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Addition of Lithium Anion of (Acetylmethylene)triphenylphosphorane to Nonracemic Sulfinimines: Total Synthesis of (+)-241D and Formal Total Synthesis of (+)-Preussin

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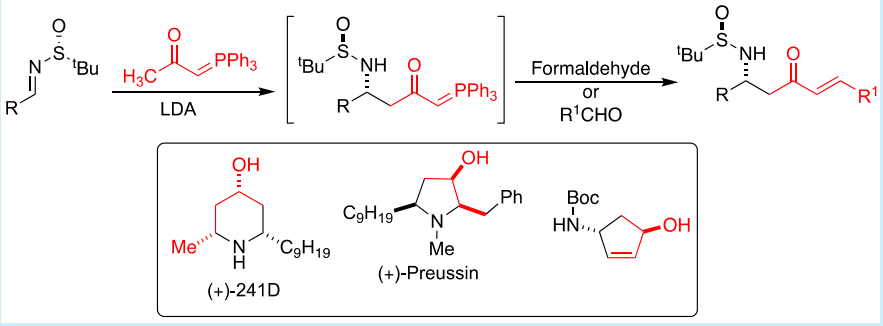

ABSTRACT: The addition of lithium anion of (acetylmethylene)triphenylphosphorane to nonracemic sulfinimines was investigated. It was found that the addition proceeded with good diastereoselectivity and further reaction of the formed sulfinimidophosphorane with several aldehydes afforded the β-sulfinamido substituted enones in good yields. The resultant enones were elaborated to the synthesis of alkaloid (+)-241D, to the formal total synthesis of (+)-preussin, and to the synthesis of aminocyclopentenol.

Substituted piperidines, piperidinones, and pyrrolidines are structural units frequently found in several alkaloid natural products.[1] These alkaloids are shown to exhibit diverse biological activities, which led to the development of different strategies for their synthesis. One of the key approaches reported for the synthesis of 2,6-disubstituted piperidin-4-ones is the intramolecular Michael addition of suitably substituted β-amino ketones containing unsaturation.[2] The Davis,[3] Troin,[4] and Sutherland[5] groups independently studied the synthesis of **2** from suitably *N*-protected β-keto phosphonates derived from corresponding β-amino acid esters. We recently disclosed the stereoselective synthesis of β-sulfinamido substituted ketones **6** from nonracemic sulfinimines **4** using a vinylogous Mukaiyama reaction and showcased their utility in the synthesis of quinolizidine and piperidinone alkaloids.[6] The synthesis of amino enones from the keto phosphonates **1** had two drawbacks. (i) Preparation of simple enones devoid of substitutions on the alkene by Wittig reaction of **1** with formaldehyde was not possible perhaps because of the elimination of the amino group. (ii) The synthesis of phosphonates was mostly restricted to derivatives of aspartic acid, β-alanine, and β-phenylalanine. Although the addition of silylenol ethers derived from several substituted methyl ketones **5** to sulfinimines was successful, the addition of silylenol ether prepared from simple methyl vinyl ketone did not proceed at all. Similarly, the addition of **5** to sulfinimines obtained from α,β-unsaturated aldehydes was futile. This prompted us to identify a suitable synthetic equivalent for procuring building blocks which are otherwise not accessible by conventional methods. Herein, we disclose the addition of the lithium anion of the Wittig ylide acetylmethylenetriphenylphosphorane ($MeCOCH{=}PPh_3$) **7** to nonracemic Davis−Ellman sulfinimines[7] and application of the formed enones in the synthesis of alkaloid (+)-241D, in the formal total synthesis of pyrrolidine alkaloid preussin and in the synthesis of amino cyclopentenol, a useful intermediate in the synthesis of carbocyclic nucleosides (Scheme 1).

The study commenced with the addition of lithium anion of **7** (generated by the deprotonation of **7** with ^{n}BuLi) to the sulfinimine **4a**. The reaction furnished the required addition

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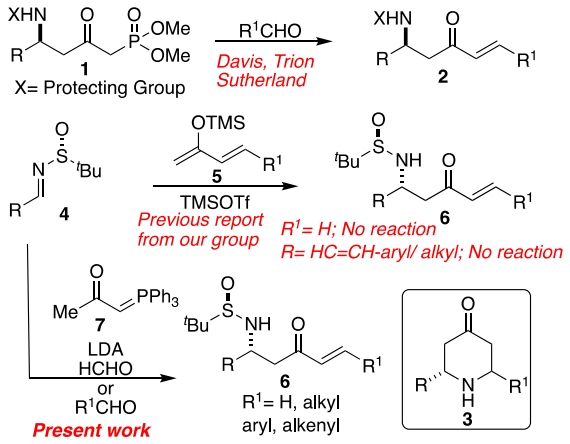
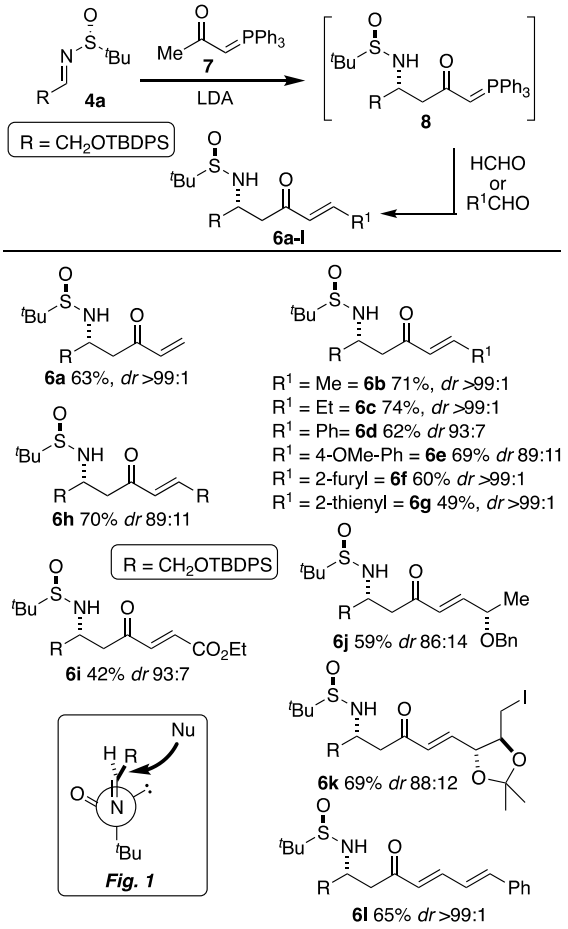
Scheme 1. Synthesis of β-Aminoenones



product **8** in 36% yield along with the product arising from the addition of ^{n}BuLi to the sulfinimine **4a**. Employing LiHMDS or KHMDS as the base did not yield any product. However, the use of LDA as a base resulted in the formation of the sulfinamidophosphorane **8**, admixed with the unreacted phosphorane. At this stage, it was difficult to estimate the diastereomeric ratio of the product phosphorane **8** by NMR analysis. Hence, we treated the crude sulfinimidophosphorane **8** with aldehydes to yield the enones **6a−h**. The diastereomeric ratio of the chromatographically purified product enones was estimated by ^{1}H NMR spectroscopy.[8] Thus, reaction of **8** with formaldehyde produced the unsubstituted enone **6a** in 63% yield and with >99:1 diastereomeric ratio. The reaction of phosphorane **8** with other aldehydes afforded the β-sulfinamido enones **6b−h** with diastereoselectivities ranging from 83:17 to >99:1 and in good yields. Reaction with aliphatic aldehydes acetaldehyde and propanaldehyde afforded the corresponding enones **6b** and **6c** in 71 and 74% yield, respectively. Reaction with benzaldehyde and 4-methoxy benzaldehyde formed the products **6d** and **6e** in 62% (*dr* 93:7) and 69% (*dr* 89:11) yield, respectively. Reaction with aromatic aldehydes containing heteroatoms such as furan-2-carbaldehyde and thiophene-2-carbaldehyde furnished the products **6f** and **6g** in 60 and 49% yields, respectively, with >99:1 diastereomeric ratio. Reaction with functionalized aldehyde such as ethylglyoxalate afforded the product **6i** in 42% yield with 93:7 diastereomeric ratio. Similarly, reaction of the phosphorane **8** with chiral aldehydes obtained from lactic acid and D-tartaric acid also yielded the corresponding enones **6j** and **6k** in 59 and 69% yields, respectively. Reaction with cinnamaldehyde yielded the product **6l** in 65% yield. The varied diastereoselectivity in the formation of product enones clearly indicate that the preliminary addition of ylide **7** to sulfinimine **4a** is non-diastereoselective. Observation of >99:1 *dr* in some of the product enones is a consequence of the diastereomeric enrichment during the column chromatography purification. All of the results are summarized in Scheme 2.

Further generalization of the protocol was exemplified by the synthesis of several unsubstituted enones **6m−t** obtained by the reaction of phosphorane **7** with different sulfinimines derived from alkyl, aryl, substituted aryl, and alkenyl aldehydes and further reaction with formaldehyde. In all cases, the reaction afforded the products with good selectivity and yields (Scheme 3). Stereochemistry of the newly formed stereogenic center was established by comparison of the physical

Scheme 2. Addition of Phosphorane 7 to Sulfinimine 4a and Further Reaction with Aldehdyes



properties of product enones with the known compounds reported in the literature and also by single crystal X-ray structure analysis of the enone **6q** (see the Supporting Information for the crystal structure). The addition of a nucleophile is from a face opposite to the sulfinyl group which can be explained by the transition state proposed by Davis and Ellman (Figure 1; Scheme 2).[9] The present synthetic strategy overcomes the drawbacks associated with other synthetic methods for the synthesis of simple β-amino enones.

After accomplishing the synthesis of the amino enones, deprotection of the sulfinyl group and subsequent aza-Michael reaction to form the 2,6-disubstituted piperidine-4-one was examined. Thus, deprotection of the sulfinyl group in **6a−l** by reaction with saturated ethereal HCl followed by neutralization with Et_3N furnished the corresponding piperidinones in good yield. Reaction of enones **6b−h**, **6k**, and **6l** furnished a separable mixture of *cis* and *trans* piperidinones **9a−17a** and **9b−17b**, respectively.[10] Enones **6f** and **6i** comprising a 2-furyl group and an ester moiety failed to produce the piperidinones and decomposed during the reaction. Enone **6j** furnished the piperidinone **16** in 78% yield. The reaction of unsubstituted enones **6a** and **6m−u** (obtained from the reaction of sulfinimines with phosphorane **7** formaldehyde) exhibited an interesting trend. The enones **6a**, **6t**, and **6u** containing an alkyl substituent at the carbon bearing the amino group cleanly furnished the corresponding 2-substitued piperidin-4-ones **18**, **19**, and **20** in 71, 73, and 81% yields, respectively. However, all of the other amino enones **6m−q** having aryl, substituted aryl,

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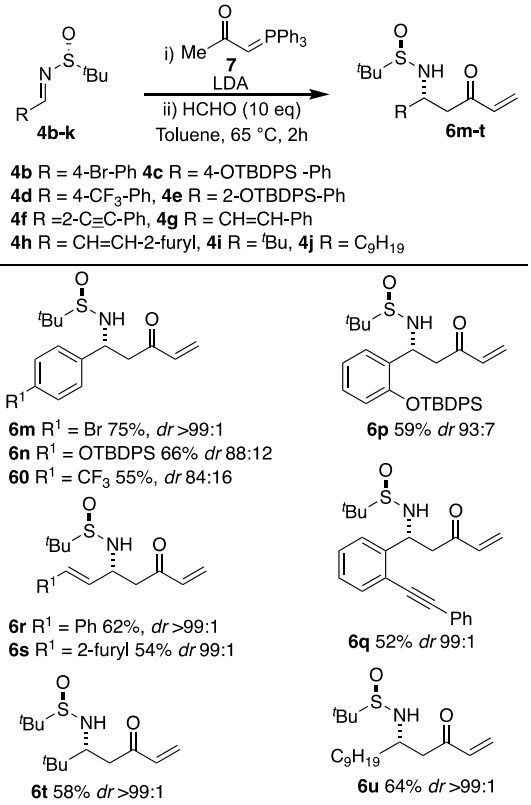
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Synthesis of Simple β-Amino Enones from Sulfinimines

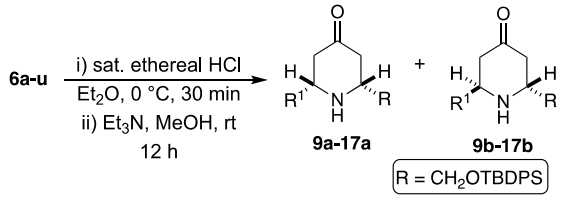


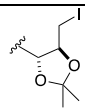
and alkenyl substitution failed to produce the piperidinones. We believe that the hydrochloride salt formed after deprotection of the sulfinyl group in **6m−q** with saturated ethereal HCl underwent an elimination of the amino group in the subsequent neutralization with Et_3N instead of the aza-Michael reaction. Such an elimination is mitigated in the reaction of enones **6a**, **6t**, and **6u** containing an alkyl substitution at the amino group (Scheme 4).

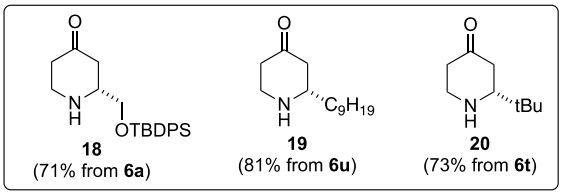
The formed piperidinones serve as excellent building blocks for the synthesis of alkaloids. The alkaloid (+)-241D **24** was isolated from the skin of the Panamanian poison frog *Dendrobates specious* by Daly and co-workers.[11] Several syntheses of this alkaloid in enantiopure form were recorded in the literature.[12] We envisioned the synthesis of (+)-241D by the reduction of the corresponding 4-piperidinone, which in turn can be obtained by the aza-Michael cyclization of suitably substituted enone. Accordingly, reaction of sulfinimine **4j** with the phosphorene **7** and further reaction with acetaldehyde afforded the enone **21** in 79% yield. Deprotection of the sulfinyl group in **21** with ethereal HCl and neutralization with Et_3N furnished a separable mixture of *cis*- and *trans*-2,6-disubstituted piperidin-4-ones **22** and **23** in 65 and 20% yield, respectively. Formation of the *cis* and *trans* isomers was confirmed by comparison of the spectral and optical rotation data with that reported by Sutherland's group.[13] Piperidinone **23** on reduction with $NaBH_4$ led to the formation of the alkaloid (+)-241D **24** as a single diastereomer in 90% yield (Scheme 5).

After the successful completion of the synthesis of alkaloid (+)-241D, the strategy was extended for the formal synthesis of the substituted pyrrolidine alkaloid (+)-preussin **28**, a natural product which is an inhibitor of cyclin-E-kinase.[14]

Scheme 4. Synthesis of Substituted Piperidin-4-ones from the Enones 6a−u

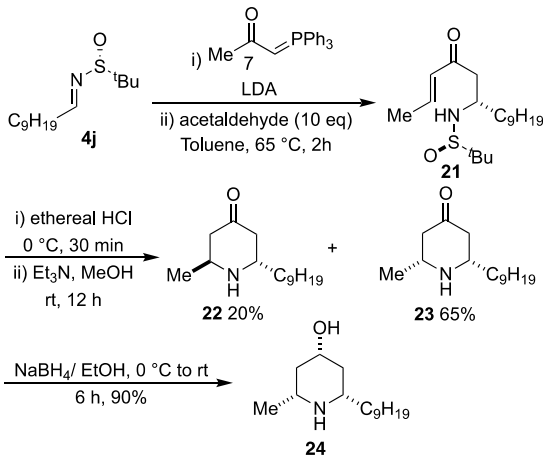


Reactant[b]	R^1	*cis* isomer (yield)[a]	*trans* isomer (yield)
6b	Me	**9a** (60%)	**9b** (18%)
6c	Et	**10a** (61%)	**10b** (27%)
6d	Ph	**11a** (50%)	**11b** (9%)
6e	4-OMe-Ph	**12a** (51%)	**12b** (32%)
6g	2-thienyl	**13a** (63%)	**13b** (34%)
6h	$CH_2OTBDPS$	**14a** (67%)	**14b** (28%)
6l	PhCH=CH	**15a** 56%	**15b** (29%)
6j		**16a** (78%)	
6k		**17a** (44%)	**17b** (43%)



[a]Yields refer to isolated yields after silica gel column chromatography. [b]Enones **6f**, **6i**, and **6m−6q** did not yield any piperidinone and decomposed during the reaction.

Scheme 5. Total Synthesis of (+)-241D



Thus, reduction of the enone **6u** under Luche reduction conditions furnished the β-sulfinamido alcohol **25** in 94% yield.[15] Deprotection of the sulfinyl group in **25** and further protection of the free amine as the Boc carbamate afforded **26** in 82% yield. The free hydroxy group in **26** was protected as its TBS ether **27** in 86% yield. The transformation of **27** to

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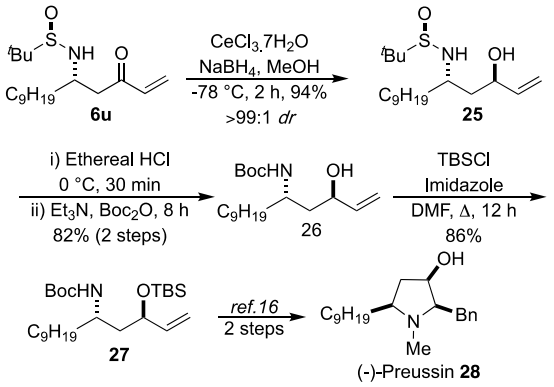
Org. Lett. XXXX, XXX, XXX−XXX

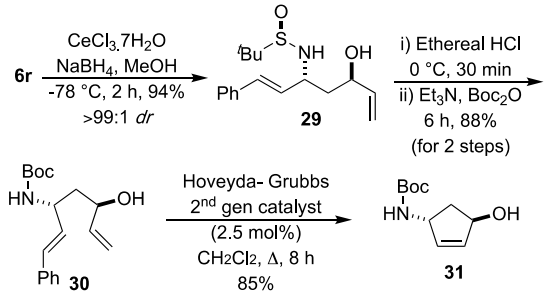
preussin involving carboamination/arylation and reduction of the Boc group was reported by the Wolfe group.[16] Hence, the present synthesis constitutes a formal synthesis of preussin (Scheme 6).

Scheme 6. Formal Total Synthesis of (−)-Preussin



We also utilized the enone **6r** as the building block in the synthesis of aminocyclopentenol derivative **31**, an intermediate for the synthesis of therapeutically important carbonucleosides.[17] For this purpose, the enone **6u** was subjected to Luche reduction to furnish the sulfinamido alcohol **29** in 80% yield. Removal of the sulfinyl group and protection of free amine as its Boc carbamate furnished **30** in 88% yield. Ring closing metathesis of **30**[18] using Hoveyda−Grubbs second generation (2.5 mol %) catalyst[19] led to the formation of the aminocyclopentenol **31** in 85% yield (Scheme 7).

Scheme 7. Synthesis of Boc-Protected Aminocyclopentenol



In conclusion, the addition of lithium enolate of the ylide (acetylmethylene)triphenylphosphorane to nonracemic sulfinimines and further Wittig reaction with several aldehydes to yield *β*-sulfinamido ketones was accomplished with good diastereoselectivity. The formed sulfinamido enones serve as excellent precursors for the synthesis of piperidine and pyrrolidine alkaloids (+)-241D and preussin and also for the synthesis of aminocyclopentenol, a useful intermediate for the synthesis of carbonucleosides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02608.

General procedures and synthesis of sulfinimines **4e,f**; general procedure for the addition of (acetylmethylene)-triphenylphosphorane **7** to sulfinimines and successive Wittig olefination reaction with aldehydes; synthesis of **6a−u** and **21**; general procedure for the synthesis of 2,6-disubstituted piperidinones using the intramolecular aza-Michael cyclization reaction; synthesis of **9a−20**; synthesis of (+)-241D; formal total synthesis of preussin; synthesis of aminocyclopentenol derivative **31b**; and X-ray crystal data (PDF)

Copies of the ^{1}H and ^{13}C NMR spectra of all new compounds and the X-ray crystal structure data of **6q** (PDF)

Accession Codes

CCDC 2017135 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated with warmth and respect to Dr. K. Nagarajan, Founder-Member of the National Organic Symposium Trust, India, on the occasion of his 90th birthday.

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