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δ-Amino β-Keto Esters, a Designed Polyfunctionalized Chiral Building Block for Alkaloid Synthesis. Asymmetric Synthesis of (*R*)-(+)-2-Phenylpiperidine and (−)-SS20846A

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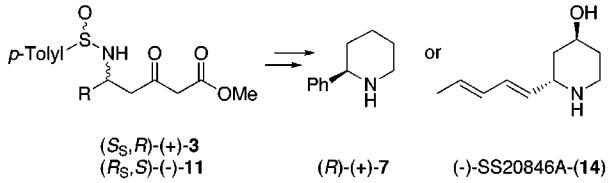
ABSTRACT



δ-Amino β-keto esters 3 and 11 are designed polyfunctionalized chiral building blocks for alkaloid synthesis and are prepared in one step from the corresponding sulfinimine (*N*-sulfinyl imine). Concise highly enantioselective four-step syntheses of 2-phenylpiperidine (7) and SS20846A (14) from 3 and 11, respectively, are described.

Polyfuctionalized chiral building blocks, which we define as molecules having at least one stereogenic center and more than one chemically differentiated functional group, have played significant roles in asymmetric synthesis and the synthesis of biologically and pharmacologically active molecules.[1] Examples include carbohydrates, amino acids, hydroxy acids, and terpenes.[1a] Since they are derived from the "chiral pool", they usually require extensive manipulation and protecting group chemistry to transform them into the desired target. Furthermore, access to both enantiomers is usually limited. More recently, designed polyfunctionalized chiral building blocks (DPFCB's) have been developed to overcome these limitations. DPFCB's are generally easily prepared in both enantiomeric forms and require a minimum of manipulation and protecting group chemistry because they are designed for a specific purpose. Examples include Johnson's enones,[2] Ojima's β-lactams,[3] Meyers' bicyclic lactams,[4] and sulfinimines (*N*-sulfinyl imines).[5] In this regard, the piperidine ring system, found in many alkaloids,[6] combined with the challenge of devising efficient strategies for the synthesis of polysubstituted examples has resulted in Comins' 1-acylpyridinium salts[7] and Husson's α-cyanomethyloxazolidines.[8] As part of a program aimed at the design and synthesis of polyfunctionalized chiral building blocks, we introduce *N*-sulfinyl δ-amino β-keto esters for

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(2) (a) Johnson, C. R. *Acc. Chem. Res.* **1998**, *31*, 333. (b) Murphy, S. T.; Bencsik, J. R.; Johnson, C. R. *Org. Lett.* **1999**, *1*, 1483.

(3) Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383.

(4) Meyers, A. I.; Brengel, G. P. *J. Chem. Soc., Chem. Commun.* **1997**, 1.

(5) For reviews on sulfinimines, see: (a) Zhou, P.; Chen, B.-C.; Davis, F. A. In *Advances in Sulfur Chemistry*; Rayner, C. M., Ed.; JAL Press Inc.: 2000; Vol. 2, pp 249−282. (b) Hua, D. H.; Chen, Y.; Millward, G. S. *Sulfur Rep.* **1999**, *21*, 211. (c) Davis, F. A.; Zhou, P.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13.

(6) For reviews on the synthesis of substitute piperidines, see: (a) Bailey, P. D.; Millwood, P. A. Smith, P. D. *J. Chem. Soc., Chem. Commun.* **1998**, 633. (b) Leclercq, S.; Daloze, D.; Braekman, J.-C. *Org. Prep. Procd. Int.* **1996**, *28*, 499. (c) Wang, C.-L. J.; Wuonola, M. A. *Org. Prep. Procd. Int.* **1992**, *28*, 585.

(7) Comins, D. L.; Joseph, S. P. In *Advances in Nitrogen Heterocycles*; Moody, C. J., Ed.; JAL Press Inc.: 1996; Vol. 2, pp 251−294.

(8) Husson, H.-P.; Royer, J. *Chem. Soc. Rev.* **1999**, *28*, 383.

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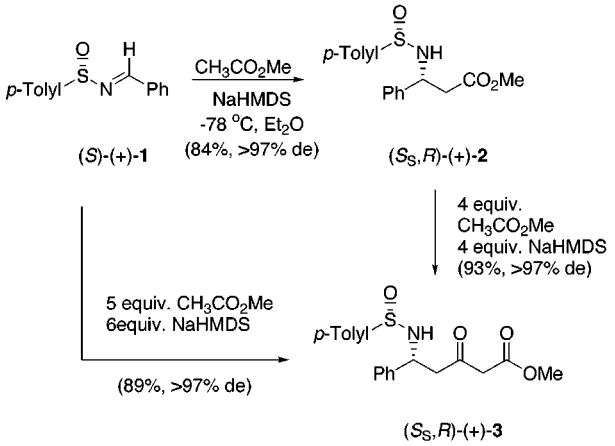
the asymmetric synthesis of alkaloids.[9] The utility of these new building blocks is illustrated in concise four-step enantioselective syntheses of (*R*)-(+)-2-phenylpiperidine (**7**) and (−)-SS20846A (**14**).

Earlier we reported that (*S*)-(+)-*N*-benzylidene-*p*-toluenesulfinamide (**1**) reacts with the sodium enolate of methyl acetate in ether at −78 °C to give *N*-sulfinyl *β*-phenylalanine **2** in 84% yield and >97% de (Scheme 1).[10] Subsequent

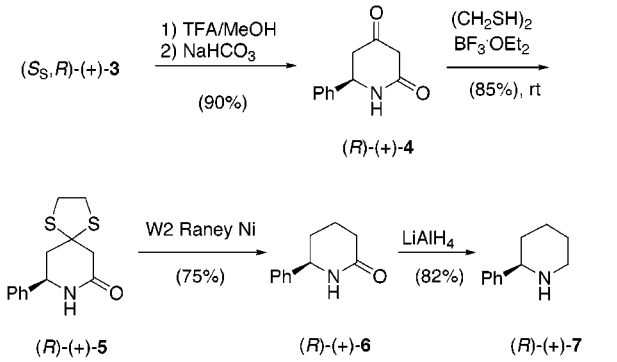
Scheme 1



treatment of **2** with 4 equiv of the sodium enolate of methyl acetate, prepared from NaHMDS and methyl acetate, affords (*S*$_S$,*R*)-(+)-methyl 3-oxo-*N*-(*p*-toluenesulfinyl)-5-amino-5-phenylpentanoate (**3**) in 93% yield following flash chromatography. The de was >97%. About 10−15% of *β*-keto ester **3** exists as the enol form in solution. Significantly, (+)-**3** can be prepared in one step, in 89% yield, by treating the sulfinimine **1** with 5 equiv of the enolate generated from 5 equiv of methyl acetate and 6 equiv of NaHMDS. The de was the same, i.e., >97%. Although the one-step method is more concise, the two-step procedure could be advantageous if the initial enolate addition was not highly diastereoselective. In this case, up-grading the diastereomeric purity of the *β*-amino ester could be performed prior to formation of the *δ*-amino *β*-keto ester.

To illustrate the utility of (+)-**3**, (*R*)-(+)-2-phenylpiperidine (**7**) was prepared in four steps from (*S*$_S$,*R*)-(+)-**3** (Scheme 2). Removal of the *N*-sulfinyl in **3** with 5 equiv of

Scheme 2



TFA in MeOH/CH_2Cl_2 gave the amine (not shown), which was passed through a short pad of silica gel to remove methyl *p*-toluenesulfinate, prior to reaction with saturated $NaHCO_3$ in CH_2Cl_2 to give (*R*)-(+)-6-phenylpiperidine-2,4-dione (**4**) as a solid in 90% yield.[11] Dione **4** was treated with 10 equiv of ethanedithiol and 2.5 equiv of $BF_3{\cdot}OEt_2$ at rt in CH_2Cl_2 for 8 h to give the thioketal (*R*)-(+)-**5**, which was isolated in 85% yield by chromatography. Next, (+)-**5** was subjected to W2 Raney nickel desulfurization in EtOH to give (*R*)-(+)-6-phenylpiperidin-2-one (**6**) in 75% isolated yield. Reduction with LAH at rt for 8 h gave an 82% yield of the volatile (*R*)-(+)-6-phenylpiperidine (**7**), which was purified by chromatography.[12] The enantiomeric purity was determined to be >98% ee by comparison of its rotation, $[\alpha]^{20}_D$ 50.0 (*c* 0.31, CH_2Cl_2), with literature values, $[\alpha]^{23}_D$ 48.4 (*c* 0.31, CH_2Cl_2), for 98% ee.[12b]

2-Substituted-4-piperidones represent an important class of building blocks for the synthesis of substituted piperidine derivatives[13] and other biologically active materials.[14] In this context the application of *δ*-amino *β*-keto esters to the synthesis of these chiral building blocks was demonstrated in the asymmetric synthesis of (−)-(2*S*,4*S*)-SS20846 A (**14**). SS20846 A (**14**) was isolated from *Steptomyces* sp. S20846[15] and is a proposed intermediate in the biosynthesis of the potent antimicrobial agent streptazolin.[16] It is also reported

(9) For references to *δ*-amino *β*-keto esters, see: (a) Li, B.; Franck, R. W. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2629. (b) Werner, R. M.; Shokek, O. Davis, J. T. *J. Org. Chem.* **1997**, *62*, 8243.

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(11) For a racemic synthesis of **4**, see: Ashton, M. J.; Hills, S. J.; Newton, C. G.; Taylor, J. B.; Tondu, S. C. D. *Heterocycles* **1989**, *28*, 1015.

(12) For earlier asymmetric syntheses of **7**, see: (a) Davis, F. A.; Szewczyk, J. M. *Tetrahedron Lett.* **1998**, *39*, 5951. (b) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8952. (c) Deziel, R.; Malenfant, E. J. *J. Org. Chem.* **1995**, *60*, 4660.

(13) See, for example: (a) Rubiralta, M.; Giralt, E.; Diez, A. *Piperidine Structure, Preparation, Reactivity and Synthetic Applications of Piperidine and its Derivatives*; Elsevier: Amsterdam, 1991. (b) Rubiralta, M.; Diez, A.; Vila, C.; Troin, Y.; Feliz, M. *J. Org. Chem.* **1991**, *56*, 6292. (c) Comins, D. L.; LaMunyon, D. H. *J. Org. Chem.* **1992**, *57*, 5807. (d) Diez, A.; Mavel, S.; Teulade, J. C.; Chavignon, O.; Sinibaldi, M. E.; Troin, Y.; Rubiralta, M. *Heterocycles* **1993**, *36*, 2451.

(14) For leading references, see: Kudzma, L. V.; Severnak, S. A.; Benvenga, M. J.; Ezell, E. F.; Ossipov, M. H.; Knight, V. V.; Rudo, F. G.; Spencer, H. K.; Spaulding, T. C. *J. Med. Chem.* **1989**, *32*, 2534.

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(16) (a) Mayer, M.; Thiericke, R. *J. Org. Chem.* **1993**, *58*, 3486. (b) Grabley, S.; Hammann, P.; Kluge, H.; Wink, J.; Kricke, P.; Zeeck, A. *J. Antibiot.* **1991**, *44*, 797.

(17) Davis, F. A.; Zhang, Y. Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1043.

(18) For leading references to sulfinimines (*N*-sulfinyl imines) chemistry, see: Davis, F. A.; Andemichael, Y. W. *J. Org. Chem.* **1999**, *64*, 8627.

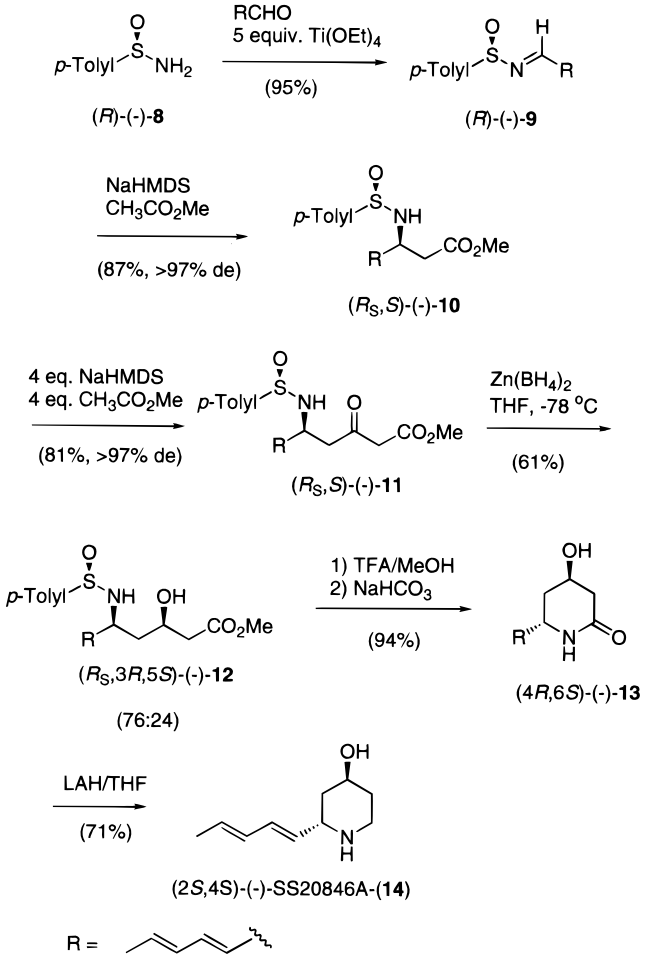
(19) The cis alkene isomer was not detected by ^{1}H NMR.

(20) Kathawala, F. G.; Prager, B.; Prasad, K.; Repic, O.; Shapiro, M. J.; Stabler, R. S.; Widler, L. *Helv. Chim. Acta* **1986**, *69*, 803.

(21) For earlier syntheses of **14**, see: (a) Ripoche, I.; Canet, J.-L.; Aboab, B.; Gelas, J.; Troin, Y. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3485. (b) Yokoyama, H.; Otaya, K.; Yamaguchi, S.; Hirai, Y. *Tetrahedron Lett.* **1998**, *39*, 5971. (c) Takemoto, Y.; Ueda, S.; Takeuchi, J.; Baba, Y.; Iwata, C. *Chem. Pharm. Bull.* **1997**, *45*, 1906. (d) Takemoto, Y.; Ueda, S.; Takeuchi, J.; Nakamoto, T.; Iwata, C. *Tetrahedron Lett.* **1994**, *35*, 8821.

to have a restrictive action on the digestive system.[15,16b] Condensation of (*R*)-(−)-*p*-toluenesulfinamide (**8**) with sorbic aldehyde in the presence of 5 equiv of $Ti(OEt)_4$, as previously described,[17,18] gave a 95% yield of sulfinimine (*R*)-(−)-**9** (Scheme 3). Since this aldehyde contained about 10% of the cis isomer, it resulted in 10% of the cis sulfinimine being formed. Crystallization from hexanes reduced the cis isomer to about 4%. Since it was expected that the cis isomer would be eliminated in subsequent steps, borne out in the second step, impure **9** was condensed with the sodium enolate of methyl acetate to give β-amino acid (R_S,*S*)-(−)-**10** in 87% yield and >97% de. With 4 equiv of the enolate, (−)-**10** gave δ-amino β-keto ester (R_S,*S*)-(−)-**11** in 81% isolated yield.[19] The one-step procedure, starting from sulfinimine (*R*)-(+)-**9**, afforded (−)-**11** in 81%. To obtained the correct epimer of **14**, it was necessary to reduce the 3-oxo group with syn selectivity, achieved using metal chelation control.[20] The best ratio (76:24, syn:anti) was obtained with $Zn(BH_4)_2$ at −78 °C in THF, affording the desired syn isomer (R_S,3*R*,5*S*)-**12** in 61% isolated yield following chromatography. Other reducing agents such as $NaBH_4$, LAH, and L-Selectride either failed to react or gave nearly equal amounts of the alcohols. Removal of the *N*-sulfinyl group and cyclization, as before, gave the trans 4-hydroxy-2-piperidone **13** in 94% yield. Reduction with LAH afforded (2*S*,4*S*)−(−)-SS20646A-(**14**) in 71% yield.[21] The enantiomeric purity was >97% as determined by comparison with literature values.[21]

Scheme 3



In summary, the one-step asymmetric sulfinimine-mediated synthesis of δ-amino β-keto esters, a designed polyfunctionalized chiral building block (DPFCB) for alkaloid synthesis, is reported. The utility of this building block was illustrated in four-step asymmetric syntheses of piperidines (*R*)-(+)-**7** and (2*S*,4*S*)-(−)-**14**. These procedures, which required no protecting group chemistry, represent some of the most concise enantioselective preparations of these alkaloids reported to date.[12,21,22]

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **1**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Selected properties: (S_S,*R*)-(+)-**3**, colorless oil; $[\alpha]^{20}_D$ 73.60 (*c* 1.63, $CHCl_3$); (*R*)-(+)-**4**, mp 166−168 °C [lit.[5] mp 167−169 °C for (±)-**4**]; $[\alpha]^{20}_D$ 124.3 (*c* 0.37, $CHCl_3$); (*R*)-**5**, colorless oil; $[\alpha]^{20}_D$ 61.9 (*c* 0.42, $CHCl_3$); (*R*)-(+)-**6**, mp 119−120 °C.; $[\alpha]^{20}_D$ 72.8 (*c* 1.2, $CHCl_3$); (*R*)-(−)-**9**, mp 89−90 °C.; $[\alpha]^{20}_D$ −1009 (*c* 1.2, $CHCl_3$); (R_S,*S*)-(−)-**10**, oil, $[\alpha]^{20}_D$ −133.9 (*c* 1.2, $CHCl_3$); (R_S,*S*)-(−)-**11**, colorless oil; $[\alpha]^{20}_D$ −78.9 (*c* 1.5, $CHCl_3$); *syn*-(−)-**12**, colorless oil; $[\alpha]^{20}_D$ −57.7 (*c* 1.3, $CHCl_3$); *trans*-(+)-**13**, white gum; $[\alpha]^{20}_D$ 90.9 (*c* 1.5, MeOH); (−)-**14**, oil; $[\alpha]^{20}_D$ −15.7 (*c* 0.51, $CHCl_3$).