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Asymmetric Synthesis of Substituted Homotropinones from *N*-Sulfinyl *β*-Amino Ketone Ketals. (−)-Euphococcinine and (−)-Adaline

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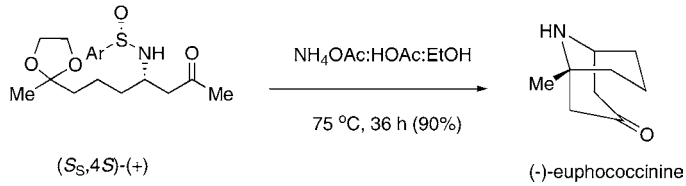
ABSTRACT



Sulfinimine-derived *N*-sulfinyl *β*-amino ketone ketals on heating with NH_4OAc:HOAc undergo a four-step intramolecular Mannich cyclization cascade reaction to give homotropinones, such as (−)-euphococcinine, in excellent yields as single isomers.

The alkaloids (+)-euphococcinine (**1**) and (−)-adaline (**3**) are examples of the 9-azabicyclo[3.3.1]nonane ring system having a quaternary stereocenter bearing a nitrogen atom (Figure 1).[1] These homotropinones are found in secretions of the *Coccinellid* beetles (lady bugs) and are potent deterrents to both spiders and ants.[2] Biosynthetic studies indicate that these alkaloids are polyacetate in origin and suggest that a piperideine ketone could be a key intermediate in their biosynthesis.[3] The piperideine ketone undergoes an intramolecular Mannich cyclization to form homotropinone. Intramolecular Mannich cyclizations have been used in the syntheses of (+)-**1**,[4] (−)-**2**,[5] and (−)-**3**.[5] However, the preparation of the chiral Mannich precursors is sometimes problematic and not easily adaptable to the preparation of analogues. Furthermore, retro-Mannich side products have been reported.[5] Other syntheses of the homotropinones include the use of ring-closing alkene metathesis and metal-mediated semipinacol rearrangements.[6−8]

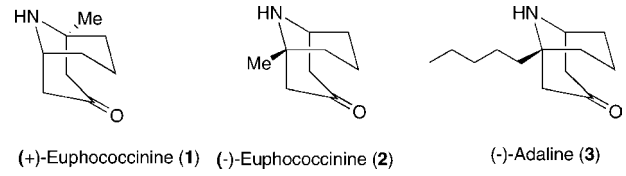


Figure 1. Homotropinones.

Recently, we introduced acyclic *N*-sulfinyl *β*-amino ketone ketals as new building blocks for the asymmetric synthesis of substituted tropinones (Figure 2).[9−11] Acid hydrolysis afforded

(1) For a review on the asymmetric synthesis of quaternary carbon stereocenters bearing a nitrogen atom, see: (a) Ramon, D. J.; Yus, M. C. *Current Org. Chem.* **2004**, *8*, 149. (b) For leading references, see: Roy, S.; Spino, C. *Org. Lett.* **2006**, *8*, 939.

(2) King, A. G.; Meinwald, J. *Chem. Rev.* **1996**, *96*, 1105.

(3) (a) Laurent, P.; Lebrun, B.; Brakeman, J.-C.; Daloze, D.; Pastells, J. M. *Tetrahedron* **2001**, *57*, 3403. (b) Tursch, B.; Daloze, D.; Braekman, J. C.; Hotele, C.; Pasteels, J. M. *Tetrahedron* **1975**, *31*, 1541.

(4) Mechelke, M. F.; Meyers, A. I. *Tetrahedron Lett.* **2000**, *41*, 4339.

(5) Yue, C.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1992**, *57*, 4211.

(6) For racemic syntheses of (±)-euphococcinine and (±)-adaline, see: (a) Davison, E. C.; Holmes, A. B.; Forbes, I. T. *Tetrahedron Lett.* **1995**, *36*, 9047. (b) Gossinger, E.; Witkop, B. *Monatsh. Chem.* **1980**, *111*, 803. (c) Gnecco Medina, D. H.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1983**, *24*, 2099.

(7) (+)-Euphococcinine, see: (a) Murahashi, S.-I.; Sun, J.; Kurosawa, H.; Imada, Y. *Heterocycles* **2000**, *52*, 557. (b) Arbour, M.; Roy, S.; Godbout, C.; Spino, C. *J. Org. Chem.* **2009**, *74*, 3806.

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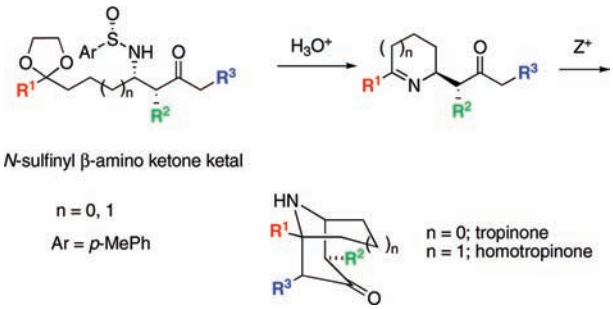
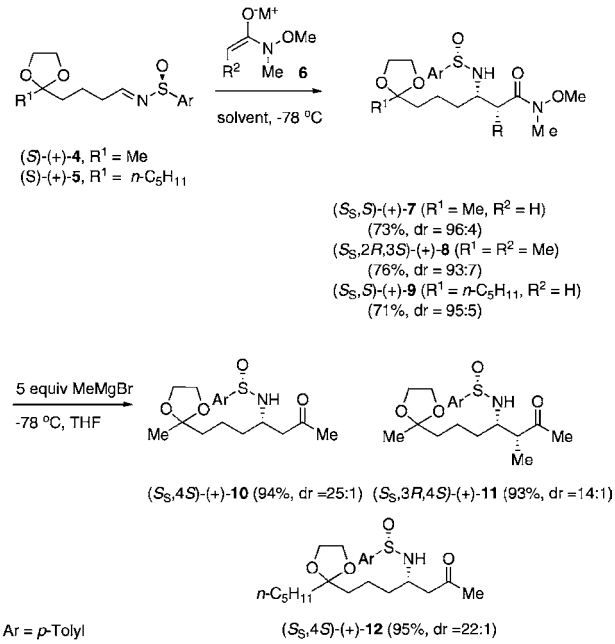


Figure 2. Intramolecular Mannich cyclization.

stable pyrrolideine ketones ($n = 0$) that rearranged to the tropinones ($n = 0$) on formation of the corresponding acyliminium ions via a Mannich cyclization. We report here the application of these building blocks for the asymmetric synthesis of substituted homotropinones ($n = 1$), including (−)-**2** and (−)-**3**. Furthermore, we demonstrate that the buffer NH_4OAc:HOAc is able to initiate a four-step intramolecular Mannich cyclization cascade reaction of the *N*-sulfinyl *β*-amino ketone ketal to form the substituted homotropinone in excellent yield and stereoselectivity.

Our synthesis begins with addition of masked oxo-sulfinimine (*S*)-(+)-**4**[12] and (+)-**5**[13] to a −78 °C solution of the preformed enolate of *N*-methoxy-*N*-methylacetamide **6** ($R^2 = H$) to give *N*-sulfinyl *β*-amino Weinreb amide ketals (+)-**7** and (+)-**9**, respectively, in good yield and high dr (Scheme 1).[14] As can

Scheme 1. Synthesis of *β*-Amino Ketals and *β*-Amino Ketone Ketals



be seen from the results summarized in Table 1, the dr's were dependent on the counterion and solvent with the

Table 1. Synthesis of the *β*-Amino Weinreb Amide at −78 °C

entry	R^1	R^2	base solvent	solvent	dr[a,b]	% yield
1	Me	H	LiHMDS	THF	88:12	76
2				Et_2O	74:26	75
3			NaHMDS	THF	75:25	78
4				Et_2O	89:11	76
5			KHMDS	THF	92:8	73
6				Et_2O	96:4	73
7	n-C_5H_{11}	H	KHMDS	THF	95:5	71
8		H	KHMDS	Et_2O	93:7	71
9	Me	Me	LiHMDS	Et_2O	88:12	
10				THF	94:6	76
11			LDA	Et_2O	84:16	
12				THF	86:14	
13			KHMDS	Et_2O	78:22	

[a] Determined by ^1H NMR on the crude reaction mixture. [b] Inseparable diastereoisomers. [c] For entries 9−13, syn:anti ratio.

potassium enolate in ether giving the best selectivity (Table 1: entries 6 and 8). Addition of (*S*)-(+)-**4** to the prochiral enolate of *N*-methoxy-*N*-methylpropylamide **6** ($R^2 = Me$) afforded (+)-**8** having the *syn* geometry based on early studies (Scheme 1).[15] Here the lithium enolate of **6** in THF gave the best selectivity (Table 1: entry 10). However, all the diastereoisomers proved to be inseparable, and in only one example (+)-**12** did the dr improve on further transformation. Reaction of these *N*-sulfinyl *β*-amino Weinreb amide ketals with 5 equiv of methylmagnesium bromide gave the corresponding methyl ketones (+)-**10** (92% de), (+)-**11** (86% de), and (+)-**12** (92% de) in excellent yields (Scheme 1).

Treatment of amino ketone (+)-**10** with 3 N aqueous HCl in MeOH and THF did not give the homotropinone but afforded the corresponding piperideine ketone (*S*)-(−)-**13** in excellent yield (Scheme 2). As we observed in the formation of tropinones from pyrrolidine ketones (Figure 2), it was necessary to first generate a reactive acyliminium ion species to effect the Mannich cyclization.[9] However, treatment of (−)-**13** with $(Boc)_2O$/DMAP resulted in no reaction and the recovery of starting material. To generate a more reactive

(8) (−)- and (+)-Adaline: (a) Ref 7b. (b) Coombs, T. C.; Zhang, Y.; Garnier-Amblard, E. C.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2009**, *131*, 876. (c) Itoh, T.; Yamazaki, N.; Kibayashi, C. *Org. Lett.* **2002**, *4*, 2469. (d) Hill, R. K.; Renbaum, L. A. *Tetrahedron* **1982**, *38*, 1959.

(9) Davis, F. A.; Theddu, N.; Gaspari, P. M. *Org. Lett.* **2009**, *11*, 1647.

(10) For a review on S−N chemistry, which includes sulfinimines and sulfinimine-derived chiral building blocks, see: Davis, F. A. *J. Org. Chem.* **2006**, *71*, 8993.

(11) For recent reviews on sulfinimine-derived chiral building blocks, see: (a) Davis, F. A.; Chao, B.; Andemichael, Y. W.; Mohanty, P. K.; Fang, T.; Burns, D. M.; Rao, A.; Szewczyk, J. M. *Heteroat. Chem.* **2002**, *13*, 486. (b) Davis, F. A.; Yang, B.; Deng, J.; Zhang, J. *ARKIVOC* **2006**, 120.

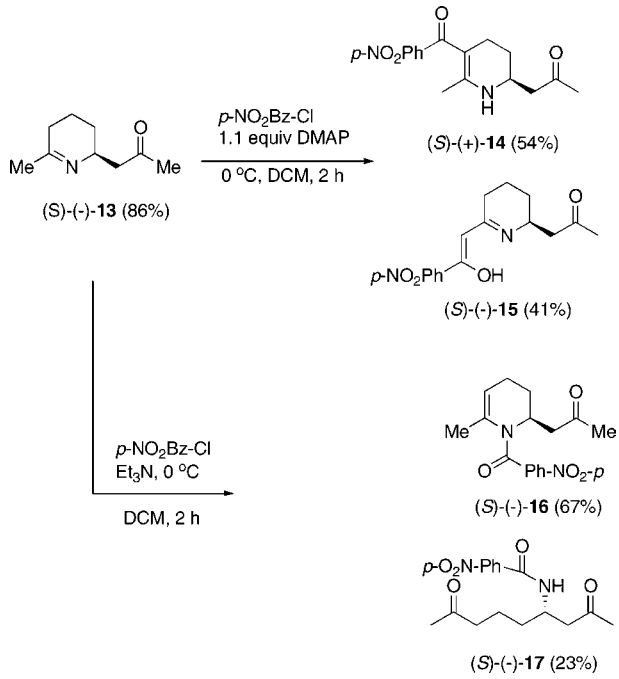
(12) Davis, F. A.; Zhang, H.; Lee, S. H. *Org. Lett.* **2001**, *3*, 759.

(13) For the synthesis of (*S*)-(+)-**5**, see the Supporting Information section.

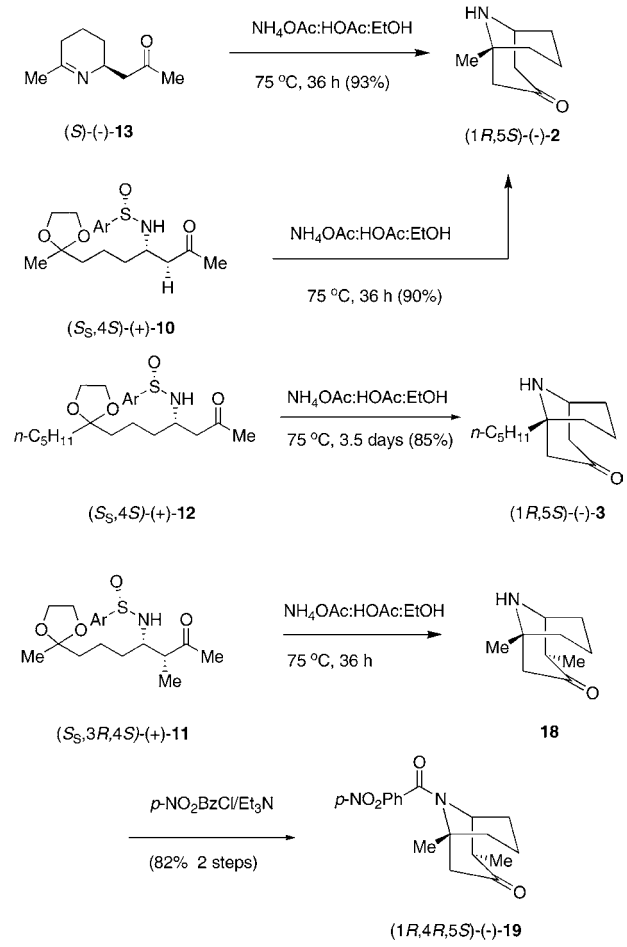
(14) For applications of Weinreb enolates in the synthesis of *N*-sulfinyl *β*-amino Weinreb amides, see: (a) Davis, F. A.; Nolt, M. B.; Wu, Y.; Prasad, K. R.; Li, D.; Yang, B.; Bowen, K.; Lee, S. H.; Eardley, J. H. *J. Org. Chem.* **2005**, *70*, 2184. (b) Davis, F. A.; Song, M. *Org. Lett.* **2007**, *9*, 2413.

(15) Prochiral enolates, including Weinreb amide enolates, afford the syn product in addition to sulfinimines. See: (a) Davis, F. A.; Yang, B. *J. Am. Chem. Soc.* **2005**, *127*, 8398. (b) Davis, F. A.; Zhang, Y.; Qiu, H. *Org. Lett.* **2007**, *9*, 833. (c) Ref 11b. (d) Davis, F. A.; Song, M.; Qiu, H.; Chai, J. *Org. Biomol. Chem.* **2009**, *7*, 5067.

Scheme 2. Generation of Acyliminium Ions



Scheme 3. Asymmetric Synthesis of Substituted Homotropinones



acyliminium ion, (−)-**13** was treated with *p*-nitrobenzoyl chloride/DMAP. To our surprise, two new compounds, (*S*)-(+)-**14** and (*S*)-(−)-**15**, were isolated resulting from C-acylation, rather than N-acylation (Scheme 2). C-Acylation has been reported for the reaction of piperideines with isocyanates and isothiocyanates.[16] Enamino ketone (+)-**14** exhibits strong NH absorption at 3325 cm^{-1} in the IR spectrum, and both (+)-**14** and (−)-**15** have exchangeable protons (D_2O). The enolic proton in piperideine (−)-**15** appears at δ 11.9 ppm in the 400 MHz ^1H NMR and is similar to that found in a related enolic piperideine.[17]

Furthermore, in (−)-**13** the C-2 methyl group appears as a doublet at δ 1.86 ppm ($CDCl_3$), whereas in (−)-**15** this group is replaced by a vinylic singlet proton at δ 5.58 ppm. The ^{13}C NMR spectra of these piperideines provide additional support for the proposed structures. In (+)-**14**, the C-2 and C-3 carbons appear at δ 148.4 and at δ 102.2 ppm, respectively, which is characteristic for enamino ketones.[18] The C-2 carbon in (−)-**15** (CD_2Cl_2) is at δ 167.1 ppm in the 100 MHz spectrum and is similar to the value of the C-2 carbon in (−)-**13**; i.e., δ 168.3 ppm. Reaction of (−)-**13** with *p*-NO_2BzCl-Et_3N at 0 °C for 2 h resulted in (*S*)-(−)-**16** and its hydrolysis product (*S*)-(−)-**17** (Scheme 2). Compound (−)-**16** most likely results from the formation of a very reactive *N*-acyliminium ion that eliminates a proton to give the enamide (Scheme 2).

In their synthesis of (+)-euphococcinine (**1**), Mechelke and Meyers used 10 equiv of ammonium acetate in acetic acid at 75 °C to initiate the Mannich cyclization.[4] When piperideine ketone (−)-**13** was subjected to these conditions, less than 20% of the homotropinone (−)-**2** was formed. However, with 25 equiv of ammonium acetate in 1:1 HOAc:EtOH (0.01 mmol) for 36 h (−)-euphococcinine (**2**) was isolated in 93% yield (Scheme 3). When (−)-**2** was resubjected to these conditions (NH_4OAc:HOAc) for varying lengths of time, retro-Mannich products were not detected, and (−)-**2** was recovered quantitatively. These results suggest that the homotropinone is the thermodynamically most stable product. We speculate that the buffer solution, NH_4OAc:HOAc, generates a moderately reactive piperideine iminium ion while simultaneously promoting ketone enolization, all under thermodynamic conditions. By contrast, *p*-NO_2BzCl-DMAP or *p*-NO_2BzCl-Et_3N generates a very reactive *N*-acyliminium ion that reacts kinetically to give C-acylation products or eliminates a proton to give the enamide (Scheme 2).

Significantly, when the acyclic *N*-sulfinyl β-amino ketone ketal (+)-**10** was subjected to the rearrangement conditions for 36 h, a 90% yield of (−)-**2** was realized. Similar treatment of (+)-**12** gave (−)-adaline (**3**) in 85% yield (Scheme 3).

(16) (a) Harada, K.; Mizoe, Y.; Furukawa, J.; Yamshita, S. *Tetrahedron* **1970**, *26*, 1579. (b) Tohda, Y.; Kawashima, T.; Ariga, M.; Akiyama, R.; Shudoh, H.; Mori, Y. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2329.

(17) A similar enolic piperideine has been reported in the synthesis of alkaloid (−)-cassine. See: Herdeis, C.; Kupper, P.; Ple, S. *Org. Biomol. Chem.* **2006**, *4*, 524.

(18) (a) Dabrowski, J.; Kamienska-Trela, K.; Kozerski, L. *Org. Magn. Reson.* **1974**, *6*, 499. (b) Tourwe, D.; Binst, G. V.; De Graaf, S. A. G.; Pandit, U. K. *Org. Magn. Reson.* **1975**, *7*, 433.

This methodology is also adaptable to the synthesis of more substituted homotropinones where (+)-**11** gave **18** as a single isomer. However, **18** could not be separated from an unknown impurity, so the reaction mixture was treated with *p*-NO_2BzCl-Et_3N to afford amide (1*R*,4*R*,5*S*)-(−)-**19** in 82% yield for the two-step sequence (Scheme 3). COSY and NOE experiments confirm the structure of (−)-**19** (see Supporting Information).

In summary, sulfinimine-derived *N*-sulfinyl β-amino ketone ketals, on heating with the buffer solution NH_4OAc:HOAc, afforded homotropinones (−)-euphoccocinine (**2**), (−)-adaline (**3**), and substituted homotropinone **18** in excellent yields.

The conversion of these *N*-sulfinyl β-amino ketone ketals directly to the corresponding homotropinones represents a four-step intramolecular Mannich cyclization cascade reaction and is the most efficient method to date for the asymmetric syntheses of substituted homotropinones. The fact that intermediates such as (−)-**13** are involved in the formation of the homotropinones provides additional support for the hypothesis that piperideine ketones are involved in the biosynthesis of this class of heterocycles.[3]

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

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