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The Total Synthesis of Enantiopure Phalarine via a Stereospecific Pictet-Spengler Reaction: Traceless Transfer of Chirality from L-Tryptophane

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Abstract

An appropriately constructed 2-substituted derivative of L-tryptophane undergoes conversion, in a single step, to a prephalarine structure. The reaction occurs in a diastereoselective fashion, leading shortly thereafter to the naturally occurring version of the alkaloid, phalarine.

Introduction

For those who take delight in the imagination of nature, as well as in its efficiency, the alkaloid phalarine would hold a special fascination. Though, at least for the moment, no promising biological activity has been asserted on behalf of phalarine (**1**),¹ it was clear from the time that we learned of its structure that our laboratory would inevitably find itself engaged in its total synthesis. We have been participants in a long-term tutorial centered on indole related alkaloids dating back to the mitomycins.^{2–11} The novelty of the propeller-like interlocking of the gramine related (EF) moiety, with the carboline related (ABC) subunit, via ring C served well to invite a variety of speculative retrosynthetic designs of a biomimetic flavor targeting phalarine. Aside from the heuristic challenges which are posed by the phalarine structure per se, it seemed likely that the struggle to accomplish its total synthesis in a concise way would offer opportunities to teach us more about the chemistry of indole-based natural products. Over the years, indoles have provided diverse contexts for posing and answering subtle questions of mechanistic nuance, which have in turn, stimulated new departures in synthesis. Particularly insightful in this regard have been alkaloids, which share with phalarine the features of dearomatized “indolic” sectors.¹² It seemed not unlikely that a total synthesis excursion directed to phalarine would oblige us to re-visit core issues which have provoked stimulating discussion and fruitful research since the 1950s.^{13–17}

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Supporting Information Available: Full experimental details, the first generation approach to **37**, alternative decarboxylation methods for **42**, analytical enantiodiscriminating HPLC data for **41** and *ent*-**41**, and diagnostic 2D NMR data for **41** are provided. This information is available free of charge via the Internet at <http://pubs.acs.org>.

Results and Discussion

Our earliest synthetic intuitions to address phalarine contemplated setting up circumstances to achieve the oxidative union of a suitably protected tetrahydro β -carboline with 3,4-dimethoxyphenol (Scheme 1).¹⁸ The systems were to be presented to allow for the possibility of a rather concise route to reach phalarine. While, in practice, some interesting instances in this regard were demonstrated, the unfettered reacting systems did not spontaneously converge such as to give rise to pre-phalarine substructures (see for instance **2** + **3** $\rightarrow$ **4** and **6** + **3** $\rightarrow$ **7**). Following these reverses, we next attempted to join the subunits with an orienting connectivity, which is more predisposed to progress toward phalarine-type architecture.

As previously reported, recourse to orchestrated mergers of the required subunits eventually found success and, in time, resulted in a total synthesis of phalarine, albeit as its racemate (*vide infra*, Scheme 2).¹⁹ For instance, the required subunits could be joined via reaction of an N-tosyl 3,3-spirosubstituted oxindole with a suitably nucleophilic aryllithium reagent (see **8** + **9** $\rightarrow$ **10**). Deprotection of the MOM group of **10** followed by acid mediated treatment, as shown, afforded **14**.²⁰ which lent itself to conversion to racemic phalarine (*rac*-**1**).¹⁹ At the mechanistic level, we envisioned that under acidic mediation **11** had cyclized to afford **12**, which suffered suprafacial 1,2-rearrangement of the Wagner–Meerwein genre,^{21,22} thereby progressing to **13** and thence to **14**.

With the total synthesis of the phalarine racemate accomplished, we projected that a clear route to produce substantially enantiopure phalarine was also at hand. The thought, naïve in hindsight, was that one had only to start with enantiopure **8** to reach enantiomerically pure **1**. In fact, as was disclosed, we were able to reach enantiopure (*S*)-**8** via L-tryptophane (Scheme 3).²⁰ This compound was coupled to the model aryllithium reagent species **15**, to provide (*S*)-**16**. After deprotection of the MOM group, the resultant phenol (*S*)-**17** was treated with CSA in the usual way to provide key intermediate **18**, but as the racemate.²⁰ Even when the reaction was interrupted at a very early stage, **18** still emerged as the racemate. Furthermore, in a control experiment, substantially enantiopure **18** was obtained by “enantiodiscriminating HPLC” (so called “chiral HPLC”)²³ and re-subjected to the conditions for cyclization of (*S*)-**17** as provided above. While there was erosion in the optical purity of **18**, the rate of racemization was far too slow to account for the conversion of enantiopure (*S*)-**17** to racemic **18**. Hence, the formation of racemic **18** does not arise from racemization of the substantially enantiopure product.²⁰

We reasoned that upon acid treatment, (*S*)-**17** undergoes cyclization by joining the tosylamino group and the ketone function to give rise formally to (*S*)-**19**. The latter would presumably undergo retro-Mannich cleavage, leading to achiral **20**. Two pathways could be envisioned for the conversion of achiral **20** to racemic **18**. In one instance, a Pictet–Spengler reaction²⁴ occurs at the α -indolic carbon of **20** (see **21**). This step would be followed by attack of the phenolic hydroxy group onto the cationic β -center of the “indolenine” moiety, leading to **18**. Alternatively, Mannich capture to reproduce **19** can be followed by a suprafacial spiro fused Wagner–Meerwein rearrangement (WMR)²¹ to give **21** (of course as the racemate) and thence **18**. While achiral **20** appears to be a necessary player in the reaction coordinate from (*S*)-**17** to racemic **18**, these two sub-variations to generate **21** are not readily distinguishable.²⁵ They differ only as to whether the penultimate pre-phalarine cyclization product **21** had arisen from the achiral iminium ion **20** by direct Pictet–Spengler reaction at C2, or only by Wagner–Meerwein-like rearrangement of **19**. In the strictest form of the latter view, a direct Pictet–Spengler reaction at C2 does not occur with the aryl group already in place.^{25,26}

We then explored the reversibility of the cyclization–“rearrangement” pathway. It was found, by interruption of the CSA-induced reaction to fashion **18**, that starting (*S*)-**17** was obtained with no detectable loss in optical integrity.²⁰ This “optical stability” could be interpreted to mean that the recovered (*S*)-**17** had never entered into the path toward **18**. Alternatively and more likely, the early steps might well be reversible but the initial achiral structure **20** is already committed to advance to product **18**. Therefore the optical purity of recovered (*S*)-**17** is not “contaminated” by racemate arising from the “return” of achiral **20** to the feedstock of starting material.

Mechanistic questions aside, the retro-Mannich cleavage sequence had undermined our hopes to synthesize optically pure phalarine from pure (*S*)-**8**, thereby frustrating our goal of determining the absolute configuration of the natural product.²⁰ Before describing how this problem was overcome, we relay results of some additional preliminary studies, which helped fashion the ultimately successful strategy. While the routes that we had described to systems such as **18** were reasonably convergent, we decided to explore a significant variation to the chemistry described above. *The thought was that we should build an indole system that already contained a suitable aromatic structure at the α -carbon.* At the β -carbon, there would already reside a β -ethylamino group modeled after tryptamine. Such systems were ultimately helpful in sharpening our mechanistic thinking on the Pictet–Spengler reaction, as well as in preparing for the ultimately successful sequence (vide infra).

As related elsewhere,²⁷ the indole type system was constructed from a sequence that started with a Castro type coupling²⁸ of a suitable acetylide (in this case, a protected butynol) and an appropriate aromatic ring that would become the precursor of the final gramine subunit of **1** (Scheme 4). After this merger, the resulting internal acetylene linkage was combined with 2-iodobenzenesulfonamide in a Larock indole synthesis.^{29,30} In this way, compound **23** was fashioned, albeit accompanied by significant amounts of the alternate indole, which arises by interchanging the functionalities at the α and β carbons. With **23** in hand, the tryptamine side chain was installed by conventional chemistry, giving rise to **24**. Happily, condensation of **24** with formalin under Pictet–Spengler conditions gave rise to **25**. This sequence provides corroboration for the feasibility of **20** as an intermediate, though it does not definitively answer the mechanistic uncertainty discussed above, as to whether the cyclization (Pictet–Spengler) step had, in fact, occurred at C2 or had first taken place at C3 followed by Wagner–Meerwein-like rearrangement (see question posed in Scheme 3).

With this more convergent (albeit less chemospecific) strategy in place, we were able to address the question of the minimum criteria necessary to realize an indolenine to phalarine-

type rearrangement. It will be recalled that at the outset of our synthesis studies, probe substrate **26** did not, in fact, rearrange to **27** under a variety of conditions;²⁰ thus, it was of considerable interest to ascertain the substitutions that enable such a rearrangement (Scheme 5). Accordingly, compound **28**, lacking the N-tosyl function and containing an *N*_b-methyl group, rather than a carbonate, was synthesized. Remarkably, after treatment with formaldehyde under Pictet–Spengler conditions, **28** gave rise to **29**.²⁷ Thus, at least in this setting, it was demonstrated that with an aryl group at C2 of the indole, and with *N*_a lacking a tosyl group at the nitrogen, cyclization occurs more rapidly at C3 and the indolenine is actually quite stable. Once again, as in the case of **28**, there was no indication that a spiroindolenine *lacking the N_a-tosyl group or an equivalent*, could subsequently be induced to undergo rearrangement to the phalarine series.

However, we did observe another reaction that demonstrates the interconnectivity of the various pathways. Thus, treatment of **29** with CSA, in the absence of formaldehyde, leads smoothly to **28**. It seems very likely that this regression arose from a retro-Mannich reaction (about which we had speculated earlier) to give iminium salt **30**, which following hydrolysis, affords **28**. Thus, it had been shown that the mechanistically relevant structures reside on a connectable energy surface.

We return now to the problem of a total synthesis of optically defined phalarine. Given the information provided above, it did not seem very likely that we could defeat the potentiality for retro-Mannich-induced loss of enantiointegrity at the quaternary β-carbon in the spiroindolenine en route to phalarine (see Scheme 3). Happily, an interesting alternative solution presented itself.^{25,31–33} A structure such as **31** would be generated in the tryptophane ester series and this would subsequently be converted to a pre-phalarine product (**32**; Scheme 6). Key intermediate **32** contains an apparently extraneous stereogenic center, but of known configuration (see circle), in addition to the *cis*-related junction centers (see asterisks), which are central to the structure of phalarine. Conversion of **32** to phalarine itself, presumably by radical mediated decarboxylation,^{34,35} would lead to the target in substantial optical purity. It would be desirable if compound **31** could be produced in a stereospecific fashion. Otherwise, it would be necessary to separate diastereoisomers from whatever reaction is used to give **32** from **31**. In any case, it would be critical to know the relative configuration of the ester and *cis*-related junction centers in **32**. Clarity, beyond doubt, is needed on the matter of relative configuration, since this relationship will define the absolute stereochemical assignment of synthetic phalarine after decarboxylation, indolization, and installation of the gramine side chain.

It was at this point that we decided to exploit the chemistry demonstrated above with the pre-existing aromatic substitution at C2 of the indole. Given the need for an enantiomerically defined amino acid corresponding to tryptophane and the lack of chemospecificity in the synthesis of **23**, the program for construction of the required substrate was revamped and we started with L-tryptophane methyl ester (**33**, Scheme 7).³⁶ Fortunately it was possible to incorporate some known chemistry for the conversion of material **33** to iodo compound **34**.³⁷ We then synthesized compound **36** to serve as a coupling partner with **35**, which was derived from **34** using standard methods. This synthesis involved creation of the borate ester linkage with a view toward a Suzuki coupling. In this fashion, the aryl group could hopefully be installed with regiocontrol. Indeed, this plan could be reduced to practice and compound **37** was in hand.³⁸ Deprotection of the MOM ether afforded **38**. Following early studies resulting in low yielding Pictet–Spengler reactions with the free primary amine, it was decided to carry out the critical cyclization when *N*_b was secondary.^{39,40} Toward this end, **38** was converted by reductive amination with benzaldehyde to **39**. Gratifyingly, treatment of **39** with formaldehyde led to formation of the pre-phalarine molecule **41** as a single diastereoisomer in excellent yield.⁴¹

At this point, it was of course critical to establish the relative configuration of the tryptophane-like methyl ester in **41**, with the *cis*-related carbon bridge of phalarine. Two lines of evidence were marshaled to deal with this problem. Initially, the relative stereochemical assignment of **41** was determined from a series of 2D NMR experiments (see Supporting Information). By establishing the positions of the indoline and methoxy-bearing aryl ring with respect to the position of the *N*-benzyl piperidine ring relative to the known chiral center, the relationship of the two unknown tetrasubstituted stereocenters (positions 2 and 3 assigned as *R* and *S* respectively, Schemes 7 and 8) was deduced.

While the NMR based deduction certainly seemed to be convincing, full confidence in the correctness of the assignment of the relative stereochemistry within **41** was so central to our final assignment of absolute stereochemistry, that additional corroboration was sought. As it turned out, it was possible to obtain compound **41** in crystalline form (mp 199–200°) suitable for crystallographic study. Indeed, this determination confirmed that the assignment of relative configurations, initially determined by NMR, was correct (Figure 1). Given the fact that we had started with L-tryptophane, the configurations of the three stereogenic centers in compound **41** could now be assigned as shown (Scheme 8), in an absolute sense.

Of course, the highly diastereoselective nature of the transformation of **39** → **41** was extremely gratifying and provided the basis for the synthesis of enantiomerically defined phalarine (vide infra). It is of interest to conjecture on the origin of the powerful diastereoselectivity in the cyclization step. This is not a simple matter, given that the mechanistic ambiguity as to the nature of the cyclization remains (see Scheme 3). In one view, the stereochemistry of the final **41** is determined by a cyclization event at C3 (β-carbon of the indole). The configurational information at C3 is transferred to C2 by suprafacial WM rearrangement, which then ultimately relays its stereochemical information to C3 by cyclization of the resident phenol group (**40a**). However, if Pictet-Spengler reaction occurs at C2, the stereochemistry at that center (i.e. α-carbon of the indole) is defined initially through the iminium–C2 cyclization event and, only subsequently, at C3 through the attack of the phenolic linkage (see **40b**). Until this issue is fully explicated, a satisfying rationalization of the basis of the face selectivity of the Pictet-Spengler reaction cannot be offered. A further complication at the level of interpretation arises from the possibilities of kinetic or thermodynamic control in each of the two cyclization modes (see **40a** and **40b**).

With the stereochemical assignment of **41** secure,⁴² we directed our attentions to completing the total synthesis of enantiopure phalarine, parenthetically allowing for the determination of its absolute configuration. Indeed, we were able to connect with an established intermediate in our earlier total synthesis of racemic phalarine¹⁹ by excision of the carboxyl group and its replacement by a hydrogen atom. Thus, ester saponification provided **42**, which was induced to decarboxylate, as shown, to provide the *N*-benzyl derivative **43** (Scheme 8).⁴³ The method used here was achieved only after significant optimization efforts for what proved to be a challenging decarboxylation step.⁴⁴ Debenzylation followed by reductive methylation provided the junction compound **14** in good yield. Since this compound, in the racemic series, had been converted to racemic **1**,¹⁹ a clear route to enantiopure phalarine was now in hand. It was only necessary to conduct the same steps as had been used in the substantially enantiopure series. This was in fact accomplished as shown.

Thus, the synthesis in the optically defined series led from **14** to optically pure intermediates **44** → **47**, which were characterized in a fashion which also included their optical rotations. In the last step of the linkage exercise, compound **47** was converted to (–)-phalarine, which was now substantially enantiomerically pure. The optical rotation of the fully synthetic phalarine obtained was –84° (*c* 0.24, MeOH); whereas, the optical rotation of natural phalarine has been reported to be –92° (*c* 0.0075, MeOH).¹ Clearly then, we had, by chance,

synthesized Nature's phalarine. The small discrepancy in the value of the levorotary direction causes us no concern for several reasons. Already, at the stage of compound **14** it was possible to resolve the two enantiomers from the racemate synthetic program by HPLC.²⁰ Correspondingly, the fully synthetic version of **14** arrived at in this work showed only one of the two peaks associated with the previously synthesized racemate.¹⁹ Therefore, we concluded that the synthetic material is substantially enantiopure at the stage of **14**.⁴⁵ Moreover, under suitable HPLC conditions, it was possible to distinguish the antipodes of the previously synthesized *rac*-phalarine. Therefore, the substantially single peak⁴⁶ exhibited by the totally synthetic (–)-phalarine prepared in the manner described above confirms its very high optical purity.⁴⁷ In short, we now know that the total synthesis of substantially optically pure (–)-phalarine has been accomplished and are confident as to the rotations quoted above.

Conclusion

In summary, it would seem as predicted above, that the total synthesis of (–)-phalarine and assignment of its absolute configuration has provided significant learning opportunities. While not all subtle mechanistic issues have been fully clarified, the work, as it stands, provides some significant insights into the chemistry of spiroindolenines, and more broadly, their intermediacy in apparent Pictet–Spengler reactions of 2-substituted indoles. This question had not previously been addressed in detail. In the case at hand, the 2-substituted indole had contained an aromatic structure wherein the pendant phenolic hydroxyl group could capture the transient cationic species at C3, thereby establishing the propeller-like display of phalarine.

Globally, the chirality inherent in L-tryptophane had been transferred to phalarine in a traceless fashion since the asymmetry initially present within the tryptophane can be discerned in the ultimate phalarine product only in a legacy sense. It is well to emphasize that our mission had been accomplished, by gathering insights from the toils of the true pioneers of indole alkaloid chemistry, and fashioning productive experiments from that corpus of hard won knowledge.^{12–18,26}

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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41. As was the case with compound **29**, the formation of **41** is completely reversible. Upon resubjection to the reaction conditions to form **41** without dessicant, **39** is cleanly recovered without any loss in optical purity (data not shown).
42. Enantiodiscriminating HPLC data supporting the enantiospecific formation of **41** and ent-**41** from **39** and ent-**39** respectively is included in the Supporting Information. These data also eliminated any concern for a loss of optical purity during Suzuki coupling to form compound **37**.
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45. Note that we had also verified complete optical purity at the stage of compound **39**.
46. We would conservatively estimate the optical purity of our synthetic phalarine as 98%.
47. Attempts to evaluate the reversibility of the late steps in the synthesis were undertaken. The thought was to subject the final optically pure phalarine to treatment with CSA, asking whether it would undergo racemization. However, in the event, this type of treatment resulted in major decomposition of phalarine, no doubt owing to the instability of gramine sidechains to acidic agents.

Figure 1.
ORTEP diagram for compound **41**.

Scheme 1.

Scheme 2.
Racemic route to phalarine.

Scheme 3.

Scheme 4.

Scheme 5.

Scheme 6.

Scheme 7.

Scheme 8.