Asymmetric Synthesis of the Carbocyclic Nucleoside Building Block (*R*)-(+)-4-Aminocyclopentenone Using δ -Amino β -Ketophosphonates and Ring-Closing Metathesis (RCM)

LETTERS 2004 Vol. 6, No. 8 1269–1272

ORGANIC

Franklin A. Davis* and Yongzhong Wu

Department of Chemistry, Temple University, Philadelphia, Pennsylvania 19122

fdavis@temple.edu

Received February 4, 2004

ABSTRACT





Amino keto-2,7-dienes undergo ring-closing metathesis (RCM) to give 4-aminocyclopentenones, valuable intermediates in the asymmetric construction of carbocyclic nucleosides. The key amino ketodienes were prepared using δ -amino β -ketophophonates, a new sulfinimine-derived chiral building block, and HWE chemistry.

(*R*)-(+)-4-Aminocyclopentenone **1** is a valuable chiral building block for the asymmetric synthesis of structurally diverse antiviral and anticancer carbocyclic nucleosides such as aristeromycin and noraristeromycin (Scheme 1).¹ For example, stereoselective reduction of **1** would provide the (1S,4R)-(+)-4-aminocyclopent-2-enol derivative **2**.² Palladium(0)-catalyzed coupling reactions, via the π -allylpalladium complex, are available for stereoselective introduction of a variety of substituents at either the hydroxy or amino positions in **2**.^{1a} For instance, Trost et al. devised methodology for conversion of the benzoate of **2** to a carbomethoxy group using phenylsulfonyl nitro-methane and an oxidative Nef reaction.³ Miller and co-workers demonstrated that nitrogen bases such as adenine could be attached with retention of configuration via the corresponding acetate.⁴ Miller has also developed a procedure for replacing the hydroxy with a carbomethoxy group.⁵ Similarly, the amino group can also be replaced with a suitable nitrogen base.⁶ Asymmetric palladium-catalyzed desymmetrization of *meso*-



⁽¹⁾ For reviews on carbocyclic nucleosides and their syntheses, see: (a) Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229. (b) Mansour, T. S.; Storer, R. *Curr. Pharm. Des.* **1997**, *3*, 227. (c) Marquez, V. E. In *Advances in Antiviral Drug Design*; De Clercq, E., Ed.; JAI Press: Greenwich, CT, 1966; Vol. 2, p 89. (d) Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S. R.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611. (e) Borthwick, A. D.; Boggadike, K. *Tetrahedron* **1992**, *48*, 571.

⁽²⁾ For related methods for the synthesis of **2**, see: (a) Schaudt, M.; Blechert, S. J. *Org. Chem.* **2003**, 68, 2913. (b) O'Brien, P.; Towers, T. D.; Voith, M. *Tetrahedron Lett.* **1998**, *39*, 8175.

⁽³⁾ Trost, B. M.; Stenkamp, D.; Pulley, S. R. Chem. Eur. J. 1995, 1, 568.

3,5-dihydroxy-1-cyclopentene was the key step in Trost's synthesis of **2**,³ while Miller employed a Diels–Alder strategy using a chiral auxiliary^{4,7} or an enzyme kinetic resolution⁸ process to obtain enantiomerically pure **2**. To date, the only asymmetric synthesis of 4-aminocyclopentenone (**1**, NAc) is that described by Zwanenburg et al., which involved the pyrolysis of tricyclic[5.2.1.0^{2,6}]decenyl enaminones.⁹ The tricyclic decadienone system was prepared in a series of steps and employed a dynamic kinetic resolution to give enantiopure material.^{9,10} We describe here a new synthesis of (*R*)-(+)-**1** that is highlighted by a novel olefin-enone ring-closing metathesis reaction and utilizes δ -amino β -ketophosphonates, new sulfinimine-derived chiral building blocks.¹¹

Initially, we envisioned that (+)-1 could be prepared using ring-closing olefin metathesis (RCM) with an appropriate amino ketodiene;¹² however, we found only a single example of RCM leading to a cyclic enone with less than six-carbons.¹³ We were also aware that the RCM reaction is sensitive to the electronic and steric properties of the alkene,^{12–14} as well as the substituent on nitrogen,^{12,15} so we knew our amino ketodiene synthesis had to be flexible enough to allow a variety of substituents to be easily installed in the alkenes and at nitrogen. Sulfinimine-derived δ -amino β -ketophosphonates appeared to meet these synthetic objectives: diversely substituted sulfinimines are readily available¹⁶ and Horner–Wadsworth–Emmons (HWE) chemistry would provide the α,β -unsaturated keto portion (Scheme 2).

Although β -ketophosphonates are well-known, there are few examples of enantiomerically pure δ -amino β -ketophosphonates.¹⁷ Nucleophilic ring opening of β -lactams with methyl phosphonate anions has generally been employed for the synthesis of enantiomerically pure samples;^{18,19} however,

(6) Jung, M. E.; Rhee, H. J. Org. Chem. **1994**, 59, 4719.

(11) For leading references to sulfinimine derived chiral building blocks, see: Davis, F. A.; Rao, A.; Carroll, P. J. *Org. Lett.* **2003**, *5*, 3855.

(12) For reviews and leading references on ring-closing metathesis, see:
(a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Hanessian, S.; Margarita, R.; Hall, A.; Johnstone, S.; Tremblay, M.; Parlanti, L. J. Am. Chem. Soc. **2002**, *124*, 13342. (c) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693. (d) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.;

Grubbs, R. H. J. Am. Chem. Soc. 2003, 125, 11360.

(13) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. J. Am. Chem. Soc. 2000, 122, 3783.

(14) Kirkland, T. A.; Grubbs, R. H. J. Org. Chem. 1997, 62, 7310.

(15) (a) Chippindale, A. M.; Davies, S. G.; Iwamoto, K.; Parkin, R. M.;
Smethurst, C. A. P.; Smith, A. D.; Rodriguez-Solla, H. *Tetrahedron* 2003, 59, 3253 and references therein. (b) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. J. Am. Chem. Soc. 1996, 118, 9606.

(16) For reviews on the chemistry of sulfinimines, see: (a) Zhou, P.; Chen, B.-C.; Davis, F. A. In *Advances in Sulfur Chemistry*; Rayner, C. M., Ed.; JAI Press: Stamford, CT, 2000; Vol. 2, pp 249–282. (b) Davis, F. A.; Zhou, P.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13. (c) Ellman, J. A.; Owens, T. D.; Tang, T. P. Acc. Chem. Res. **2002**, *35*, 984.

(17) For a review, see: McKenna, C. E.; Kashemirov, B. A. Top. Curr. Chem. 2002, 220, 201.

(18) (a) Baldwin, J. E.; Adlington, R. M.; Russell, A. T.; Smith, M. L. *Tetrahedron* **1995**, *51*, 4733. (b) Lee, H. K.; Kim, E.-K.; Pak, C. S. *Tetrahedron Lett.* **2002**, *43*, 9641.



this procedure lacks generality, and β -lactams with diverse functionality are not easily available. We found that the reaction of sulfinimine-derived β -amino esters²⁰ with lithium dimethyl methyl phosphonate produced N-sulfinyl δ -amino β -ketophosphonates in excellent yield. Thus, treatment of N-sulfinyl β -amino esters (S_{S},R) -(+)-4 with 5 equiv of lithium dimethyl methylphosphonate afforded the corresponding N-sulfinyl δ -amino β -ketophosphonates (S_S,R)-(+)-5 in 81–83% isolated yield (Scheme 2). Lesser amounts of lithium phosphonate resulted in incomplete reaction. Workup consisted of flash chromatography followed by Kugelrohr distillation to remove the excess dimethyl methylphosphonate. Next (+)-5 was treated with 10 equiv of acetaldehyde followed by DBU to afford the α,β -unsaturated amino ketone (+)-6 in nearly quantitative yield. The 16.4 Hz coupling constant suggests that (+)-6 has the *E* geometry. The β -amino ester (+)-4 was prepared by reaction of the sulfinimine (S)-(+)- 3^{20} with an excess of the sodium enolate of methyl acetate, as previously described.²¹

Initial studies aimed at ring closure using RCM were performed using amino ketodienes (+)-**6a** (R = H) and **6b** (R = Me) with Grubb's first-generation catalyst **I** (Scheme 3). With 2–30 mol % catalyst, for up to 40 h in refluxing DCM, no reaction was observed and starting material was quantitatively recovered (Table 1, entries 1 and 3). With the second-generation catalyst **II**, **6a** and **6b** gave (+)-**9** in 85 and 25% yields, respectively (Table 1, entries 2 and 4). Because we believed that the *N*-sulfinyl group may be poisoning the catalyst, **6a** and **6b** were transformed into *N*-Ts derivatives (-)-**7a** and **7b** in 83 and 85% yields, respectively, by *m*-CPBA oxidation. The *N*-Boc derivatives (-)-**8** were also prepared in 85–89% yield by reaction of (+)-**6** with

(20) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Reddy, G. V.; Portonovo, P. S.; Zhang, H.; Fanelli, D.; Reddy, T.; Zhou, P.; Carroll, P. J. J. Org. Chem. **1997**, 62, 2555.

⁽⁴⁾ Ghosh, A.; Ritter, A. R.; Miller, M. J. J. Org. Chem. 1995, 60, 5808.
(5) Mineno, T.; Miller, M. J. J. Org. Chem. 2003, 68, 6591.

⁽⁷⁾ Vogt, P. F.; Hansel, J.-G.; Miller, M. J. Tetrahedron Lett. 1997, 38, 2803.

⁽⁸⁾ Mulvihill, M. J.; Gage, J. L.; Miller, M. J. J. Org. Chem. 1998, 63, 3357.

⁽⁹⁾ Ramesh, N. G.; Klunder, A. J. H.; Zwanenburg, B. J. Org. Chem. 1999, 64, 3635.

⁽¹⁰⁾ Bakkeren, F. J. A. D.; Ramesh, N. G.; de Goot, D.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron Lett.* **1996**, *37*, 8003.

⁽¹⁹⁾ Rudisill, E. E.; Whitten, J. P. Synthesis 1994, 85.

⁽²¹⁾ Davis, F. A.; Reddy, R. E.; Szewczyk, J. M. J. Org. Chem. 1995, 60, 7037.



TFA/MeOH followed by treatment with Boc₂O/Et₃N and the catalyst DMAP. Results of RCM cyclization of these amino ketodienes derivatives with catalysts **I** and **II** are summarized in Table 1. Inspection of Table 1 reveals that in all cases, with one exception, both catalysts gave good to excellent yields of the amino cyclopentenones, **1**, **9**, and **10**, when R = H in amino ketodienes **6a**, **7a**, and **8a** (Table 1, entries 2, 5, 6, 9, and 10). The exception was *N*-sulfinylamino ketodiene (+)-**6a** where there was no reaction with catalysts **I** (Table 1, entry 1). When R = Me in **6b**, **7b**, and **8b**, no

 Table 1. Ring-Closing Metathesis of Amino Ketodienes with

 Grubb's Catalysts in DCM at Reflux

			products
	amino		(% isolated
entry	ketodiene	catalyst/conditions	yields)
1	(+)-6a (R = H)	I (2–30 mol %) 40 h	NR
2		II (5 mol %) 16 h	(R)-(+)- 9 (85)
3	(+)- 6b (R = Me)	I (2-30 mol %) 40 h	NR
4		II (5 mol %) 16 h	(R)-(+)- 9 (25)
5	(-)-7a (R = H)	I (2 mol %) 18 h	(R)-(+)- 10 (94)
6		II (5 mol %) 18 h	(R)-(+)- 10 (95)
7	(−)- 7b (R = Me)	I (2-30 mol %) 40 h	NR
8		II (5 mol %) 18 h	(R)-(+)- 10 (8)
9	(-)- 8a (R = H)	I (2 mol %) 18 h	(R)-(+)-1 (97)
10		II (2 mol %) 16 h	(R)-(+)-1 (97)
11	(–)- 8b (R = Me)	I (2 mol %) 16 h	NR
12		II (2 mol %) 16 h	(R)-(+)- 1 (21)
13	(+)-13a (R = H)	I (20 mol %) 18 h	(+)-14 (58)
14		II (5 mol %) 18 h	(+)-14 (93)
15	(+)- 13b (R = Me)	I (10 mol %) 16 h	NR
16		II (5 mol %) 16 h	(+)- 14 (84)

reaction was observed with catalyst **I** (Table 1, entries 3, 7, and 11), and poor yields of 8-25% were noted for catalyst **II** (Table 1, entries 4, 8, and 12). These results suggest a steric effect in which the methyl group R may hinder formation of the initial "ruthenacycle" necessary for meta-thesis. While the poor results with (+)-6 and catalyst **I**, which is less reactive than **II**, suggest mild poisoning of the catalyst by the *N*-sulfinyl moiety, additional studies will be necessary to confirm this.

The *N*-Boc group in (R)-(+)-1 was removed by treatment with 1.5 N HCl to give the hydrochloride (R)-(+)-11 in quantitative yield (Scheme 4). Luche reduction (NaBH₄/



CeCl₃) afforded a separable 8:1 mixture of diastereomeric 1,4-amino alcohols and a 76% yield of the major diastereoisomer (1*S*,4*R*)-(+)-**2**. These materials had properties consistent with literature values, which further establishes their structures.^{8,10} With 2.3 equiv of MeLi at -40 °C, (*R*)-(+)-**1** gave a 10:1 mixture of isomeric alcohol (Scheme 4). The major isomer (1*S*,4*R*)-(+)-**12** was isolated in 75% yield, and NOE studies were used to determine its structure. Methylmagnesium bromide resulted in lower ratios (2:3) and incomplete reaction. The stereochemistry of the methyllithium reaction is consistent with attack of this reagent from the sterically least hindered direction. Roy and Schneller reported related results.²²

Amino ketodiene (S_S,R) -(+)-**6a** was stereoselectively reduced with LiHBEt₃ (Super-Hydride) at -78 °C to give exclusively (+)-**13** in 76% isolated yield (Scheme 5). The anti stereochemistry was assigned to (+)-**14** on the basis of similar reductions of *N*-sulfinyl β -amino ketones²³ and its conversion to a product of known absolute configuration (see below). With catalysts **I** and **II**, (+)-**13a** (R = H) gave 58 and 93% isolated yields, respectively, of the amino cyclopentenone (+)-**14** (Table 1, entries 13 and 14). With (+)-**13b** (R = Me), there was no reaction with catalyst **I**, but **II** afforded (+)-**14** in 84% yield (Table 1, entries 15 and 16). These results may suggest that the metathesis process is

⁽²²⁾ Roy, A.; Schneller, S. W. J. Org. Chem. 2003, 68, 9269.

⁽²³⁾ Davis, F. A.; Prasad, K. R.; Nolt, B. M.; Wu, Y. Org. Lett. 2003, 5, 925.



inhibited to some extent by the electron-deficient nature of the α , β -unsaturated carbonyl unit (Table 1, compare entries 1 and 2 with entries 13 and 14), but additional studies are necessary to validate this hypothesis.²⁴

Treatment of the *N*-Boc 1,4-amino alcohol (-)-15, prepared as before from (+)-13a, with 5 mol % catalyst I resulted in the 1,4-amino alcohol carbocycle (+)-16 in 91% yield (Scheme 5). This material had properties consistent with literature values²⁵ and confirms the anti stereochemistry for the reduction of the β -amino ketones (+)-6. Furthermore, this result illustrates that it is possible to readily obtain the *trans*-1,4-amino alcohol carbocycle (+)-16 by stereoselective reduction of the amino ketodiene prior to RCM cyclization.

In summary, ring-closing metathesis has been employed in the asymmetric synthesis of (*R*)-(+)-aminocyclopentenone **1**, a valuable chiral building block for the synthesis of antiviral and anticancer carbocyclic nucleosides. δ -Amino β -ketophosphonates, a new sulfinimine-derived chiral building block, and HWE chemistry were employed in the synthesis of the key amino ketodienes units.

Acknowledgment. We thank Seung H. Lee for preliminary studies. This work was supported by a grant from the National Institute of General Medical Sciences 57870.

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.

OL049795V

^{(24) (}a) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. J. Am. Chem. Soc. **1993**, 115, 9856. (b) Rutjes, F. P. J. T.; Schoemaker, H. E. Tetrahedron Lett. **1997**, 38, 677. (c) Krikstolaityte, S.; Hammer, K.; Undheim, K. Tetrahedron Lett. **1998**, 39, 7595. (d) Paquette, L. A.; Efremov, I. J. Am. Chem. Soc. **2001**, 123, 4492.

⁽²⁵⁾ Wu, Y.; Woster, P. M. J. Med. Chem. 1992, 35, 3196.