

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

John D. Trzupke,[†] Dongjoo Lee,[†] Brendan M. Crowley,[†] Vasilios M. Marathias,[‡] and Samuel J. Danishefsky^{*,†,§}

Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, New York, New York 10065, Pfizer Global Research and Development, 200 Cambridgepark Drive, Cambridge, Massachusetts 02140, and Department of Chemistry, Columbia University, Havemeyer Hall, 3000 Broadway, New York, New York 10027

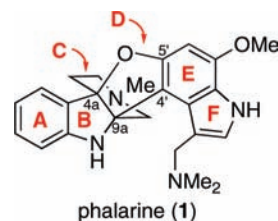
Received April 19, 2010; E-mail: s-danishefsky@ski.mskcc.org

Abstract: An appropriately constructed 2-substituted derivative of L-tryptophan undergoes conversion to a prephalarine structure in a single step. 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 (**1**) would hold a special fascination. Although, at least for the moment, no promising biological activity has been asserted on behalf of phalarine,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 moiety (EF) with the carboline-related subunit (ABC) via ring C served well to invite a variety of speculative retrosynthetic designs of a biomimetic flavor targeting phalarine. Aside from the heuristic challenges 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 that in turn have 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 likely that a total synthesis excursion directed to phalarine would oblige us to revisit core issues that have provoked stimulating discussion and fruitful research since the 1950s.^{13–17}



Results and Discussion

Our earliest synthetic intuitions for addressing phalarine contemplated setting up circumstances designed 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 some interesting instances in this regard were demonstrated in practice, the unfettered reacting systems did not spontaneously converge to give rise to prephalarine substructures (e.g., see **2** + **3** \rightarrow **4** and **6** + **3** \rightarrow **7**). Following these reverses, we next attempted to join the

[†] Sloan-Kettering Institute for Cancer Research.

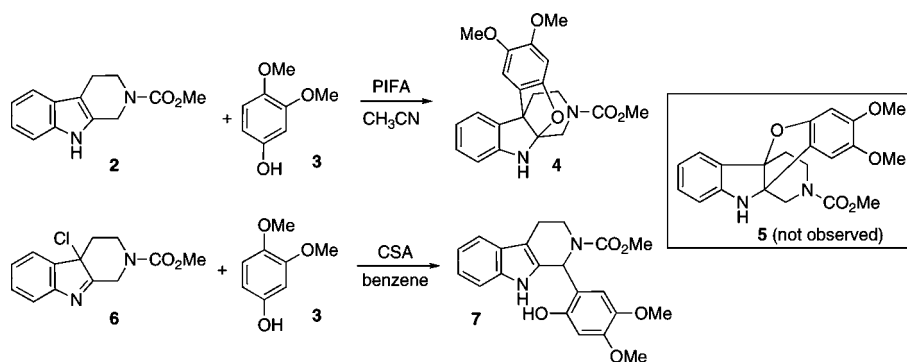
[‡] Pfizer Global Research and Development.

[§] Columbia University.

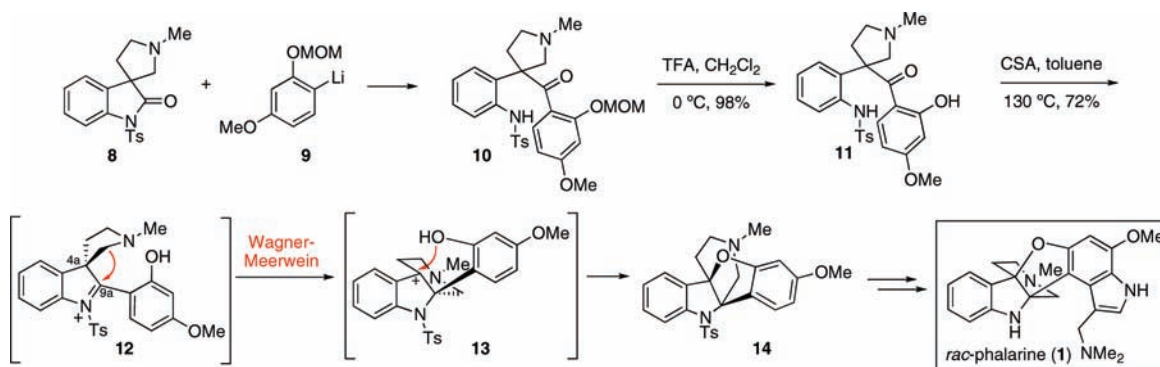
- (1) Anderton, N.; Cockrum, P. A.; Colegate, S. M.; Edgar, J. A.; Flower, K.; Gardner, D.; Willing, R. I. *Phytochemistry* **1999**, *51*, 153–157.
- (2) Danishefsky, S.; Doehner, R. *Tetrahedron Lett.* **1977**, 3031–3034.
- (3) Danishefsky, S.; Regan, J.; Doehner, R. *J. Org. Chem.* **1981**, *46*, 5255–5261.
- (4) Danishefsky, S. J.; Schkeryantz, J. M. *Synlett* **1995**, 475–490.
- (5) Depew, K. M.; Marsden, S. P.; Zatorska, D.; Zatorski, A.; Bornmann, W. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11953–11963.
- (6) Lin, S.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 512–515.
- (7) Lin, S.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1967–1970.
- (8) Lin, H.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 36–51.
- (9) Depew, K. M.; Danishefsky, S. J.; Rosen, N.; Sepp-Lorenzino, L. *J. Am. Chem. Soc.* **1996**, *118*, 12463–12464.
- (10) Edmondson, S.; Danishefsky, S. J.; Sepp-Lorenzino, L.; Rosen, N. *J. Am. Chem. Soc.* **1999**, *121*, 2147–2155.
- (11) Schkeryantz, J. M.; Woo, J. C. G.; Siliphaivanh, P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11964–11975.

- (12) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell Publishing: Malden, MA, 2000; pp 324–379.
- (13) Jackson, A. H.; Smith, P. *Chem. Commun. (London)* **1967**, 264–266.
- (14) Jackson, A. H.; Smith, A. E. *Tetrahedron* **1968**, *24*, 403–413.
- (15) Iyer, R.; Jackson, A. H.; Shannon, P. V. R.; Naidoo, B. *J. Chem. Soc., Perkin Trans. 2* **1973**, 872–878.
- (16) Jackson, A. H.; Naidoo, B.; Smith, P. *Tetrahedron* **1968**, *24*, 6119–6129.
- (17) Ganesan, A.; Heathcock, C. H. *Tetrahedron Lett.* **1993**, *34*, 439–440.
- (18) Chan, C.; Li, C.; Zhang, F.; Danishefsky, S. J. *Tetrahedron Lett.* **2006**, *47*, 4839–4841.

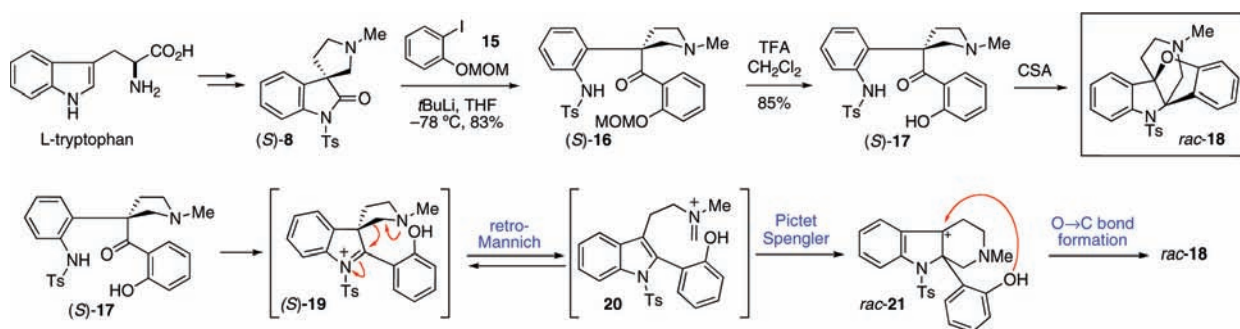
Scheme 1



Scheme 2. Route to Racemic Phalarine



Scheme 3



subunits with an orienting connectivity that is more predisposed to progress toward a 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 (see below; Scheme 2).¹⁹ For instance, the required subunits could be joined via reaction of an *N*-tosyl-3,3-spiro-substituted oxindole with a suitably nucleophilic aryllithium reagent (see **8** + **9** → **10**). Deprotection of the methoxymethyl ether (MOM) group of **10** followed by acid-mediated treatment, as shown in Scheme 2, 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**.

Having accomplished the total synthesis of the phalarine racemate, we projected that a clear route for producing 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*-tryptophan (Scheme 3).²⁰ This compound was coupled to the model aryllithium reagent species derived from **15** to provide (*S*)-**16**. After deprotection of the MOM group, the resultant phenol (*S*)-**17** was treated with camphorsulfonic acid (CSA) in the usual way to provide key intermediate **18**, which was formed 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

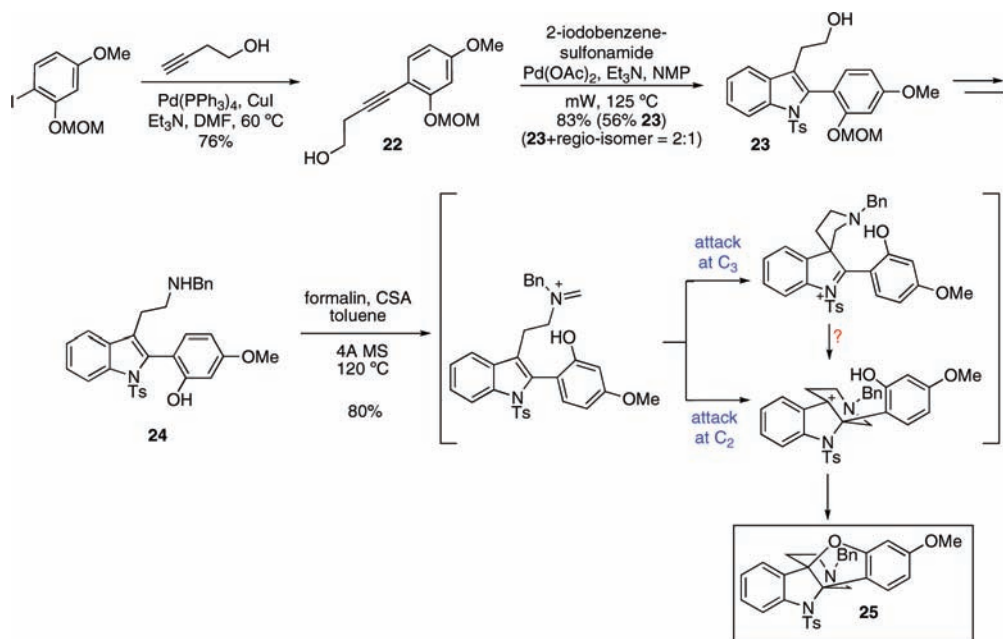
(19) Li, C.; Chan, C.; Heimann, A. C.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 1448–1450. The absolute configuration of nature's phalarine remained unknown until the present study.

(20) Li, C.; Chan, C.; Heimann, A. C.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 1444–1447.

(21) Starling, S. M.; Vonwiller, S. C.; Reek, J. N. H. *J. Org. Chem.* **1998**, *63*, 2262–2272.

(22) Olah, G. A. *Acc. Chem. Res.* **1976**, *9*, 41–52.

Scheme 4



obtained by “enantiodiscriminating HPLC” (so-called “chiral HPLC”)²³ and resubjected 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 low to account for the conversion of enantiopure (*S*)-**17** to racemic **18**. Hence, the formation of racemic **18** did 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, formally giving rise 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 would occur at the α -indolic carbon of **20** (see **21**). This step would be followed by attack of the phenolic hydroxy group at the cationic β -center of the “indolenine” moiety, leading to **18**. Alternatively, Mannich capture to reproduce **19** could 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** appeared to be a necessary player in the reaction coordinate from (*S*)-**17** to racemic **18**, these two subvariations for generating **21** were not readily distinguishable.²⁵ They differ only in regard to whether the penultimate prephalarine cyclization product **21** arises from the achiral iminium ion **20** by direct Pictet–Spengler reaction at C2 or by only a 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. By interruption of the CSA-induced reaction to fashion **18**, it was found that the starting material (*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, with the initial achiral structure **20** already being committed to advance to product **18**. Therefore, the optical purity of recovered (*S*)-**17** would not be “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 of synthesizing 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 will relay results of some additional preliminary studies that 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 in 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 in regard to the Pictet–Spengler reaction as well as in preparing for the ultimately successful sequence (see below).

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, an unprotected 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 arising from interchange of the functionalities at the α and β

(23) Even modest reflection is sufficient to reveal the noncoherence of the term chiral HPLC. With considerable misgivings, we employ it here for purposes of communicating our results. We urge that in the future, the nonfathomable term “chiral HPLC” be discontinued in favor of “enantiodiscriminating HPLC”.

(24) Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030–2036.

(25) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797–1842.

(26) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *Tetrahedron* **1963**, *19*, 247–288.

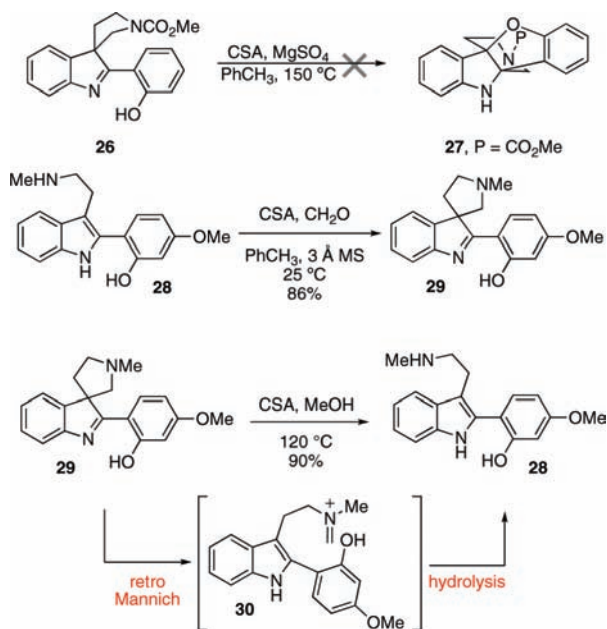
(27) Trzupek, J. D.; Li, C.; Chan, C.; Crowley, B. M.; Heimann, A. C.; Danishefsky, S. J. *Pure Appl. Chem.* **2010**, in press.

(28) Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313–3315.

(29) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689–6690.

(30) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652–7662.

Scheme 5



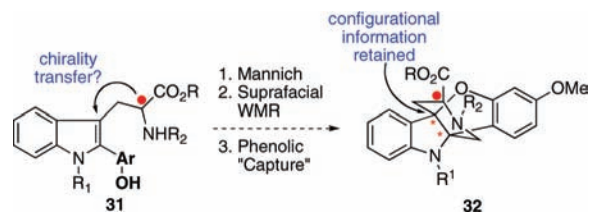
carbons. With **23** in hand, the tryptamine side chain was installed by conventional chemistry, giving rise to **24**. Happily, condensation of **24** with formalin under Pictet–Spengler conditions gave rise to **25**. This sequence provided corroboration of the feasibility of **20** as an intermediate, although it did not definitively answer the mechanistic uncertainty discussed above concerning whether the cyclization (Pictet–Spengler) step in fact occurs at C2 or first takes place at C3 and then is followed by a Wagner–Meerwein-like rearrangement (see the 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 of rearrangement. It should be recalled that at the outset of our synthesis studies, probe substrate **26** did not in fact rearrange to give **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 carbamate 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 no tosyl group at nitrogen *N*_a, 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: treatment of **29** with CSA in the absence of formaldehyde led 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 affords **28** after hydrolysis. Thus, it had been shown that the mechanistically relevant structures reside on a connectable energy surface.

We return now to the problem of the total synthesis of optically defined phalarine. Given the information provided

Scheme 6



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 tryptamine ester series, and this would subsequently be converted to a prephalarine product (**32**; Scheme 6). Key intermediate **32** contains an apparently extraneous stereogenic center with known configuration (indicated by the solid red circle) in addition to the cis-related junction centers (indicated by the asterisks) that 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 the diastereoisomers produced by 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**. Without a doubt, clarity on the matter of relative configuration was needed, since this relationship defines 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. In view of the need for an enantiomerically defined amino acid corresponding to tryptophan 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*-tryptophan methyl ester (**33**; Scheme 7).³⁶ Fortunately, it was possible to incorporate some known chemistry for the conversion of **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. The synthesis of **36** 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 was accomplished in practice, placing compound **37** 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

(31) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086–1087.

(32) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558–10559.

(33) Waldmann, H.; Schmidt, G.; Henke, H.; Burkard, M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2402–2403.

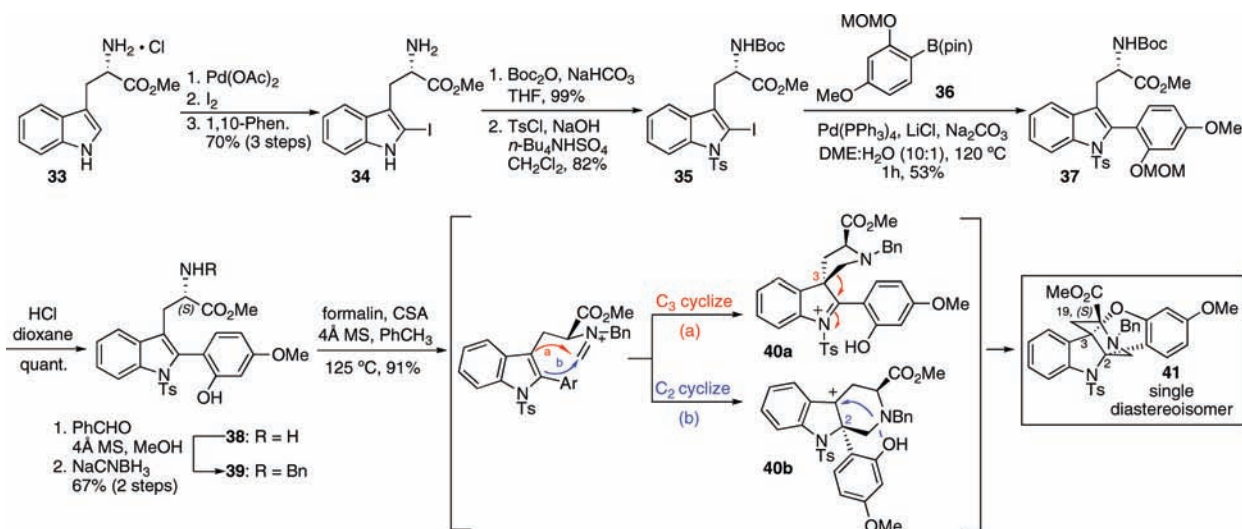
(34) Yoshimi, Y.; Itou, T.; Hatanaka, M. *Chem. Commun.* **2007**, 5244–5246.

(35) Barton, D. H. R.; Herve, Y.; Potier, P.; Thierry, J. *Tetrahedron* **1988**, *44*, 5479–5486.

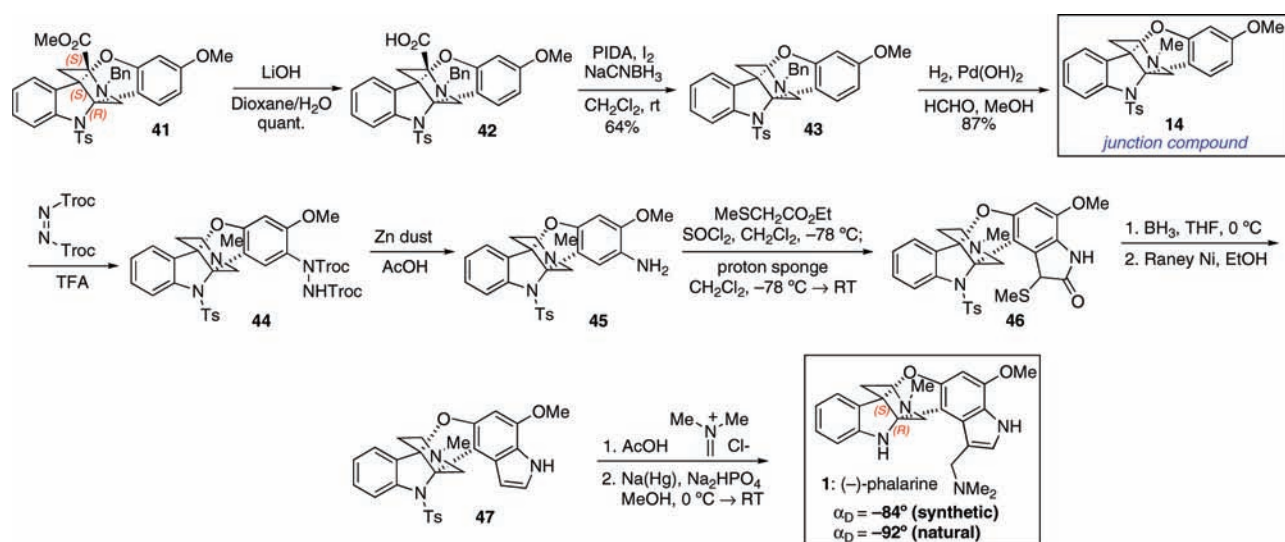
(36) An alternative method utilizing the Schollkopf auxiliary is described in the Supporting Information.

(37) Vicente, J.; Saura-Llamas, I.; Bautista, D. *Organometallics* **2005**, *24*, 6001–6004.

Scheme 7



Scheme 8



out the critical cyclization with N_b being a secondary amine.^{39,40} Toward this end, **38** was converted to **39** by reductive amination with benzaldehyde. Gratifyingly, treatment of **39** with formaldehyde led to the formation of the prephalarine 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 tryptophan-like methyl ester in **41** with respect to 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 the Supporting Information). By establishing the positions of the indoline and the methoxy-bearing aryl ring with respect to the position of the *N*-benzylpiperidine 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; see 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 the 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 analysis was correct (Figure 1). On the basis of the fact that we had started with *L*-tryptophan, the absolute configurations of the three stereogenic centers in compound **41** could then be assigned as shown in Scheme 8.

(38) The modest reaction yield was a result of competitive formation of the reduced product and detosylation of **37** under the reaction conditions. Although we could not verify the level of optical purity here, it was observed that reactions using either a stronger base or higher temperatures tended to erode the optical purity of isolated **37**.

(39) Soerens, D.; Sandrin, J.; Ungemach, F.; Mokry, P.; Wu, G. S.; Yamanaka, E.; Hutchins, L.; DiPierro, M.; Cook, J. M. *J. Org. Chem.* **1979**, *44*, 535–545.

(40) Ungemach, F.; DiPierro, M.; Weber, R.; Cook, J. M. *J. Org. Chem.* **1981**, *46*, 164–168.

(41) As was the case with compound **29**, the formation of **41** was completely reversible. Upon resubjection to the reaction conditions for formation of **41** without desiccant, **39** was cleanly recovered without any loss in optical purity (data not shown).

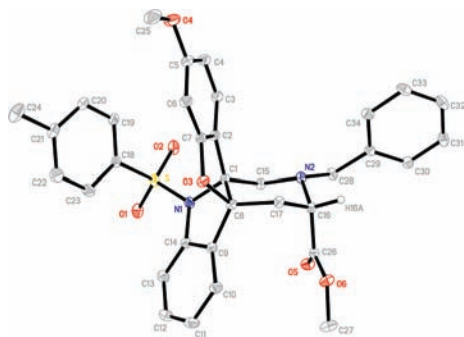


Figure 1. ORTEP diagram for compound **41**.

Of course, the highly diastereoselective nature of the transformation of **39** to **41** was extremely gratifying and provided the basis for the synthesis of enantiomerically defined phalarine (see below). It is of interest to conjecture about the origin of the powerful diastereoselectivity in the cyclization step. This is not a simple matter, in view of the fact that the mechanistic ambiguity regarding the nature of the cyclization remains (see Scheme 3). In one view, the stereochemistry of **41** is determined by a cyclization event at C3 (the β -carbon of the indole). The configurational information at C3 is transferred to C2 by suprafacial WMR, 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., the α -carbon of the indole) is defined initially through the iminium–C2 cyclization event and only subsequently at C3 through the attack by 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 attention 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, providing *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 Debonylation followed by reductive methylation provided the junction compound **14** in good yield. Since in the racemic series this compound 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** through **47**, which were characterized in a fashion that 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 Thus, it was clear that by chance we had synthesized nature's phalarine. The small discrepancy in the value of the levorotary direction caused us no concern for several reasons. As early as 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** obtained in this work showed only one of the two peaks associated with the previously synthesized racemate.¹⁹ Therefore, we concluded that the synthetic material was 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 confirmed 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 about the rotations quoted above.

Conclusion

In summary, it would seem that as predicted above, the total synthesis of (–)-phalarine and the assignment of its absolute configuration has provided significant learning opportunities. While not all of the 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 has not previously been addressed in detail. In the case at hand, the 2-substituted indole 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*-tryptophan was transferred to phalarine in a traceless fashion, since the asymmetry initially present within the tryptophan could be discerned in the ultimate phalarine product only in a legacy sense. It is important to emphasize that our mission was 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}

Acknowledgment. This work was supported by the National Institutes of Health (Grant HL25848 to S.J.D.). We acknowledge Dr. Lori Gavrin, Dr. John McKew, Dr. John Ellingboe, Dr. Walt Massefski, and Dr. Oliver McConnell at PGRD for supporting the NMR-based efforts to assign the relative stereochemistry of **41**.

(42) Enantiodiscriminating HPLC data supporting the enantiospecific formation of **41** and *ent*-**41** from **39** and *ent*-**39**, respectively, are included in the Supporting Information. These data also eliminated any concern about a loss of optical purity during the Suzuki coupling to forge compound **37**.

(43) Boto, A.; Hernández, R.; Suárez, E. *J. Org. Chem.* **2000**, *65*, 4930–4937.

(44) Several variants of free-radical-based decarboxylations were attempted. The more successful varieties are described in the Supporting Information.

(45) It should be noted that we 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 in order to determine whether it would undergo racemization. However, in the event, this type of treatment resulted in major decomposition of phalarine, no doubt resulting from the instability of gramine side chains toward acidic agents.

We also thank Kevin Yurkerwich and Professor Gerard Parkin for solving the X-ray structure of **41**. The National Science Foundation (CHE-0619638) is thanked for funding to acquire an X-ray diffractometer. S.J.D. also thanks Rebecca Wilson for stimulating discussions on the work described herein as well as on the rendering of the manuscript.

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**, diagnostic 2D NMR data for **41**, and crystallographic data for **41** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA1030968