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

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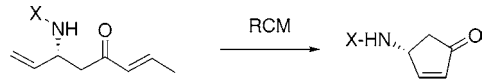
ABSTRACT

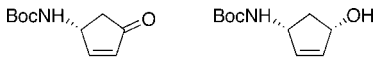


X = *p*-TolylS(O)-, Ts, Boc

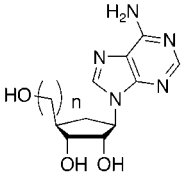
Amino keto-2,7-dienes undergo ring-closing metathesis (RCM) to give 4-aminocyclopentenones, valuable intermediates in the asymmetric construction of carbocyclic nucleosides. The key amino ketodienes were prepared using *δ*-amino *β*-ketophophonates, a new sulfinimine-derived chiral building block, and 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 (1*S*,4*R*)-(+)-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*-

Scheme 1



(*R*)-(+)-**1** (1*S*,4*R*)-(+)-**2**



Aristeromycin (n = 1)
Noraristeromycin (n = 0)

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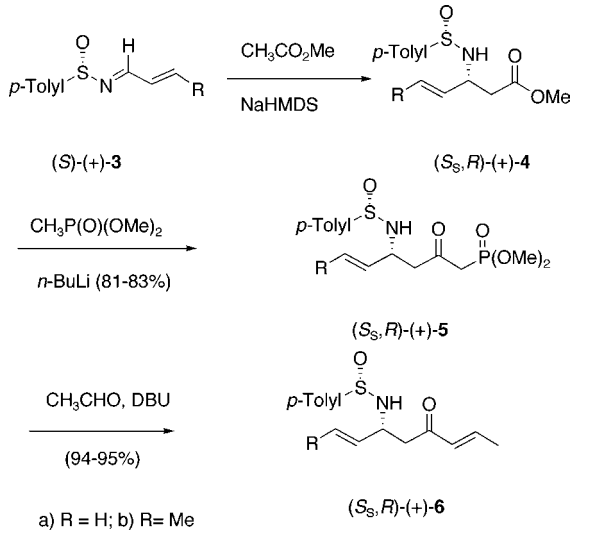
3,5-dihydroxy-1-cyclopentene was the key step in Trost's synthesis of **2**,[3] while Miller employed a Diels−Alder strategy using a chiral auxiliary[4,7] or an enzyme kinetic resolution[8] process to obtain enantiomerically pure **2**. To date, the only asymmetric synthesis of 4-aminocyclopentenone (**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 available[16] 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, this procedure lacks generality, and β-lactams with diverse functionality are not easily available. We found that the reaction of sulfinimine-derived β-amino esters[20] 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]

Scheme 2



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

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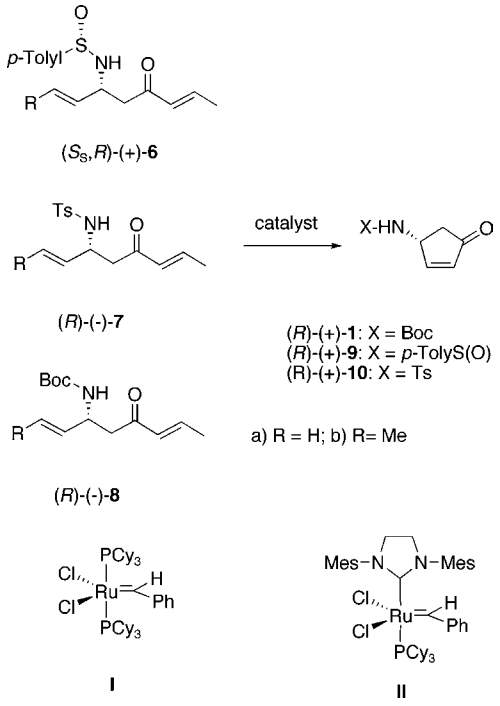
Scheme 3



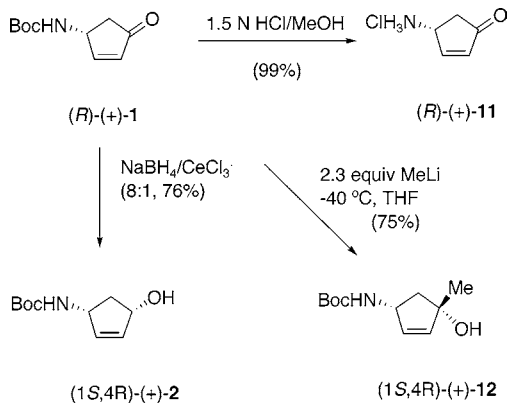
TFA/MeOH followed by treatment with Boc_2O/Et_3N and the catalyst DMAP. Results of RCM cyclization of these amino ketodienes derivatives with catalysts **I** and **II** are summarized in Table 1. Inspection of Table 1 reveals that in all cases, with one exception, both catalysts gave good to excellent 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 catalyst **I** (Table 1, entry 1). When R = Me in **6b**, **7b**, and **8b**, no 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 metathesis. 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.

Table 1. Ring-Closing Metathesis of Amino Ketodienes with Grubb's Catalysts in DCM at Reflux

entry	amino ketodiene	catalyst/conditions	products (% isolated 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)

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 ($NaBH_4/CeCl_3$) 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]

Scheme 4



Amino ketodiene (S_S,*R*)-(+)-**6a** was stereoselectively reduced with $LiHBEt_3$ (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 ketones[23] 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

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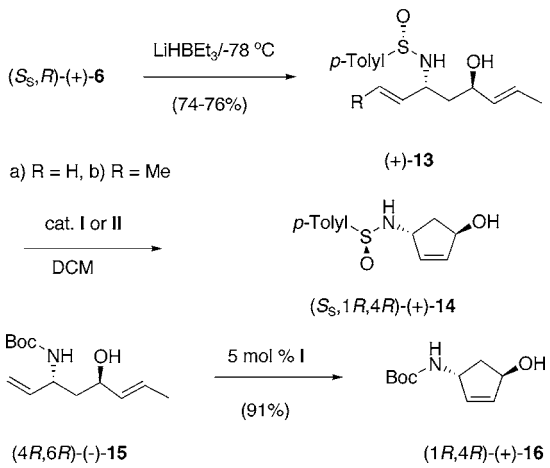
Scheme 5



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 values[25] 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.

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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.

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