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

Franklin A. Davis,* He Xu, Yongzhong Wu, and Junyi Zhang

Department of Chemistry, Temple University, Philadelphia, Pennsylvania 19122

fdavis@temple.edu

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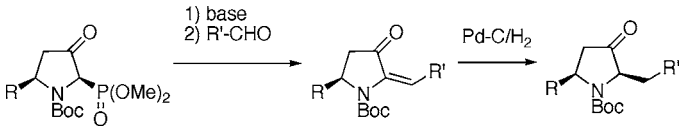
ABSTRACT



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

(1) (a) Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod*. **2005**, *68*, 1556. (b) O'Hagan, D. *Nat. Prod. Rep*. **2000**, *17*, 435 and references therein. (c) Leclercq, S.; Braekman, J. C.; Daloze, D.; Pasteels, J. M. *Prog. Chem. Org. Nat. Prod*. **2000**, *79*, 115. (d) Daly, J. W.; Garraffo, H. M.; Spende, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: New York, 1999; Vol 13, Chapter 1.

(2) Chiral auxiliaries or ligands: (a) Kim, B. H.; Lee, H. B.; Hwang, J. K.; Kim, Y. G. *Tetrahedron: Asymmetry* **2005**, *16*, 1215. (b) Nyerges, M.; Bendell, D.; Arany, A.; Hibbs, D. E.; Coles, S. J.; Hursthouse, M. D.; Groundwater, P. W.; Meth-Cohn, O. *Synlett* **2003**, 947. (c) Fache, F.; Schultz, E.; Tomasino, M. L.; Lemaire, M. *Chem. Rev*. **2000**, *100*, 2159. (d) Sweet, J. A.; Cavallari, J. M.; Price, W. A.; Ziller, J. W.; McGrath, D. V. *Tetrahedron: Asymmetry* **1997**, *8*, 207. (e) Whitesell, J. K. *Chem. Rev*. **1989**, *89*, 1581.

(3) For leading references to the asymmetric synthesis of pyrrolidines, see: Vasse, J.-L.; Joosten, A.; Denhez, C.; Szymoniak, J. *Org. Lett*. **2005**, *7*, 4887.

(4) For recent reviews on the chemistry of sulfinimines, see: (a) Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003. (b) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res*. **2002**, *35*, 984. (c) Senanayake, C. H.; Krishnamurthy, D.; Lu, Z.-H.; Han, Z.; Gallou, I. *Aldrichimica Acta* **2005**, *38*, 93.

(5) For reviews on sulfine-derived chiral building blocks, see: (a) Davis, F. A.; Yang, B.; Deng, J.; Wu, Y.; Zhang, Y.; Rao, A.; Tang, T.; Goswami, R.; Prasad, K. R.; Nolt, B. M.; Anilkumar, G. *Phosphorus, Sulfur Silicon* **2005**, *180*, 1109.

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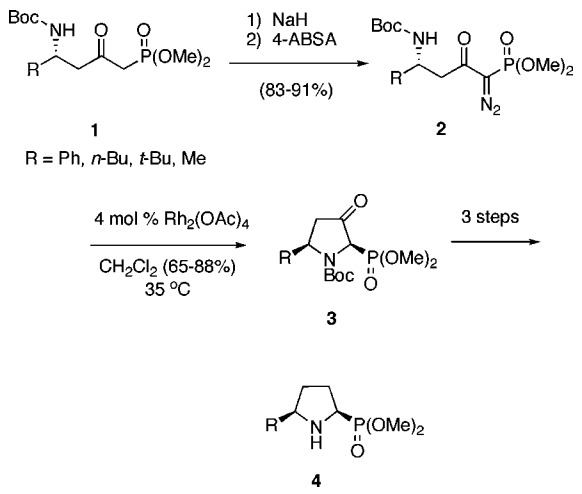
carbenoid N−H insertion from a δ-amino α-diazo β-ketophosphonate **2** (Scheme 1). The resulting 3-oxo pyrrolidine

Scheme 1

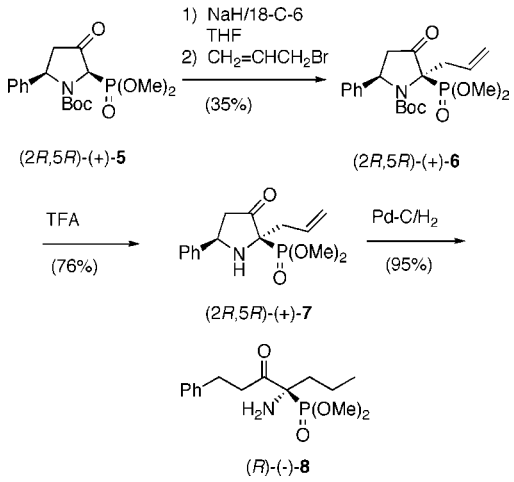


phosphonates **3** were elaborated in three steps to **4**.[5e] The α-diazo compounds **2** were readily prepared from the corresponding sulfinimine-derived δ-amino β-ketophosphonates **1**, by treatment with 4-acetamidobenzenesulfonyl azide (4-ABSA).[6] The phosphonates **1** are prepared in three steps 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 to 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/H_2, 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]

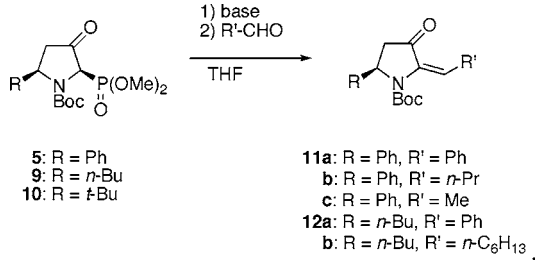
(6) For recent examples of sulfinimine-derived chiral building blocks, see: (a) β-Amino ketones: Davis, F. A.; Yang, B. *J. Am. Chem. Soc*. **2005**, *127*, 8398. (b) *syn*- and *anti*-2,3-diamino esters: Davis, F. A.; Deng, J. *Org. Lett*. **2005**, *7*, 621. (c) δ-Amino β-keto esters enaminones: Davis, F. A.; Zhang, J.; Li, Y.; Xu, H.; DeBrosse, C. *J. Org. Chem*. **2005**, *70*, 5413. (d) α-Amino 1,3-dithioketals (α-amino ketones and aldehydes): Ramachandar, T.; Chai, J.; Skucas, E. *Tetrahedron Lett*. **2006**, *47*, 2743 and ref 11. (e) δ-Amino β-ketophosphonates: Davis, F. A.; Wu, Y.; Xu, H.; Zhang, J. *Org. Lett*. **2004**, *6*, 4523. (f) δ-Amino β-keto esters: Davis, F. A.; Deng, J. *Tetrahedron* **2004**, *60*, 5111. (g) Aziridine 2-phosphonates: Davis, F. A.; Ramachandar, T.; Wu, Y. *J. Org. Chem*. **2003**, *68*, 6894. (h) 2*H*-Azirine 3-phosphonates: Davis, F. A.; Wu, Y.; Yan, H.; Prasad, K. R.; McCoull, W. *Org. Lett*. **2002**, *4*, 655.

Scheme 2



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

Scheme 3



decomposed after standing for ca. 6−10 h 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*-butrylaldehyde using NaH or *t*-BuOK as the base 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 Et_3N 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 Et_3N (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).

(7) Davis, F. A.; Wu, Y. *Org. Lett*. **2004**, *6*, 1269.

(8) For leading references to the chemistry of α-amino ketones, see ref 5d.

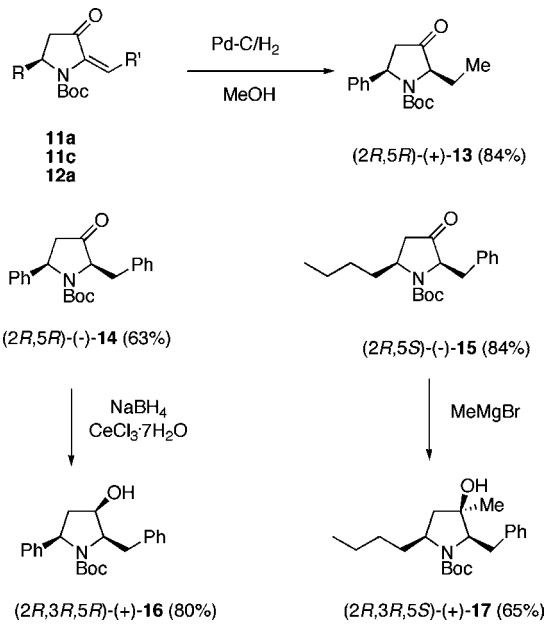
Table 1. HWE Reaction of 3-Oxo Pyrrolidine Phosphonates with Aldehydes

entry	phosphonate (R=)	aldehyde	base	enone (% yield)[a]
1	(+)-**5** (Ph)	PhCHO	TEA	NR[b]
2			DBU	NR
3			NaH	**11a** (93)
4		*n*-PrCHO	NaH	**11b** (32)
5			*t*-BuOK	**11b** (26)
6			LiCl/DBU	**11b** (69)
7			LiCl/Et_3N	**11b** (70)
8		MeCHO	LiCl/DBU	**11c** (70)
9	(−)-**9** (*n*-Bu)	PhCHO	LiCl/DBU	**12a** (66)
10		n-C_6H_{13}CHO	LiCl/DBU	**12b** (75)
11	(+)-**10** (*t*-Bu)	PhCHO	NaH	NR

[a] Isolated yield. [b] No reaction, starting material recovered.

Hydrogenation, Pd−C/H_2, 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

Scheme 4



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**−**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 methyl magnesium 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 polyoxypeptine amino acid segment (−)-3-hydroxy-3-methylproline.[10] It is worth noting that the rotamers of the Boc *tert*-butyl group in (+)-**17** appear as a broad peak between 1.47 and 1.23 ppm in the ^{1}H 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 pharoh'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 $NaBH_4$ to give the alcohol (+)-**19** as a single isomer (Scheme 5). Dehydration was first explored with I_2/imidazole/Ph_3P, and although it gave the desired 3,4-dehydropyrrolidine (−)-**20** as indicated by ^{1}H NMR, it could not be satisfactorily purified. A better procedure proved to be the conversion of the alcohol into the mesylate with $MeSO_2Cl/Et_3N$ followed by treatment with potassium *t*-butoxide to give (−)-**20** in 52% yield. Hydrogenation (Pt−C/H_2) 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

(9) (a) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183. (b) Rathke, M. W.; Nowak, M. *J. Org. Chem.* **1985**, *50*, 2624.

(10) Davis, F. A.; Deng, J. *Tetrahedron* **2004**, *60*, 5111.

(11) Davis, F. A.; Ramachandar, T.; Liu, H. *Org. Lett.* **2004**, 6, 3393.

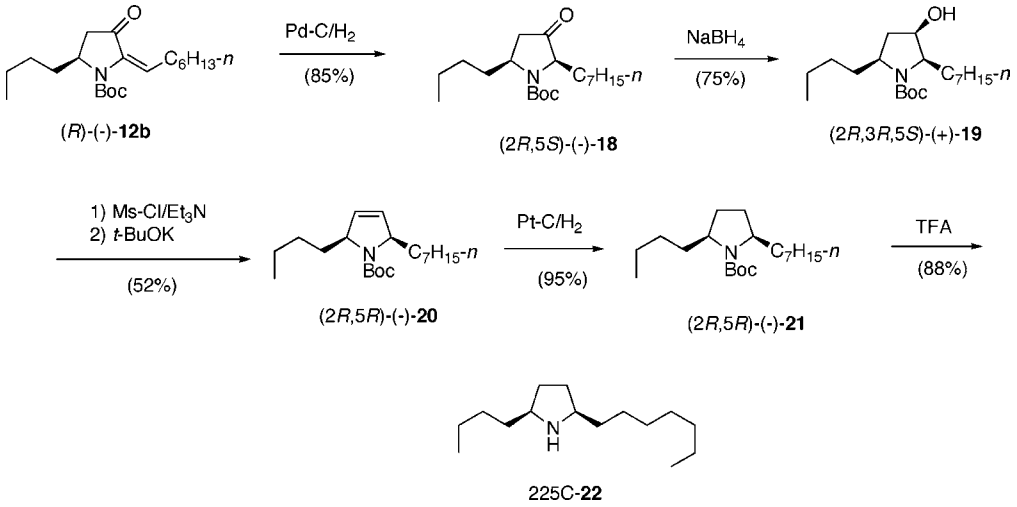
(12) (a) Leclercq, S.; Braekman, J. C.; Daloze, D.; Pasteels, J. M. The defensive Chemistry of Ants. *Prog. Chem. Org. Nat. Prod.* **2000**, *79*, 115. (b) See ref 1d, page 2.

(13) (a) Garraffo, H. M.; Simon, L. D.; Daly, J. W.; Spande, T. F. *Tetrahedron* **1994**, *50*, 11329. (b) Pedder, D. J.; Fales, H. M.; Jaouni, T.; Blum, M.; MacConnell, J.; Crewe, R. M. *Tetrahedron* **1976**, *32*, 2275.

(14) (a) Schmitz, E.; Sonenschein, H.; Grundemann, C. *J. Prakt. Chem.* **1980**, *322*, 261. (b) Ritter, R. J.; Persoons, C. *J. Neth. J. Zool.* **1975**, *25*, 261.

(15) (a) Shiosaki, K.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1229. (b) Arseniyadis, S.; Huang, P. Q.; Piveteau, D.; Husson, H.-P. *Tetrahedron* **1988**, *44*, 2457.

Scheme 5



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, in seven steps (six operations) and 21% overall yield from (−)-**9**, illustrates the utility of the new protocol.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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