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Asymmetric Synthesis of Polyfunctionalized Pyrrolidines from Sulfinimine-Derived Pyrrolidine 2-Phosphonates. Synthesis of Pyrrolidine 225C

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Abstract

The Horner-Wadsworth-Emmons reaction of aldehydes with sulfinimine-derived 3-oxo pyrrolidine phosphonates represents a new method for the asymmetric synthesis of ring-functionalized *cis*-2,5-disubstituted 3-oxo pyrrolidines.

Enantiopure polyfunctionalized pyrrolidines are found in pharmaceuticals and in numerous natural products.¹ They are also valuable chiral building blocks for the synthesis of more complex derivatives, including the pyrrolizidine and indolizidine alkaloids.¹ Enantiopure pyrrolidines are also useful chiral auxiliaries and ligands for asymmetric syntheses.² Although many methods have been reported for the synthesis of pyrrolidines, the continuing challenge is to design more concise methods, particularly enantiopure examples that have ring functionality that can provide access to more complex derivatives.³

Recent efforts in our group have focused on the asymmetric syntheses of sulfinimine-derived chiral building blocks and the development of related methods for the enantioselective synthesis of amine derivatives, particularly nitrogen heterocycles.^{4,5} We require these building blocks to be easily prepared in both enantiomerically pure forms and to provide entry to diverse classes of organonitrogen compounds with a minimum of chemical manipulation and protecting-group chemistry. In this context we wish to report that 3-oxo pyrrolidine 2-phosphonates and the Horner-Wadsworth-Emmons (HWE) reaction afford enantiopure *cis*-2,5-disubstituted 3-oxo pyrrolidines that are readily elaborated to functionalized pyrrolidines suitable for further elaboration.

Earlier we introduced an efficient asymmetric synthesis of *cis*-2,5-disubstituted pyrrolidine phosphonates **4**, proline surrogates, via the highly stereoselective intramolecular metal carbenoid N-H insertion from a δ -amino α -diazo β -ketophosphonate **2** (Scheme 1). The resulting 3-oxo pyrrolidine phosphonates **3** were elaborated in three steps to **4**.^{5e} The α -diazo compounds **2** were readily prepared from the corresponding sulfinimine-derived δ -amino β -ketophosphonates **1**, by treatment with 4-acetamidobenzenesulfonyl azide (4-ABSA).⁶ The phosphonates **1** are prepared in three-steps from an *N*-sulfinyl β -amino ester. We reasoned that 3-oxo pyrrolidine phosphonates **3** would be good substrates for the asymmetric synthesis of

2,5-disubstituted pyrrolidines provided that the corresponding C-2 β -ketophosphonate anion is sufficiently reactive to be alkylated and/or participate in the HWE reaction with aldehydes.

Treatment of dimethyl (2*R*,5*R*)-(+)-*N*-(*tert*-butoxycarbonyl)-3-oxo-5-pyrrolidine 2-phosphonate (**5**) with NaH in the presence of 18-crown-6 followed by reaction with iodomethane or benzyl bromide resulted in complex mixtures. However, with allyl bromide a 35% isolated yield of the quaternary phosphonate (2*R*,5*R*)-(+)-**6** was obtained as a mixture of rotamers (Scheme 2). A single pyrrolidine phosphonate (+)-**7** was obtained on removal of the *N*-Boc group with TFA. Hydrogenation, Pd-C/H₂, of (+)-**7** resulted in ring opening at the benzylic position to give the stable acyclic α -amino ketone phosphonate (*R*)-(-)-**8** in 95% yield. α -Amino ketones are notoriously unstable entities even when suitably *N*-protected, so it is likely that steric hindrance, provided by the large phosphonate group, inhibits undesirable intermolecular reactions of this moiety in (-)-**8**.⁷

Next, treatment of (+)-**5** with NaH followed by benzaldehyde produced the 2-benzylidene pyrrolidine (*R*)-(-)-**11a** in over 90% yield following purification by flash chromatography (Scheme 3). It was noted that enone (-)-**11a** slowly decomposed after standing for ca 6-10 hours to uncharacterizable materials and was therefore used in subsequent reactions within this time period. Similar results were observed for the HWE reaction of 3-oxo pyrrolidine phosphonates **9** and **10** (Table 1).

Reaction of (+)-**5** with *n*-butylaldehyde using NaH or *t*-BuOK as the bases resulted in low yields of the corresponding enone **11b** (Table 1, entries 4 and 5). This is probably due to the presence of α -protons in the aldehyde, which could promote aldol-type reactions. The use of weaker bases such as DBU and Et₃N in the presence of lithium salts has been reported to be an effective system for the HWE reaction.⁸ Indeed, the yield of **11b** improved from 26-32% to 69-70% with LiCl in DBU or Et₃N (Table 1, entries 6 and 7). Steric factors, caused by the large *tert*-butyl group in (+)-**10** (*R* = *t*-Bu) are likely responsible for our inability to effect the HWE reaction with benzaldehyde (Table 1, entry 11).

Hydrogenation, Pd-C/H₂ of the 2-alkylidene 3-oxo pyrrolidines **11a**, **11c**, and **12a** readily afforded the corresponding *cis*-2,5-disubstituted 3-oxo pyrrolidines **13**, **14**, and **15** in good yield as single isomers (Scheme 4). It is reasonable to assume that hydrogen is added from the least hindered direction affording the *cis* isomer. This assumption was confirmed in our synthesis of 225C (**22**). 3-Oxo pyrrolidines **11** and **12**, **13**, **14**, and **15** have not previously been reported and are expected to be useful new chiral building blocks and templates for the asymmetric synthesis of more complex pyrrolidines. To explore their utility in asymmetric synthesis we briefly examined several transformations of the 3-oxo group in these heterocycles.

Luche reduction of (-)-**14** gave the all *cis* 2,3,5-trisubstituted pyrrolidine (+)-**16** in 80% yield (Scheme 4). The stereochemistry of (+)-**16** is based on the reasonable assumption that hydride adds from the least hindered direction and is supported by our earlier studies on the synthesis of the antifungal 3-hydroxy pyrrolidine (+)-preussin.⁹ 3-Hydroxy pyrrolidine (+)-**17** was prepared in 65% yield and obtained as a single isomer on treatment of (-)-**15** with excess methylmagnesium bromide. It is assumed that MeMgBr adds to the carbonyl group from the least hindered direction and this assumption is supported by our recent synthesis of the polyoxypeptide amino acid segment (-)-3-hydroxy-3-methylproline.¹⁰ It is worth noting that the rotamers of the Boc *t*-butyl group in (+)-**17** appear as a broad peak between 1.47 and 1.23 ppm in the ¹H NMR and coalesce to a singlet at 50 °C.

Having demonstrated the facile functional group manipulations of *cis*-2,5-disubstituted 3-oxo pyrrolidines, we next turned our attention to the asymmetric synthesis of pyrrolidine 225C (**22**) to highlight an application of our new building block. Pyrrolidine 225C and related *cis*-2,5-disubstituted pyrrolidines have been of interest in studies of ant venom toxins of the

genus *Solenopisis*.¹¹ Although *trans*-2,5-disubstituted pyrrolidines are the major components of the ant venom, their structural elucidation requires preparation of the *cis* isomers.¹² Furthermore, *cis* pyrrolidine isomers have been detected as trail pheromones of the pharaoh's ant *Monomorium pharonis*.¹³ Only two multistep asymmetric syntheses of 225C have been reported.¹⁴ Hydrogenation of alkylidene pyrrolidine (-)-**12b** gave the 3-oxo pyrrolidine (-)-**18**, which was reduced with NaBH₄ to give the alcohol (+)-**19** as a single isomer (Scheme 5). Dehydration was first explored with I₂/imidazole/Ph₃P and although it gave the desired 3,4-dehydropyrrolidine (-)-**20** as indicated by ¹H NMR, it could not be satisfactorily purified. A better procedure proved to be the conversion of the alcohol into the mesylate with MeSO₂Cl/Et₃N followed by treatment with potassium *t*-butoxide to give (-)-**20** in 52% yield. Hydrogenation (Pt-C/H₂) and removal of the *N*-Boc group (TFA) resulted in pyrrolidine 225C (**22**) in 84% yield for the two steps (Scheme 5). The specific rotation of (-)-**21** was -1.2, whereas the specific rotation of pyrrolidine 225C (**22**) was 0. This result has also been reported by others and may be due to the fact that the compound has nearly a meso structure.¹⁴ All attempts to prepare the MTPA amide of **22** were unsuccessful, as also noted by Shiosaki and Rapoport.^{14a}

In summary, a new method has been introduced for the asymmetric synthesis of ring-functionalized pyrrolidines employing sulfinimine-derived 3-oxo pyrrolidine phosphonates and the Horner-Wadsworth-Emmons reaction. Reduction of the resulting 3-oxo alkylidene pyrrolidines affords stereodefined *cis*-2,5-disubstituted 3-oxo pyrrolidines, which are useful new building blocks for the asymmetric construction of more complex pyrrolidines. A concise asymmetric synthesis of pyrrolidine 225C, seven steps (six operations) 21% overall yield from (-)-**9**, illustrates the utility of the new protocol.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.

Scheme 5.

Table 1

HWE Reaction of 3-Oxo Pyrrolidine Phosphonates with Aldenydes.

entry	phosphonate (R =)	aldehyde	base	enone (% yield) ^a
1	(+) - 5 (Ph)	PhCHO	TEA	NR ^b
2			DBU	NR
3		<i>n</i> -PrCHO	NaH	11a (93)
4			NaH	11b (32)
5			<i>t</i> -BuOK	11b (26)
6			LiCl/DBU	11b (69)
7			LiCl/Et ₃ N	11b (70)
8	(-) - 9 (<i>n</i> -Bu)	MeCHO	LiCl/DBU	11c (70)
9		PhCHO	LiCl/DBU	12a (66)
10		<i>n</i> -C ₆ H ₁₃ CHO	LiCl/DBU	12b (75)
11	(+) - 10 (<i>t</i> -Bu)	PhCHO	NaH	NR

^a Isolated yield.^b No reaction, starting material recovered.