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Asymmetric Synthesis of Substituted Prolines from δ-Amino β-Ketoesters. Methyl (2*S*,5*R*)-(+)-5-Phenylpyrrolidine-2-carboxylate

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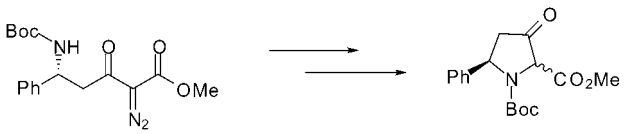
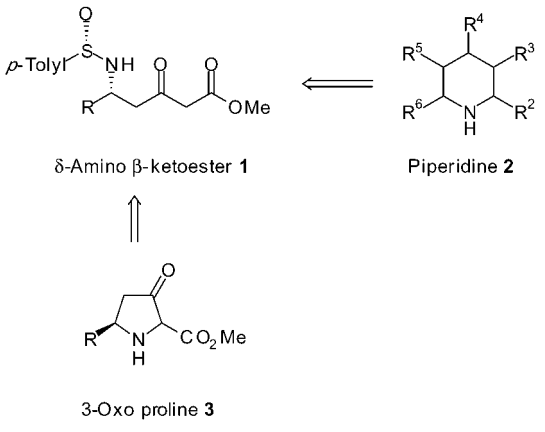
ABSTRACT



Metal carbenoid chemistry is used to convert δ-amino β-ketoesters into 5-substituted 3-oxo prolines, which expands the utility of this class of polyfunctionalized chiral building blocks.

Recent efforts in our laboratory have focused on the applications of *N*-sulfinyl δ-amino β-ketoesters **1**, a new polyfunctionalized chiral building block for piperidine **2** alkaloid synthesis (Scheme 1). These building blocks can be prepared in one pot from sulfinimines (*N*-sulfinyl imines) and can be readily converted to the target piperidine with a minimum of chemical manipulation and protecting group chemistry. In this manner expeditious enantioselective syntheses of (*R*)-(−)-2-phenylpiperidine,[1] (−)-(2*S*,4*S*)-SS20846A,[1] the proposed biosynthetic intermediate of the antimicrobial agent streptazolin, the quinolizidine alkaloid (−)-lasubine II,[2] all four stereoisomers of 4-hydroxypipecolic acid,[3] and the dendrobate alkaloid (+)-241D and its C-4 epimer have resulted.[4] The versatility of these building blocks could be greatly expanded if methods could be devised for linking the δ-amino group with the α-carbon, which should result in a functionalized 5-substituted 3-oxo proline **3** (Scheme 1). Substituted prolines are examples of conformationally restricted α-amino acids and as such are in demand for modifications of peptides that result in their enhanced bioavailability and metabolic stability. In this paper we report studies aimed at preparing substituted prolines from **1**, as well as a concise asymmetric synthesis of methyl (2*S*,5*R*)-(+)-5-phenylpyrrolidine-2-carboxylate (**18**).

Scheme 1



A method that appears to be ideally suited for linking the nitrogen and α-carbon atoms in (S_S,*R*)-(+)-methyl 3-oxo-5-phenyl-5-(*p*-toluenesulfinylamino)pentanoate (**4**)[3] is metal carbenoid chemistry.[5] Indeed the intramolecular N−H inser-

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(3) Davis, F. A.; Fang, T.; Chao, B.; Burns, D. M. *Synthesis* **2000**, 2106.
(4) Davis, F. A.; Chao, B.; Rao, A. *Org. Lett.* **2001**, *3*, 3169.

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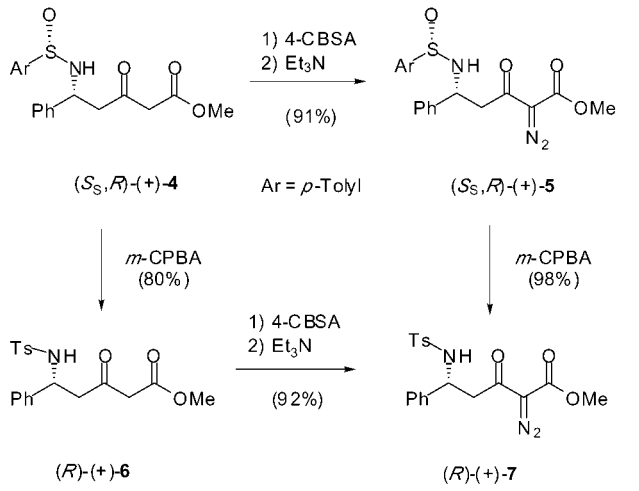
tion reactions of amino α-diazoketones catalyzed by metals have been used to prepare nitrogen heterocycles,[5,6] such as β-lactams,[7] pyrrolidinones,[8,9] piperidinones,[8,9] and pipecolic acid.[10] The requisite α-diazo compound (S_S,*R*)-(+)-**5** was readily prepared in 91% yield by diazo transfer from commercially available (4-carboxybenzene)sulfonyl azide (*p*-CBSA) and triethylamine (Scheme 2). Since metal carbenoid

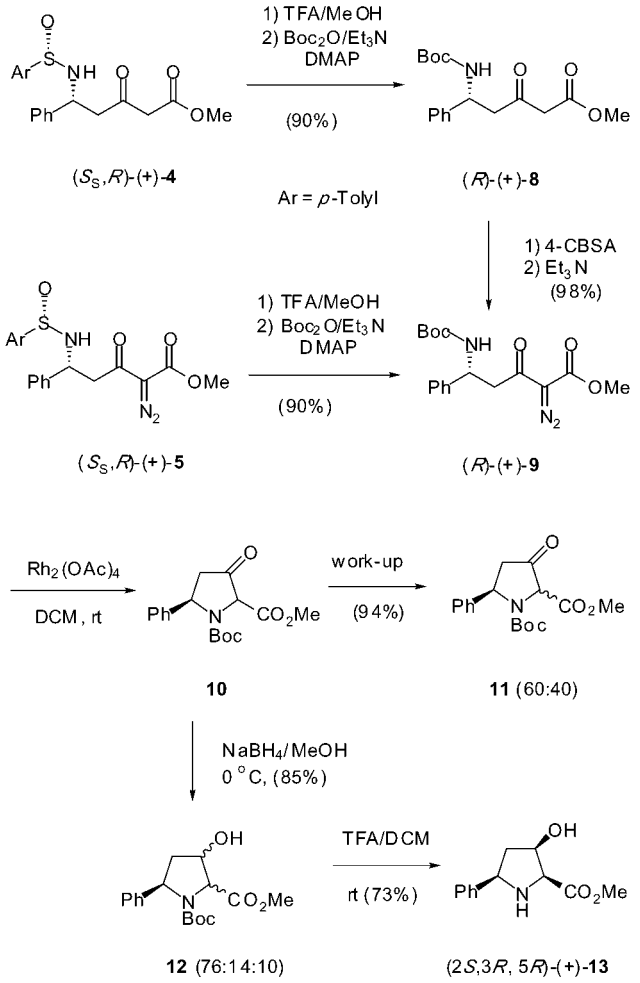
Scheme 2



insertion into the N−H bond of a sulfinamide has not been reported, the corresponding *N*-tosyl derivative (*R*)-(+)-**7** was prepared via two different methods.[11] First the diazo sulfinamide **5** was oxidized to **7** in 98% yield using *m*-chloroperbenzoic acid (*m*-CPBA). Alternatively this material was prepared by diazo transfer from *N*-tosyl δ-amino β-ketoester **6** (Scheme 2). The diazo compounds are stable and readily purified by flash chromatography.

Diazo compounds (+)-**5** or (+)-**7** were treated in DCM or benzene with 3 mol % of $Rh_2(OAc)_4$ at room temperature or reflux for 2 h. Removal of the solvent and chromatography gave a complex mixture of products that could not be characterized. Since the majority of intramolecular carbenoid N−H insertions involve amides,[7−10] the *N*-Boc derivative (*R*)-(+)-**9** was prepared as outlined in Scheme 3. The sulfinyl group in (+)-**4** was removed with 5.0 equiv of TFA in MeOH to give the amine salt (not shown). The solution was concentrated, dissolved in THF, and treated with Boc_2O/Et_3N

Scheme 3



and a catalytic amount of DMAP. The *N*-Boc-protected δ-amino β-ketoester (*R*)-(+)-**8** was obtained in 90% yield for the two steps. Next, diazo transfer using 4-CBSA/Et_3N gave (*R*)-(+)-**9** in nearly quantitative yield. Remarkably, (*R*)-(+)-**9** can also be prepared from the *N*-sulfinyl diazo compound (+)-**5** in 90% yield using the one-pot deprotection/protection protocol (Scheme 3). It is reported that α-keto diazo compounds are unstable in the presence of strong acids such as TFA.[9]

With 3 mol % of $Rh_2(OAc)_4$, (*R*)-(+)-**9** gave the desired oxo proline **10** as a single diastereoisomer in near quantitative crude yield (Scheme 3). In solution this material reverts to an 85:15 mixture of cis:trans isomers and, on chromatographic purification, a 60:40 isomer mixture **11** (vide infra). NOE and NOESY experiments to determine the structure of crude **10** were inconclusive. However, reduction of **10** (85:15 mixture) with $NaBH_4$/MeOH gave a 76:14:10 mixture of alcohols **12** in 85%. Deprotection, TFA/DCM, and purification gave the major isomer (2*S*,3*R*,5*R*)-(+)-**13** in 73% yield. NOSEY experiments revealed that **13** had the cis arrangement of substituents (Scheme 3) and strongly suggested that the rhodium carbenoid species inserts into the N−H bond of **9** to furnish the cis proline derivative **10**.

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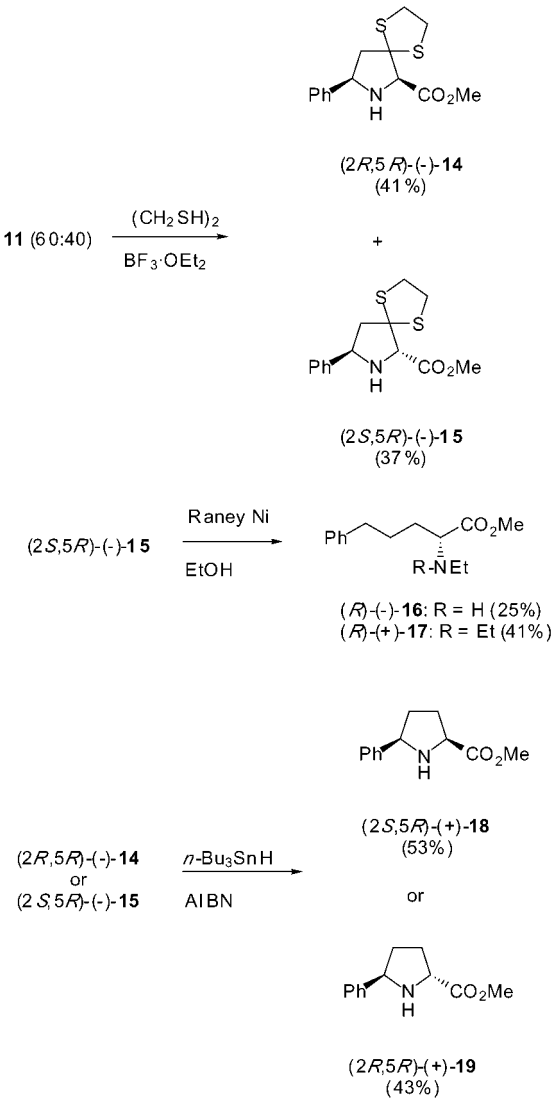
Scheme 4

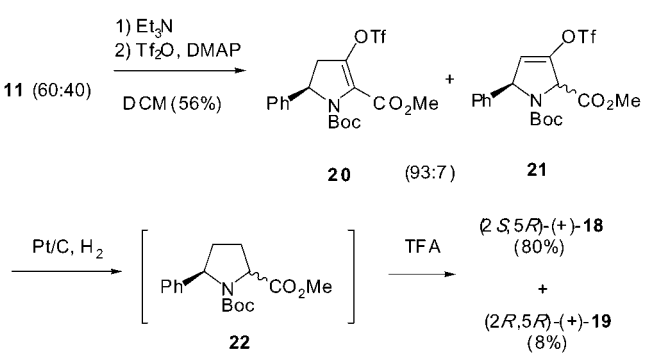


(+)-RP 66803 is a nonpeptide cholecystokinin (CCK) antagonist that contains a *cis*-(2*S*,5*R*)-(+)-5-phenylpyrrolidine-2-carboxylate segment.[12] Cholecystokinin is a brain-gut peptide hormone that is thought to regulate a number of physiological process in mammalian species. This proline has been prepared in enantiopure form by a Friedel−Crafts reaction that employs a protected 5-methoxy L-proline to give a cis/trans mixture that could be separated by chromatography.[12] A 13-step asymmetric synthesis of methyl *cis*-(2*R*,5*R*)-(+)-5-phenylpyrrolidine-2-carboxylate (**18**) was recently described by Larcheveque and co-workers starting from an optically pure α-hydroxy acid.[13] Removal of the 3-oxo group in **11** could result in a more expeditious synthesis of (+)-**18** provided that the cis and trans isomers can be efficiently separated somewhere in the synthesis.

The 60:40 oxo proline mixture **11** was treated with 10 equiv of 1,2-ethanedithiol and 2.5 equiv of $BF_3{\cdot}OEt_2$ to give a separable cis:trans mixture of thioketals (−)-**14** and (−)-**15** in 41% and 37% yield, respectively (Scheme 4). The cis geometry was assigned to (−)-**14** on the basis of its conversion to (+)-**18** and further supports an assertion that the major isomer in **11** has the same cis geometry. Next Raney-nickel desulfurization of (−)-**15** in ethanol, expected to furnish *trans*-**19**, resulted in a ring opening to produce the *N*-ethyl and *N*,*N*-diethyl α-amino acids (*R*)-(−)-**16** and (*R*)-(+)-**17** in 25% and 41% yield. While metal-catalyzed reductive ring opening of aziridines to α-amino acids is well-known,[14] opening of larger ring systems such as pyrrolidines under these conditions is, to the best of our knowledge, unknown. Reductive amination, resulting from acetaldehyde in the ethanol solvent, is the likely source of **16** and **17**. Desulfurization of (−)-**14** and (−)-**15** using tributyltin hydride[15] gave *cis*-(2*S*,5*R*)-(+)-**18**[13] and *trans*-(2*R*,5*R*)-(+)-**19**[12] in 53% and 43% isolated yields, respectively (Scheme 4).

Although our asymmetric synthesis of (+)-**18** was more efficient than those reported earlier,[12,13] it was not as concise as first envisioned: epimerization at C-2 in **10** required separation of an almost 1:1 mixture of dithiane isomers **14** and **15**. The reduction of a vinyl triflate to an alkane, as described by Comins,[15] could provide a more efficient route to (+)-**18** (Scheme 5). Thus reaction of **11** (60:40 mixture)

Scheme 5



with 1.1 equiv of Et_3N at −78 °C in DCM followed by addition of Tf_2O and a catalytic amount of DMAP resulted after 1.5 h in a 93:7 inseparable regioisomeric mixture of vinyl triflates **20** and **21** in 56% yield (Scheme 5). Starting material **11** (36%) was also recovered. All attempts to date to improve the yield by varying the reaction conditions resulted in much poorer ratios of **20** and **21**. Hydrogenation of **20** and **21** over a platinum catalyst afforded an 85:15 ratio of cis:trans **22**. The fact that the cis:trans ratio of **22** is less than **20**:**21** suggests that the hydrogenation was not completely stereospecific. Deprotection (TFA) afforded (+)-**18** and (+)-**19** and purification by preparative TLC furnished an 80% yield of *cis*-(2*S*,5*R*)-**18** for the two steps.

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In summary, methodology has been devised for the asymmetric construction of 5-substituted 3-oxo prolines from δ-amino β-ketoesters by linking the nitrogen and α-carbon atoms using metal carbenoid chemistry. This new protocol greatly expands the utility of these versatile polyfunctionalized chiral building blocks. A concise enantioselective synthesis of methyl (2*S*,5*R*)-(+)-5-phenylpyrrolidine-2-carboxylate (**18**) has been achieved.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **5**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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