling with **23** (Scheme 3). Since Fürstner had also reported the conversion of (±)-**23** to (±)-roseophilin,[5a] we were unprepared for the difficulty that we experienced in duplicating his work. Ketone **23** is readily enolizable; therefore Fürstner's procedure called for lithiation of **10** at C8, transmetalation with cerium trichloride, and addition of the furylcerium species to **23**. Our initial attempts to duplicate this reaction failed completely, and only starting materials were isolated. A series of control experiments showed that lithiation of **10** was taking place. Deuteration or stannylation at C8 of **10** took place efficiently. Our suspicion that the quality of the cerium trichloride was to blame for our failure did not appear to be valid, since lithiation of **10** and treatment with cerium trichloride, followed by cyclohexanone, led to the expected product. Furthermore, addition of methylcerium dichloride or butylcerium

Scheme 3[a]



[a] (a) i. *s*-BuLi, THF, −50 °C, 30 min; ii. $CeCl_3$, −78 to −50 °C, 30 min; −50 °C, 1 h; iii. **23** (0.3 equiv), −78 °C to room temperature; (b) i. xs TBAF, 50 °C, 18 h; ii. aqueous HCl, 65% (two steps from **23**).

dichloride to **23** also led to the anticipated tertiary alcohols. The cerium trichloride for each of the experiments was dried, in two ways, according to the procedure described by Imamoto and according to Fürstner's protocol, which lent further support to our conviction that the quality of the reagent was good.[15] However, addition of cerium trichloride to the solution of lithio **10** always led to a heterogeneous mixture, and it is a truism that heterogeneous reactions are often difficult to reproduce. We were particularly perplexed by the ease with which we were able to add methyl- and butylcerium dichloride to **23**. Consideration of this result led us to the solution of the problem. Methyllithium and *n*-butyllithium are both strongly basic, and the transmetalation to cerium is undoubtedly very fast. The furyllithium species which is derived from **10** is much less basic, and the transmetalation step with cerium trichloride is much slower and was not proceeding to completion. By following Fürstner's conditions which call for transmetalation to cerium during 2 h at −78 °C and the use of 4 equiv of the furylcerium species, we were generating mixtures of furylcerium and furyllithium species. Since **10** was used in a 4-fold excess over **23**, there was always enough furyllithium present in solution to convert **23** to the enolate before any addition of the furylcerium could take place. The key to success was to ensure that the transmetalation proceeded to completion, and the key modification of Fürstner's conditions was to warm the solution of the furyllithium with cerium chloride from −78 to −50 °C during 30 min, maintain that temperature for 1 h, and then cool the solution containing the furylcerium species to −78 °C again before adding **23**. Under these conditions, complete consumption of **23** took place to produce the labile alcohol **36**. When the addition reaction was performed on larger scale, it was possible to detect a change in the appearance of the reaction mixture after warming. After warming to −50 °C, the reaction was still heterogeneous, but there was considerably less suspended material than before. Warming the solution much above −50 °C led to extensive decomposition of the anion. Deprotection of the two silicon-containing protecting groups in **36** with TBAF, followed by exposure to aqueous HCl in a separatory funnel, led to roseophilin hydrochloride in 65% overall yield from **23** as a brilliant purple solid. Synthetic roseophilin was identical with natural material from Professor Seto's group, which was kindly provided by Professor Yoichi Hayakawa.

(15) (a) Takeda, N.; Imamoto, T. *Org. Synth.* **1998**, *76*, 228−238. See also: (b) Dimitrov, V.; Kostova, K.; Genov, M. *Tetrahedron Lett.* **1996**, *37*, 6787−6790.

Conclusions

This concludes a description of an enantioselective total synthesis of natural (22*R*,23*R*)-roseophilin in 15 steps and in 7.0% overall yield from 5-hexenal **13**, taking into consideration the loss during crystallization of **22**. The asymmetric cyclopentannelation reaction proved to be very well-matched to this problem: we were able to prepare slightly more than 100 mg of optically pure roseophilin. It is noteworthy that the auxiliary is "traceless": it is lost during the cyclization step.

The difficulties that we and others have experienced[16] in carrying out the final steps according to Fürstner's protocols highlights an often overlooked fact about total synthesis: attention to seemingly trivial detail can be decisive to the success or failure of a reaction. In this case, it is conceivable that the particle size of the cerium trichloride was finer in Fürstner's experiments than in ours. A larger surface area for the insoluble (or partly soluble) reagent would have resulted in faster kinetics for the transmetalation step.

Experimental Section

(*R*)-3-But-3-enyl-2-hydroxy-5-methylene-4-(methylethyl)cyclopent-2-en-1-one 12. To a solution of allene **17-H** (1.240 g, 5.953 mmol) in THF (30 mL) at −78 °C was added *n*-BuLi (2.50 mL, 2.46 M in hexanes, 6.15 mmol). After 20 min, a solution of amide **16** (871 mg, 3.67 mmol) in THF (30 mL) at −78 °C was added via cannula. The reaction mixture was warmed from −78 to −30 °C over 1 h, cooled to −78 °C, and quenched by rapid addition, through a large bore cannula, to HCl in HFIP/TFE (generated by addition of 7.5 mL of acetyl chloride to a solution of 30 mL of HFIP and 30 mL of TFE) at −78 °C. The flask was removed from the cooling bath, warmed to room temperature, and diluted with saturated $NaHCO_3$, pH 7 buffer, brine, and EtOAc. The aqueous phase was extracted with EtOAc (3×), and the combined organic extracts were washed with brine (1×) and dried over $MgSO_4$. Purification by flash column chromatography on silica (5% to 10% EtOAc in hexanes) gave cyclopentenone **12** (589 mg, 78% yield, 86% ee) as a colorless oil: $R_f = 0.35$ (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (s br, 1H), 6.10 (s, 1H), 5.83 (ddt, $J = 17.1$, 10.5, 6.1 Hz, 1H), 5.41 (s, 1H), 5.07 (dd, $J = 17.1$, 1.5 Hz, 1H), 4.99 (d br, $J = 10.5$ Hz, 1H), 3.20 (s br, 1H), 2.77 (m, 1H), 2.45−2.22 (m, 3H), 2.15 (sept d, $J = 7.1$, 2.9 Hz, 1H), 1.10 (d, $J = 7.1$ Hz, 3H), 0.65 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.8, 151.1, 144.4, 141.7, 137.4, 116.7, 115.3, 47.1, 30.7, 29.1, 25.9, 21.7, 16.3; IR (neat) 3310 (br), 2965, 1680, 1625 cm^{-1}; EIMS *m*/*z* 206 (M^+, 35), 164 (79), 163 (100), 135 (65), 123 (91), 122 (43), 117 (36); HREIMS calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1283; chiral HPLC (25 × 1 cm Chiralcel OD column, 1 mL/min, 254 nm; 2.5/97.5 2-propanol/hexanes) t_R = 23.8 min (major), t_R = 25.4 min (minor).

Roseophilin. To a solution of furan **10** (378 mg, 1.07 mmol) in THF (15 mL) at −50 °C was added *s*-BuLi (1.10 mL, 0.97 M in cyclohexane, 1.1 mmol). After 30 min, the solution was cooled to −78 °C and transferred via cannula to a suspension of $CeCl_3$ (372 mg, 1.51 mmol; dried according to ref 15a; residual water was removed with *t*-BuLi, see: Paquette, L. A. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1995; Vol. 2, p 1035) in THF (15 mL) at −78 °C. The solution was warmed to −50 °C over 30 min, maintained at −50 °C for 1 h, and cooled to −78 °C. A solution of ketone **23** (119 mg, 0.295 mmol) in THF (15 mL) at −78 °C was added. The reaction mixture was warmed from −78 °C to room temperature over 15 h and diluted with saturated $NaHCO_3$, water, and ether. The aqueous phase was extracted with ether (4×), and the combined organic extracts were washed with brine (1×), dried over Na_2SO_4, concentrated, and filtered through neutral aluminum oxide (activated, ∼150 mesh; eluted with hexanes followed by EtOAc). Crude alcohol **36** was dissolved in THF (40 mL), and TBAF (2.0 mL, 1.0 M in THF, 2 mmol) was added. The reaction mixture was heated

(16) We thank professors Dale Boger and Barry Trost for discussing their results with us prior to publication. Boger, D. L.; Hong, J. *J. Am. Chem. Soc.* **2001**, *123*, 8515−8519.

to 50 °C for 18 h and diluted with ether, water, and saturated $NaHCO_3$. The aqueous phase was extracted with ether (4×), and to the combined organic extracts was added 1 M HCl. After 5 min of agitation, the two-phase system was neutralized with saturated $NaHCO_3$ and diluted with brine, and the organic phase was dried over Na_2SO_4. Purification by flash column chromatography on neutral aluminum oxide (activated, ~150 mesh; eluted with CH_2Cl_2 to 10−20% EtOAc in CH_2Cl_2; fractions containing roseophilin were combined, concentrated, diluted with ether, and acidified with concentrated hydrochloric acid) gave synthetic roseophilin hydrochloride (94 mg, 65%) as a red solid: $R_f = 0.58$ (20% EtOAc in hexanes; aluminum oxide); ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.89 (s br, 1H), 13.64 (s br, 1H), 7.28 (t, $J = 2.7$ Hz, 1H), 6.94 (s, 1H), 6.30 (t br, $J = 2.0$ Hz, 1H), 6.20 (s, 1H), 4.15 (s, 3H), 3.84 (dd, $J = 4.6$, 3.2 Hz, 1H), 3.60 (m, 1H), 2.85 (ddd, $J = 13.2$, 5.4, 3.7 Hz, 1H), 2.72 (d, $J = 6.1$ Hz, 1H), 2.10 (m, 1H), 2.03 (dt, $J = 14.6$, 5.4 Hz, 1H), 1.86−1.79 (m, 2H), 1.40−1.29 (m, 2H), 1.21 (m, 1H), 1.08−0.83 (m, 6H), 1.02 (d, $J = 6.6$ Hz, 3H), 0.80 (d, $J = 6.6$ Hz, 3H), 0.47−0.36 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 165.9, 160.3, 159.3, 144.7, 135.6, 132.8, 126.7, 119.5, 116.8, 112.0, 110.9, 96.3, 60.0, 55.4, 51.6, 34.0, 33.0, 28.22, 28.20, 27.9, 27.5, 26.9, 24.8, 24.4, 21.4, 19.6; IR (neat) 3015 (br), 2940, 1615, 1575 cm^{-1}; ESIMS *m*/*z* 453.2 $[M + 1]^+$; chiral HPLC (25 × 1 cm Chiralcel OD column, 1 mL/min, 306 nm; 1/99/0.1 2-propanol/hexanes/Et_2NH) $t_R = 22.3$ min.

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Supporting Information Available: Experimental procedures and spectroscopic data for **17-H**, **32**, and **33**. Experimental procedures for **18**−**23** and **11**. ^{1}H and ^{13}C NMR, IR, and mass spectra for **17** and for roseophilin. Chiral HPLC traces for the recrystallization of **22**, and for racemic, natural, and synthetic roseophilin. Circular dichroism spectra for natural and synthetic roseophilin. ^{1}H NMR spectra for **11**, **12**, **14**−**16**, **18**−**20**, **22**, **23**, and **30**−**33** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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