ORGANIC LETTERS

2008
Vol. 10, No. 7
1433−1436

Asymmetric Synthesis of *cis*- and *trans*-2,5-Disubstituted Pyrrolidines from 3-Oxo Pyrrolidine 2-Phosphonates: Synthesis of (+)-Preussin and Analogs

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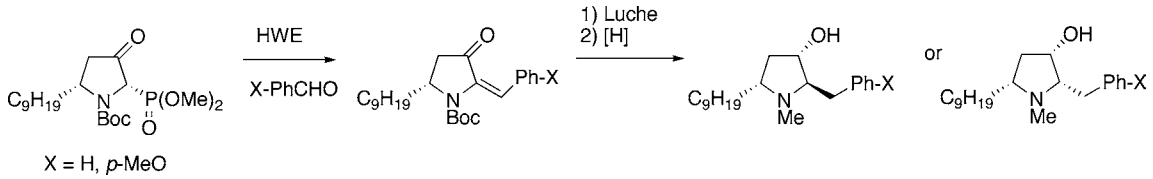
Received February 4, 2008

ABSTRACT



Pyrrolidine enones, derived from 3-oxo pyrrolidine 2-phosphonates and a HWE reaction with aldehydes, on Luche reduction give pyrrolidine allylic alcohols. The alcohols on hydrogenation (Pd/H_2) give *cis*-2,5-disubstituted pyrrolidines and on treatment with TFA-$NaBH_3CN$ undergo a hydroxy directed reduction to *trans*-2,5-disubstituted pyrrolidines.

Cis- and *trans*-disubstituted 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 developed for their preparation, the continuing challenge is to design more concise methods, principally enantiopure examples that have ring functionality that can provide access to more complex derivatives.[3] This is particularly true for *trans*-2,5-disubstituted pyrrolidines for which there are few general methods of preparation in enantiopure form.[4] In this context, we describe general methodology for the asymmetric synthesis of functionalized *cis*- and *trans*-2,5-disubstituted pyrrolidines from a common intermediate derived from 3-oxo pyrrolidine 2-phosphonate, a sulfinimine-derived chiral building block.[5]

Earlier we reported an efficient asymmetric synthesis of 3-oxo pyrrolidine 2-phosphonates such as (2*R*,5*R*)-(+)-**1**, which involved a highly stereoselective intramolecular metal carbenoid N−H insertion from a δ-amino α-diazo β-ketophosphonate.[6] These building blocks undergo the Horner−Wadsworth−Emmons (HWE) reaction with various aldehydes, such as benzaldehyde, to give the corresponding enones in good yield (Scheme 1).[7] Enone (5*R*)-(−)-**2** proved to be relatively unstable and decomposed on purification. Hydrogenation of (−)-**2** provided a good yield of the *cis*-2,5-disubstituted 3-oxo pyrrolidine (−)-**3**, and this methodol-

(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 cited 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. *Synlet* **2003**, 947. (c) Fache, F.; Schulz, E.; Tommasino, 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.

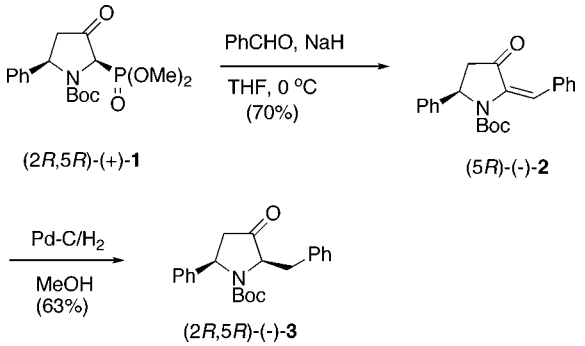
(4) For leading references to the asymmetric synthesis of *trans*-2,5-disubstituted pyrrolidines, see: Davis, F. A.; Song, M.; Augustine, A. *J. Org. Chem*. **2006**, *71*, 2779.

(5) Davis, F. A.; Wu, Y.; Xu, H.; Zhang, J. *Org. Lett*. **2004**, *6*, 4523.

(6) Davis, F. A.; Xu, H.; Wu, Y.; Zhang, J. *Org. Lett*. **2006**, *8*, 2273.

10.1021/ol800255r CCC: $40.75
Published on Web 03/11/2008

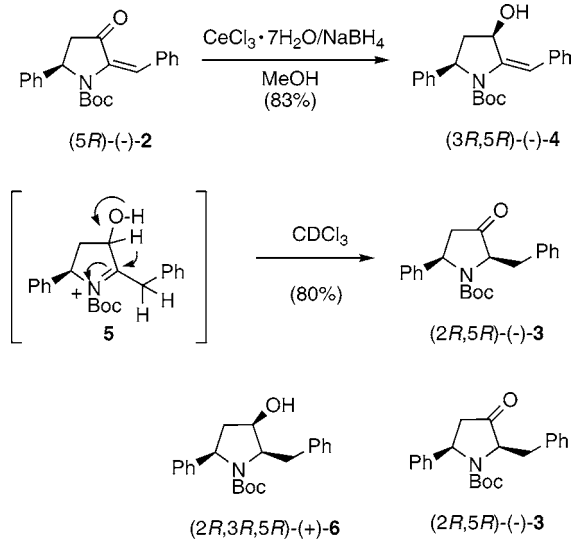
Scheme 1



ogy was employed in the asymmetric synthesis of the Pharaoh's ant pheromone pyrrolidine 225C.[6]

The utility of these new pyrrolidine enone chiral building blocks could be greatly expanded if there was a way to transform them into *trans*-2,5-disubstituted pyrrolidines. We reasoned that this might be accomplished via a hydroxy-directed hydrogenation of the pyrrolidine exocyclic double bond in (−)-**2**.[8] To this aim, a Luche reduction of (−)-**2** with $CeCl_3 \cdot 7H_2O/NaBH_4$ gave the crude allylic alcohol (−)-**4** in 83% yield. Unexpectedly, on standing in $CDCl_3$ over 8 h, this material rearranged to 3-oxo pyrrolidine (−)-**3** (Scheme 2). We suggest that under acidic conditions, protonation of

Scheme 2

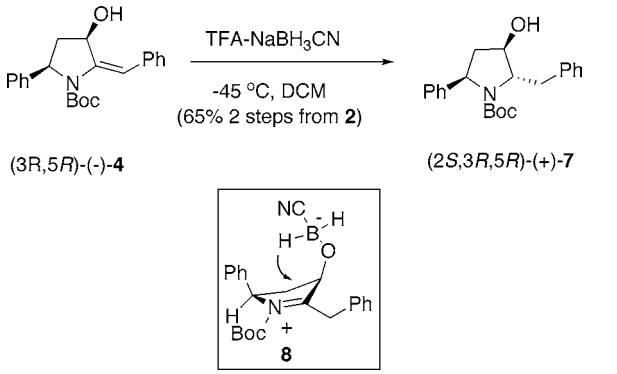


Pd-C/H_2	(40%)	(30%)
Pd-C/H_2/Et_3N	(80%)	(0%)

(−)-**4** results in formation of an iminium ion **5** that rearranges to the more thermodynamic stable product 3-oxo pyrrolidine (−)-**3**. Hydrogenation of (−)-**4** (Pd−C/H_2) afforded both (+)-**6** (40%) and (−)-**3** (30%), indicating that rearrangement is competing with reduction. Consistent with the idea that the rearrangement of (−)-**4** to (−)-**3** is acid catalyzed is the fact that hydrogenation in the presence of Et_3N gives only the pyrrolidine alcohol (+)-**6** (Scheme 2).

With the crude allylic alcohol, (−)-**4**, in hand, we next explored its reduction with various hydrogenation catalysts. Disappointingly, hydrogenation in CH_2Cl_2 at various pressures of H_2 (1−3 atm) with Ir(COD)py(PCy_3)PF_6 (Crabtree) and Rh[(NBD)(DIPHOS-4)]BF_4 catalysts either resulted in no reaction or decomposition. Gratifyingly, reduction of crude (−)-**4** with sodium cyanoborohydride in the presence of trifluoroacetic acid (TFA) afforded the *trans*-2,5-disubstituted pyrrolidine (+)-**7** in 65% yield as a single isomer for the two-step sequence (Scheme 3).[9] These results are

Scheme 3



consistent with hydride being delivered intramolecularly to the iminium ion via the hydroxyl group as shown in **8** (Scheme 3).[10] To confirm our stereochemical assignments and to illustrate the utility of this new methodology we report the concise asymmetric syntheses of (+)-preussin and its *trans* and *p*-methoxyphenyl analogs.

(+)-Preussin and Analogs. The alkaloid (+)-preussin (**17a**, Scheme 5) is a powerful antifungal agent,[11] which also exhibits antiviral activity[12] as well as inducing apoptosis in

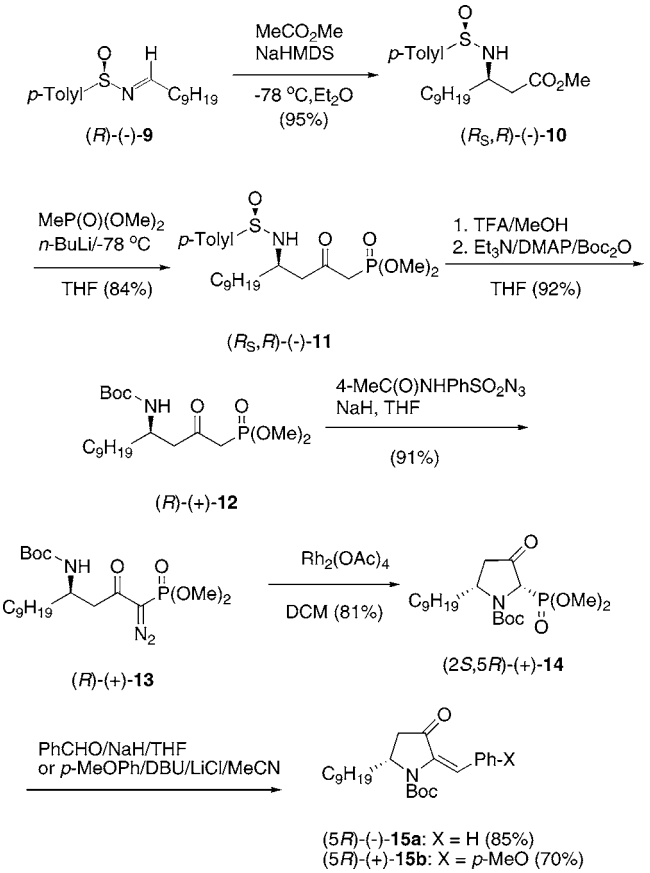
(7) For recent examples of sulfinimine-derived chiral building blocks, see (a) *β*-Amino ketones: Davis, F. A.; Yang, B. *J. Am. Chem. Soc.* **2005**, *127*, 8398. (b) Davis, F. A.; Song, M. *Org. Lett.* **2007**, *9*, 2413. (c) *syn*- and *anti*-2,3-Diamino esters: Davis, F. A.; Deng, J. *Org. Lett.* **2005**, *7*, 621. (d) Davis, F. A.; Zhang, Y.; Li, D. *Tetrahedron Lett.* **2007**, *48*, 7838. (e) *δ*-Amino *β*-keto esters enaminones: Davis, F. A.; Zhang, J.; Li, Y.; Xu, H.; DeBrosse, C. *J. Org. Chem.* **2005**, *70*, 5413. (f) α-Amino 1,3-dithioketals (α-amino ketones and aldehydes): Ramachandar, T.; Chai, J.; Skucas, E. *Tetrahedron Lett.* **2006**, *47*, 2743. (g) Davis, F. A.; Ramachandar, T. *Tetrahedron Lett.* **2008**, *49*, 870. (h) *δ*-Amino *β*-ketophosphonates: see reference 5. (i) *δ*-Amino *β*-ketoesters: Davis, F. A.; Deng, J. *Tetrahedron* **2004**, *60*, 5111. (j) 2*H*-Aziridne 2-carboxylates: Davis, F. A.; Liu, H.; Zhou, P.; Fang, T.; Reddy, G. V.; Zhang, Y. *J. Org. Chem.* **1999**, *64*, 7559. (k) Aziridine 2-phosphonates: Davis, F. A.; Ramachandar, T.; Wu, Y. *J. Org. Chem.* **2003**, *68*, 6894. (l) 2*H*-Azirine 2-carboxylates: Davis, F. A.; Liu, H.; Liang, C.-H.; Reddy, G. V.; Zhang, Y.; Fang, T.; Titus, D. D. *J. Org. Chem.* **1999**, *64*, 8929. (m) 2*H*-Azirine 3-Phosphonates: Davis, F. A.; Wu, Y.; Yan, H.; Prasad, K. R.; McCoull, W. *Org. Lett.* **2002**, *4*, 655. (n) 2*H*-Azirine 3-carboxylates: Davis, F. A.; Deng, J. *Org. Lett.* **2007**, *9*, 1707.

(8) (a) Evans, D. A.; Morrissey, M. M. *Tetrahedron Lett.* **1984**, *25*, 4637. (b) Del Valle, J. R.; Goodman, M. *J. Org. Chem.* **2003**, *68*, 3923.

(9) Because of the acid sensitivity of the allylic alcohol it was briefly dried (Na_2SO_4) and used immediately in the next step without purification.

(10) (a) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560. (b) Halab, L.; Belec, L.; Lubell, W. D. *Tetrahedron* **2001**, *57*, 6439.

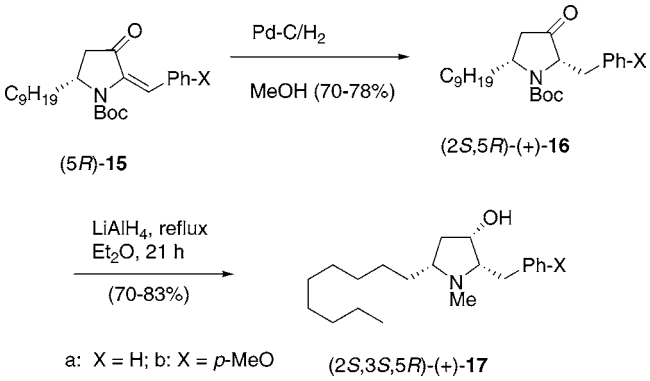
Scheme 4



certain human cancer cell lines.[13] For these reasons, (+)-**17a** has been a popular target for methods development with more than 22 different routes, of varying degrees of efficiency, reported.[14] However, as pointed out by Wolfe, nearly all of these syntheses use phenylalanine as the source of the phenyl group in (+)-**17a** and as such there are no reported analogues of preussin involving modification of the aryl moiety.[14] Furthermore, the asymmetric synthesis of *trans*-preussin analogs have not been described.[15]

The common intermediate in our synthesis of (+)-preussin (**17a**) and its analogs is (+)-3-oxo pyrrolidine 2-phosphonate (2*S*,5*R*)-(+)-**14**, which was prepared in six steps (five operations) in 54% overall yield from sulfinimine (*R*)-(−)-**9** using methodology developed earlier.[6] The HWE reaction of (+)-**14** with benzaldehyde or *p*-methoxybenzaldehyde using NaH or DBU−LiCl afforded the crude

Scheme 5

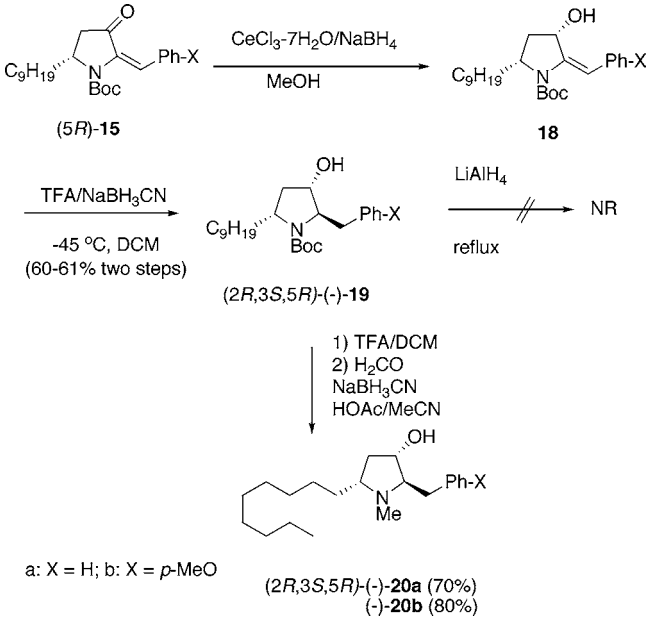


enones (−)-**15a** and (+)-**15b** in 85 and 71% yield, respectively (Scheme 4).

With pyrrolidine enones (−)-**15a** and (+)-**15b** in hand, reduction with Pd−C/H_2/Et_3N afforded *cis*-2,5-disubstituted 3-oxo pyrrolidines (+)-**16a** and (+)-**16b** in 70 and 78% isolated yields, respectively (Scheme 5). Reduction of (+)-**15** first with 6 equiv of $LiAlH_4$ in refluxing ether for 16 h followed by an additional 6 equiv of $LiAlH_4$ and refluxing for 5 h afforded (2*S*,3*S*,5*R*)-(+)-preussin (**17a**) and the *p*-methoxyphenyl analog (2*S*,3*S*,5*R*)-(+)-**17b** in 83 and 70% yields, respectively.[7i] This one-pot reduction sequence stereoselectively transforms the 3-oxo group into the *cis*-alcohol and the *N*-Boc to an *N*-methyl group (Scheme 5). Our asymmetric synthesis of (+)-preussin (**17a**), 9 steps (7 operations) in 28% overall yield from sulfinimine (−)-**9**, is one of the most efficient to date.

To prepare the *trans* analogs of preussin, the 3-oxo group in (5*R*)-**15** was reduced (Luche) to the *cis*-allylic alcohol **18**

Scheme 6



(11) (a) Schwartz, R. E.; Liesch, J.; Hensens, O.; Zitano, L.; Honeycutt, S.; Garrity, G.; Fromtling, R. A.; Onishi, J.; Monaghan, R. *J. Antibiot.* **1988**, 1774. (b) Johnson, J. H.; Phillipson, D. W.; Kahle, A. D. *J. Antibiot.* **1989**, 1184.

(12) Achenbach, T. V.; Slater, P. E.; Brummerhop, H.; Bach, T.; Muller, R. *Antimicrob. Agents Chemother*. **2000**, *44*, 2794.

(13) Kinzy, T. G.; Harger, J. W.; Carr-Schmid, A.; Kwon, J.; Shastry, M.; Justice, M.; Dinman, J. D. *Virology* **2002**, *300*, 60.

(14) Bertrand, M. B.; Wolfe, J. P. *Org. Lett.* **2006**, *8*, 2353 and references cited therein.

(15) A nonstereoselective synthesis of all eight isomers of preussin, separated by chiral HPLC, has been described. Okue, M.; Watanabe, H.; Kasahara, K.; Yoshida, M.; Horinouchi, S.; Kitahara, T. *Biosci. Biotechnol. Biochem*. **2002**, *66*, 1093.

which was in turn treated with TFA-$NaBH_3CN$ to give corresponding *trans*-2,5-disubstituted pyrrolidine alcohols (−)-**19** in moderate yields (Scheme 6). Attempts to reduce the *N*-Boc groups in (−)-**19** to *N*-Me groups by refluxing with $LiAlH_4$ were unsuccessful. Increased steric hindrance at the *N*-Boc site, as a consequence of the *trans* relationship of the 2,5-substitutents, is undoubtedly responsible for this. Reductive amination solved this problem and afforded the *trans* analogs (−)-**20a** and (−)-**20b** in 70 and 80% yields, respectively.

In summary, sulfinimine-derived enantiopure 3-oxo pyrrolidine 2-phosphonates undergo the HWE reaction with aldehydes to give pyrrolidine enones that on Luche reduction give the pyrrolidine allylic alcohols. Hydrogenation of the allylic alcohol afforded the *cis*-2,5-disubstituted pyrrolidines. Pyrrolidine allylic alcohols on treatment with TFA-$NaBH_3CN$ undergo a novel intramolecular hydroxy directed reduction resulting in *trans*-2,5-disubstituted pyrrolidines. This new methodology was employed in the asymmetric synthesis of the potent antifungal agent (+)-preussin and in the first asymmetric syntheses of its *trans* analogue and analogues in which the preussin aryl moiety has been structurally modified.

Acknowledgment. This work was supported by grants from the National Institute of General Medicinal Sciences (GM57878 and GM51982) and Boehringer Ingelheim Pharmaceuticals.

Supporting Information Available: Experimental details and ^1H, ^{13}C, and ^{31}P NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL800255R