Tetrahedron 66 (2010) 4769–4774

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Highly enantioselective formal aza-Diels–Alder reactions with acylhydrazones and Danishefsky's diene promoted by a silicon Lewis acid

Sharon K. Lee, Uttam K. Tambar, Nicholas R. Perl, James L. Leighton *

Department of Chemistry, Columbia University, 3000 Broadway, MC 3117, New York, NY 10027, United States

ARTICLE INFO

Article history:
Received 2 February 2010
Received in revised form 8 March 2010
Accepted 9 March 2010
Available online 15 March 2010

Keywords:
Silicon Lewis Acid
Aza-Diels–Alder
Acylhydrazones
Danishefsky's Diene
Casopitant

ABSTRACT

Silicon Lewis acid **3** is effective for the promotion of highly enantioselective cycloaddition reactions of acylhydrazones with Danishefsky's diene (formal aza-Diels–Alder reactions). The reactions are conducted at ambient temperature for 15 min, and produce the products in good yield and with high levels of enantioselectivity. A remarkable solvent-dependent reversal in the sense of absolute stereochemical induction has been observed. The method has been applied to an efficient and stereoselective synthesis of the neurokinin 1 receptor antagonist casopitant.

1. Introduction

Piperidines (and derivatives thereof) represent one of the more important heterocyclic motifs in all of medicinal chemistry and they appear with some frequency in both approved drugs and in ongoing drug development programs (Fig. 1). Although it is difficult to quantify, it seems likely that synthetic accessibility and inaccessibility play at least some role in influencing the direction that such programs take with respect to the piperidine substructures. Ideally, the synthetic chemistry should reach a point where any desired piperidine structure with any substitution pattern could be accessed rapidly and efficiently. While this is certainly a lofty goal, it is also a worthwhile one, as the drug discovery process might be made more efficient if questions of ready synthetic accessibility were removed from the equation.

The diene–imine [4+2] cycloaddition (aza-Diels–Alder) reaction provides a direct and potentially powerful entry into substituted piperidine derivatives, and its full development as a practical synthetic method with wide scope is a highly desirable goal. Many research groups have recognized this need, and there have as a result been several reports of effective enantioselective variants involving the use of Danishefsky's diene and various aldimine derivatives.[1] Given the effectiveness of our family of chiral silicon Lewis acids in the promotion of a variety of transformations of acylhydrazones,[2] we decided to investigate what would be a formal aza-Diels–Alder reaction in this context with Danishefsky's diene.[3]

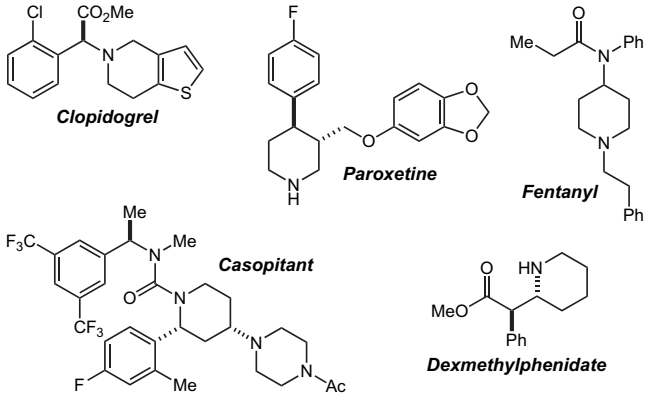


Figure 1. Piperidine containing bioactive compounds.

We did so both to add to the list of reactions that are effectively promoted by these extraordinarily simple and practical Lewis acids toward the goal of a 'universal' Lewis acid, and as the first step in a program devoted to the development of a more general solution to the asymmetric aza-Diels–Alder reaction.

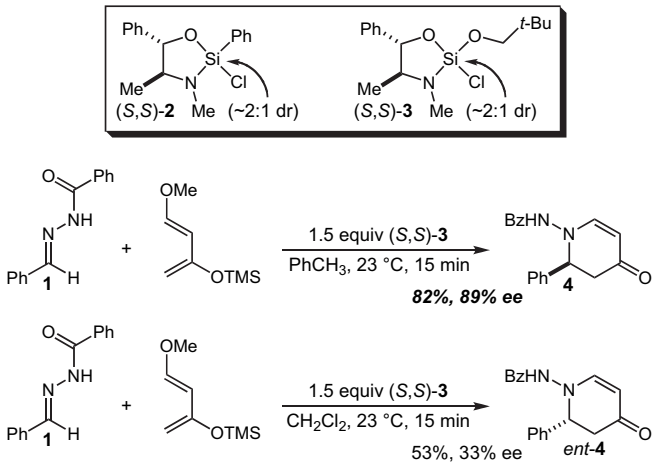
2. Results and discussion

The investigation began with the reaction of benzaldehyde-derived benzoylhydrazone **1** and Danishefsky's diene in the

* Corresponding author.

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.03.036

presence of silicon Lewis acids (Scheme 1). We had at our disposal phenylsilane **2** and neo-pentoxysilane **3**. While **2** has proven effective for a variety of transformations of acylhydrazones, it proved ineffective for the addition of silyl ketene acetals in Mannich reactions.[2e] Indeed this ineffectiveness was the necessity that mothered the invention of silane **3**, which performed very well in the enantioselective Mannich reactions.[2e] Because of the fact that the formal aza-Diels–Alder reactions that are the subject of this investigation are, mechanistically, Mannich reactions followed by cyclization, it was therefore not entirely surprising when initial experiments revealed that **2** was ineffective for the reaction of hydrazone **1** with Danishefsky's diene. The product dihydropyridinone derivative **4** was formed, but in low yields and with poor (<40% ee) enantioselectivity. Happily, the Mannich analogy held as silane **3** proved very much more effective, and when the reaction was conducted in toluene at ambient temperature for 15 min, **4** was isolated in 82% yield and 89% ee.

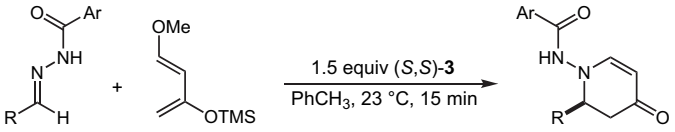


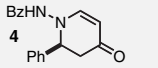
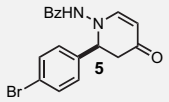
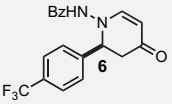
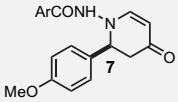
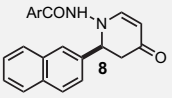
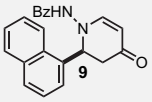
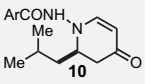
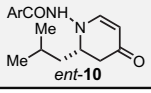
Scheme 1. Initial discovery of competent silane Lewis acid catalysts.

Along the way, a curious solvent effect was observed: when the same reaction (with (*S*,*S*)-**3**) was conducted in CH_2Cl_2, *ent*-**4** was obtained in 53% yield and 33% ee (Scheme 1). While we have previously observed significant differences in the magnitude of the enantioselectivity in various reactions based only on a solvent switch, this is the first time we have observed a turnover in the sense of absolute stereochemical induction. The mechanistic origin of this effect is not at all clear as it appears to be nucleophile-dependent, and we note that the phenomenon did not occur in the aforementioned Mannich reactions with silyl ketene acetals, rendering the effect even more mysterious.

A brief survey of the reaction scope was carried out with respect to the hydrazone structure (Table 1). As shown, the reaction is generally successful with a range of aromatic R groups (products **4**–**9**, entries 1–6) providing good yields and enantioselectivities. Occasionally the parent benzoylhydrazone required electronic tuning for optimal results as in entries 4 and 5. In order to establish the scope with respect to aliphatic R groups, isovaleraldehyde-derived hydrazones were investigated as well, and initial results were discouraging as the reactions produced **10** with poor efficiency and enantioselectivity (e.g., entry 7). In the course of our attempts to optimize this transformation CH_2Cl_2 was evaluated as solvent, and this consistently led to the production of *ent*-**10** as the major product establishing that the solvent-dependent reversal in absolute stereochemical induction described in Scheme 1 is not an anomalous result limited to hydrazone **1**. Additionally, the levels of enantioselectivity obtained in reactions run in CH_2Cl_2 were promising, and upon optimization *ent*-**10** was obtained in 81% yield and 92% ee (entry 8), albeit using 2.0 equiv of the silane (*S*,*S*)-**3**.

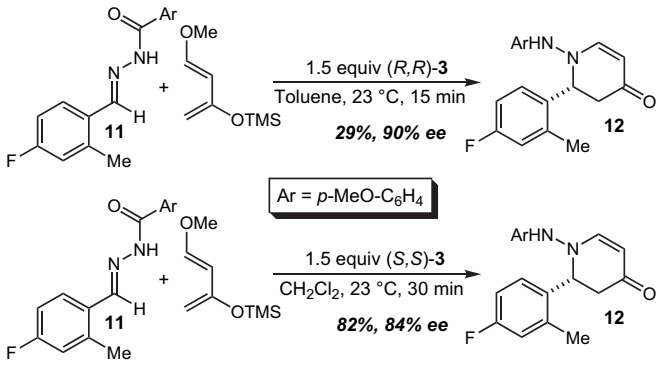
Table 1
Enantioselective aza-Diels–Alder reactions with acylhydrazones and Danishefsky's diene



Entry	R	Ar	Product	Yield (%)	ee (%)
1	Ph	Ph		82	89
2	*p*-Br–C_6H_4	Ph		72	89
3	*p*-CF_3–C_6H_4	Ph		77	90
4	*p*-MeO–C_6H_4	*p*-CF_3–C_6H_4		73	90
5	2-Naphthyl	*p*-CF_3–C_6H_4		85	90
6	1-Naphthyl	Ph		58	87
7	*i*-$PrCH_2$	*p*-MeO–C_6H_4		33	45
8[a]	*i*-$PrCH_2$	*p*-MeO–C_6H_4		81	92

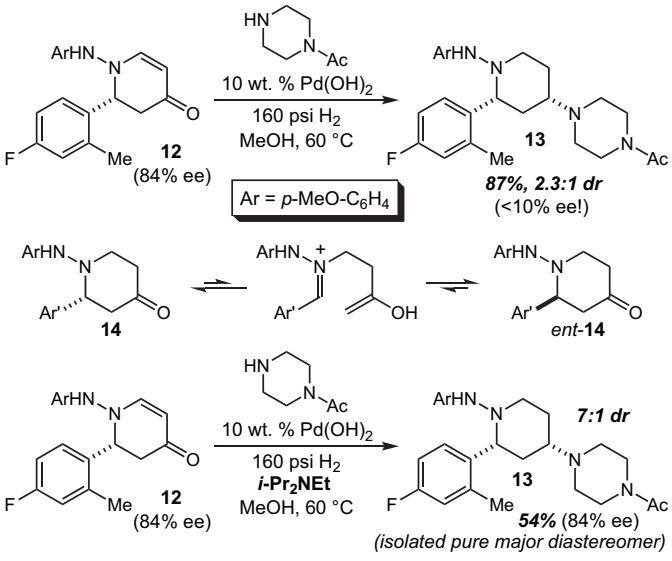
[a] This reaction was performed in CH_2Cl_2 with 2.0 equiv of (*S*,*S*)-**3** and 3.0 equiv of Danishefsky's diene.

As a demonstration of the power of this method rapidly to deliver complex piperidine structures, we undertook the development of a brief and efficient synthesis of casopitant, a neurokinin 1 receptor antagonist (Fig. 1).[4] Hydrazone **11** was prepared and because the synthesis required the opposite sense of absolute stereochemical induction from that seen in Table 1, it was treated with the enantiomeric silane (*R*,*R*)-**3** and Danishefsky's diene under the standard conditions (Scheme 2). While we were delighted to find that the desired product **12** was produced in 90% ee, the efficiency of the reaction was poor as **12** was isolated in only 29% yield. During the course of our attempts to optimize the efficiency of this transformation, the reaction was conducted in CH_2Cl_2. As described above, we expected a solvent-dependent reversal in the absolute sense of stereochemical induction, and thus (*S*,*S*)-**3** was employed in this experiment. Gratifyingly, the steric hinderance of the *ortho* methyl group (which is presumably responsible for the poor efficiency of the reaction in toluene (cf. Table 1, entry 6)) seems to have a beneficial effect in this case, as **12** was obtained in 82% yield and 84% ee, a dramatic improvement over the enantioselectivity observed in the reaction of hydrazone **1** in CH_2Cl_2 (see Scheme 1, above).



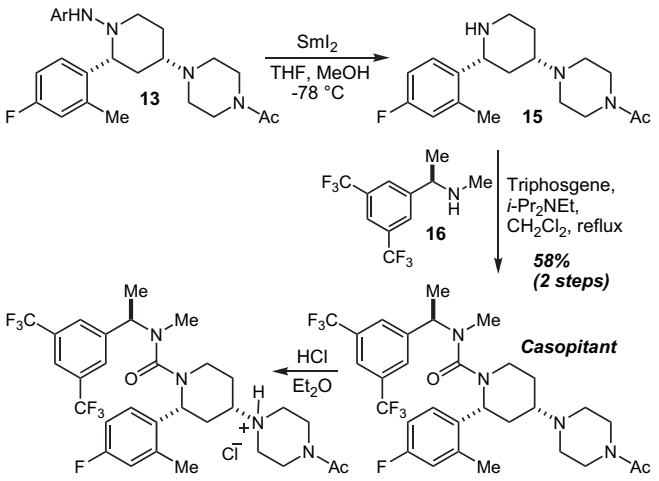
Scheme 2. Optimization of the aza-Diels–Alder reaction with hydrazone **11**.

With efficient access to **12** in enantiomerically enriched form secured, we turned to the next stereochemical challenge, a diastereoselective reductive amination to install the piperazine ring. Reduction of the alkene was also required and a tandem reduction/reductive amination employing metal-catalyzed hydrogenation seemed an attractive possibility. Subjection of **12** to $Pd(OH)_2$-catalyzed hydrogenation in the presence of 1-acetylpiperazine did indeed lead to the production of the desired product **13** as the major product of a 2.3:1 mixture of diastereomers isolated in 87% yield (Scheme 3). Hopeful that we might optimize this reaction for improved diastereoselectivity, we viewed this as a positive result until we discovered that **13** had been produced in nearly racemic form (<10% ee).[5] In considering the mechanism of this racemization, ketone **14**, the product of the initial alkene reduction, seemed the likely culprit, and we hypothesized that a retro-Mannich/Mannich reaction sequence was responsible for the racemization, presumably catalyzed by traces of acid. If this was correct, it seemed that a simple solution might be to simply add base to the reaction. Indeed, when the tandem reduction/reductive amination reaction was repeated in the presence of Hunig's base under otherwise identical conditions, **13** was isolated in 54% yield with complete retention of optical activity.[6] Surprisingly, we also observed a significant boost in the diastereoselectivity of the reductive amination to 7:1. While one explanation for this is that the Hunig's base is somehow directly impacting the kinetic selectivity, the significantly reduced overall yield of this reaction raises the possibility that the minor (trans) diastereomer is selectively destroyed under these conditions. Either way, we had in hand a synthetically viable one-pot tandem reduction/reductive amination that produced **13** in 54% isolated yield.



Scheme 3. Development of a tandem reduction/diastereoselective reductive amination reaction.

Completion of the synthesis was straightforward (Scheme 4): reductive cleavage of the hydrazide N–N bond with SmI_2[7] proceeded smoothly and the unpurified product **15** was subjected to urea formation with known amine **16**[8] and triphosgene to give casopitant in 58% overall yield (consistent with the fact that **15** went into the urea formation with 84% ee, a minor amount (~11.5:1) of a diastereomer was formed in this reaction as well). Formation of the HCl salt was carried out for the purposes of identification, and the ^1H NMR spectrum of the HCl salt in DMSO-d_6 matched the reported signals.[4] Overall, the synthesis proceeds in four steps from hydrazone **11** in 26% overall yield.



Scheme 4. Completion of the synthesis of casopitant.

3. Conclusion

Silane Lewis acid **3** is effective for the enantioselective promotion of (formal) aza-Diels–Alder (ADA) reactions of acylhydrazones with Danishefsky's diene, adding to the versatility of this practical family of silicon Lewis acids. The reactions are extraordinarily simple to perform, and generally provide for good yields and enantioselectivities. An unusual solvent-dependent reversal in the sense of absolute stereochemical induction was observed, but the mechanistic basis for this effect remains mysterious as the phenomenon seems to be limited to this particular reaction. A brief and stereoselective synthesis of the neurokinin 1 receptor antagonist casopitant has been developed based on the use of the ADA reaction reported herein. The synthesis establishes the utility of the method in allowing rapid access to stereochemically and functionally complex bioactive piperidine derivatives.

4. Experimental

4.1. General

All reactions were carried out under an atmosphere of nitrogen in flame- or oven-dried glassware with magnetic stirring unless otherwise indicated. Degassed solvents were purified by passage through an activated alumina column. Silane Lewis acids (*S*,*S*)-**3** and (*R*,*R*)-**3** were prepared from (*S*,*S*)- and (*R*,*R*)-pseudoephedrine,

respectively, using the previously reported procedure.[2e] 4-Fluoro-2-methylbenzaldehyde, 1-acetylpiperazine, *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene), benzhydrazide, 4-methoxybenzhydrazide, and 4-trifluoromethylbenzhydrazide were purchased from Aldrich. Amine **16** was prepared according to a literature procedure.[9] ^{1}H NMR spectra were recorded on a Bruker DPX-400 (400 MHz) spectrometer and are reported in part per million from $CDCl_3$ internal standard (7.26 ppm), CD_3OD internal standard (4.78 ppm and 3.31 ppm), or $(CD_3)_2SO$ internal standard (2.50 ppm). Data are reported as follows: (s=singlet, br s=broad singlet, br d=broad doublet, br t=broad triplet, d=doublet, t=triplet, q=quartet, quin=quintet, m=multiplet, dd=doublet of doublets, ddd=doublet of doublet of doublets, sept=septet; coupling constant(s) in hertz; integration). Proton decoupled ^{13}C NMR spectra were recorded on a Bruker DPX-300 (75 MHz) spectrometer and are reported in parts per million from $CDCl_3$ internal standard (77.23 ppm), CD_3OD internal standard (49.15 ppm), or $(CD_3)_2SO$ internal standard (39.51 ppm). Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrometer. Optical rotations were recorded on a Jasco DIP-1000 digital polarimeter. Low-resolution mass spectra were obtained on a JEOL HX110 mass spectrometer in the Columbia University Mass Spectrometry Laboratory.

4.2. Representative procedure for the aza-Diels–Alder reaction

*4.2.1. Product **4** (Table 1, entry 1).* To a solution of silane (*S*,*S*)-**3** (151 mg, 0.48 mmol) in toluene (3 mL) was added hydrazone **1** (71 mg, 0.32 mmol). After 3 min Danishefsky's diene (110 mg, 0.64 mmol) was added. After 15 min, the reaction was quenched by the addition of 1 N HCl (5 mL) and the resulting mixture was stirred for 5 min. The mixture was extracted with ethyl acetate (3×5 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by flash chromatography (2:3 hexanes/EtOAc) provided the product (**4**) as a yellow oil (76 mg, 82%). Analysis by chiral HPLC (Daicel Chiralpak AD-H, 80:20 hexane/isopropanol, 1.0 mL/min, 254 nm) gave 89% ee for the product. $[\alpha]_D^{22}$ −151.2 (*c* 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.39–7.35 (m, 1H), 7.27–7.20 (m, 9H), 7.16 (d, *J*=7.6 Hz, 1H), 5.14–5.09 (overlap, 2H), 2.83 (dd, *J*=16.4, 15.1 Hz, 1H), 2.53 (ddd, *J*=16.7, 4.5, 1.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.2, 167.3, 157.1, 137.4, 132.5, 131.4, 129.2, 129.0, 128.7, 127.6, 127.0, 102.2, 65.5, 44.8; IR (thin film) 3240, 3064, 3006, 1663, 1636, 1519 cm^{-1}; LRMS (FAB$^+$) calcd for $C_{18}H_{16}N_2O_2$ ([M+H]$^+$): 293.3, found: 293.3 ([M+H]$^+$).

*4.2.2. Product **5** (Table 1, entry 2).* After reaction and workup as in the representative procedure above, the title compound was isolated as an oil (72% yield). Analysis by chiral HPLC (Daicel Chiralpak OD, 90:10 hexane/isopropanol, 1.0 mL/min, 254 nm) gave 89% ee for the product. $[\alpha]_D^{22}$ −189.62 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.52–7.34 (m, 6H), 7.26–7.24 (overlap, 3H), 5.23–5.18 (overlap, 2H), 2.91–2.81 (m, 1H), 2.65–2.57 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.7, 167.1, 157.0, 136.5, 132.6, 132.4, 131.2, 129.2, 128.8, 127.0, 122.9, 102.7, 64.9, 44.7; IR (thin film) 3240, 3005, 1655, 1584 cm^{-1}; LRMS (FAB$^+$) calcd for $C_{18}H_{15}BrN_2O_2$ ([M+H]$^+$): 371.2, found: 371.2 ([M+H]$^+$).

*4.2.3. Product **6** (Table 1, entry 3).* After reaction and workup as in the representative procedure above, the title compound was isolated as an oil (77% yield). Analysis by chiral HPLC (Daicel Chiralpak AD-H, 90:10 hexane/isopropanol, 0.8 mL/min, 254 nm) gave 90% ee for the product. $[\alpha]_D^{22}$ −205.6 (*c* 1.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.62 (d, *J*=7.8 Hz, 2H), 7.51–7.47 (m, 3H), 7.41–7.39 (m, 2H), 7.35–7.24 (m, 3H), 5.31 (dd, *J*=15.2, 5.1 Hz, 1H), 5.22 (dd, *J*=8.5, 1.1 Hz, 1H), 2.85 (dd, *J*=16.9, 14.5 Hz, 1H), 2.62 (dd, *J*=16.6, 4.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.4, 167.1, 157.2, 141.6, 131.1 (q, *J*=17.7 Hz), 131.1, 128.8, 128.0, 127.0, 126.2 (q, *J*=4.3 Hz), 123.7 (q, *J*=270.6 Hz), 65.1, 44.7; IR (thin film) 3244, 3041, 3007, 1662, 1582 cm^{-1}; LRMS (FAB$^+$) calcd for $C_{19}H_{15}F_3N_2O_2$ ([M+H]$^+$): 361.3, found: 361.2 ([M+H]$^+$).

*4.2.4. Product **7** (Table 1, entry 4).* After reaction and workup as in the representative procedure above, the title compound was isolated as an oil (73% yield). Analysis by chiral HPLC (Daicel Chiralpak AD-H, 80:20 hexane/ethanol, 1.0 mL/min, 254 nm) gave 90% ee for the product. $[\alpha]_D^{22}$=−150.6 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (br s, 1H), 7.58 (d, *J*=8.5 Hz, 2H), 7.44 (d, *J*=7.5 Hz, 2H), 7.28–7.20 (overlap, 2H), 6.88–6.83 (m, 2H), 5.20 (d, *J*=8.1 Hz, 1H), 5.15 (dd, *J*=15.2, 4.7 Hz, 1H), 2.92 (dd, *J*=17.1, 15.0 Hz, 1H), 2.61 (ddd, *J*=16.6, 4.6, 1.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.4, 166.0, 160.0, 156.5, 134.8, 134.1 (q, *J*=34.6 Hz), 129.0, 128.8, 127.5, 125.8 (q, *J*=3.7 Hz), 123.3 (q, *J*=272.9 Hz), 64.9, 55.3, 44.9; IR (thin film) 3227, 2992, 1646, 1579 cm^{-1}; LRMS (FAB$^+$) calcd for $C_{20}H_{17}F_3N_2O_3$ ([M+H]$^+$): 391.4, found 391.2 ([M+H]$^+$).

*4.2.5. Product **8** (Table 1, entry 5).* After reaction and workup as in the representative procedure above, the title compound was isolated as an oil (85% yield). Analysis by chiral HPLC (Daicel Chiralpak OD, 80:20 hexane/isopropanol, 1.0 mL/min, 254 nm) gave 90% ee for the product. $[\alpha]_D^{22}$ −151.2 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (br d, *J*=8.9 Hz, 1H), 7.87–7.78 (m, 4H), 7.55–7.50 (m, 5H), 7.39 (br d, *J*=8.3 Hz, 2H), 7.31 (d, *J*=8.0 Hz, 1H), 5.44 (dd, *J*=16.8, 3.8 Hz, 1H), 5.31 (d, *J*=8.4 Hz, 1H), 3.08 (dd, *J*=17.8, 15.9 Hz, 1H), 2.75 (dd, *J*=16.8, 3.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.0, 166.1, 156.6, 134.6, 134.5, 134.1 (q, *J*=33.3 Hz), 133.4, 133.2, 129.4, 127.9, 127.8, 127.5, 127.4, 126.9, 126.8, 125.8 (q, *J*=3.3 Hz), 124.1, 123.2 (q, *J*=273.1 Hz), 102.9, 65.7, 44.9; IR (thin film) 3233, 3057, 3010, 1660, 1657, 1586 cm^{-1}; LRMS (FAB$^+$) calcd for $C_{23}H_{17}F_3N_2O_2$ ([M+H]$^+$): 411.4, found 411.3 ([M+H]$^+$).

*4.2.6. Product **9** (Table 1, entry 6).* After reaction and workup as in the representative procedure above, the title compound was isolated as an oil (58% yield). Analysis by chiral HPLC (Daicel Chiralpak OD, 80:20 hexane/isopropanol, 1.0 mL/min, 254 nm) gave 87% ee for the product. $[\alpha]_D^{22}$ −132.0 (*c* 2.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.91 (d, *J*=7.6 Hz, 1H), 7.86 (d, *J*=8.6 Hz, 1H), 7.73–7.37 (m, 7H), 7.24–7.20 (m, 2H), 7.14–7.12 (overlap, 2H), 6.05–5.99 (m, 1H), 5.35 (m, 1H), 3.28 (m, 1H), 2.82 (br d, *J*=17.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.0, 167.5, 157.1, 134.1, 132.8, 132.3, 131.3, 130.7, 129.3, 128.5, 126.9, 126.0, 125.4, 122.6, 102.1, 43.8; IR (thin film) 3236, 3067, 3007, 1641, 1575 cm^{-1}; LRMS (FAB$^+$) calcd for $C_{22}H_{18}N_2O_2$ ([M+H]$^+$): 343.4, found 343.9 ([M+H]$^+$).

*4.2.7. Product ent-**10** (Table 1, entry 8).* To a solution of silane (*S*,*S*)-**3** (1.34 g, 4.26 mmol) in dichloromethane (28 mL) was added the hydrazone (R=*i*-PrCH_2, Ar=*p*-MeO–C_6H_4) (500 mg, 2.13 mmol). After 3 min Danishefsky's diene (1.10 g, 6.39 mmol) was added. After 15 min, the reaction was quenched by the addition of 1 N HCl (10 mL) and the resulting mixture was stirred for 5 min. The mixture was extracted with dichloromethane (3×20 mL) and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by flash chromatography (2:3 hexanes/EtOAc) provided the product as a yellow oil (522 mg, 81% yield). Analysis by chiral HPLC (Daicel Chiralpak AD-H, 90:10 hexane/isopropanol, 1.0 mL/min, 254 nm) gave 92% ee for the product. $[\alpha]_D^{22}$ +52.4 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 7.82 (d, *J*=9.1 Hz, 2H), 7.12 (d, *J*=8.6 Hz, 2H), 6.96 (d, *J*=8.6 Hz, 2H), 5.07 (d, *J*=7.6 Hz, 1H), 4.10–4.06 (m, 1H), 3.87 (s, 3H), 2.75 (dd, *J*=16.9, 5.0 Hz, 1H), 2.41 (dd, *J*=15.8, 11.5 Hz, 1H), 1.65–1.50 (overlap, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.7, 166.2, 163.2, 156.6, 129.3, 123.5, 114.2, 100.7, 59.2, 55.5, 41.9, 39.5, 24.3, 23.7, 21.4; IR

(thin film) 3234, 1657, 1606, 1579 cm^{-1}; LRMS (FAB^+) calcd for $C_{17}H_{22}N_2O_3$ ($[M+H]^+$): 303.4, found: 303.3 ($[M+H]^+$).

4.3. Synthesis of hydrazone 11

To a solution of 4-fluoro-2-methylbenzaldehyde (5.0 g, 36 mmol) in ethanol (160 mL) was added 4-methoxybenzhydrazide (5.5 g, 33 mmol). The reaction mixture was stirred for 5 h and filtered. The collected solids were washed with hexanes and dried to provide a white solid (8.3 g, 82% yield). ^1H NMR (400 MHz, CD_3OD) δ 8.54 (s, 1H, C*H*═N), 8.01 (dd, *J*=10.9, 5.7 Hz, 1H, Ar–*H*), 7.85–7.81 (m, 2H, Ar–*H*), 6.96–6.94 (m, 2H, Ar–*H*), 6.91–6.87 (overlap, 2H, Ar–*H*), 3.78 (s, 3H, Ar–OC*H*$_3$), 2.40 (s, 3H, Ar–C*H*$_3$); ^{13}C NMR (75 MHz, CD_3OD) δ 166.8, 165.0 (d, *J*=226.1 Hz), 164.5, 147.4, 141.7, 130.7, 130.0, 129.9, 126.0, 118.1 (d, *J*=21.7 Hz), 115.0, 114.7 (d, *J*=22.3 Hz), 56.0, 19.3; IR (thin film) 3221, 3042, 1643, 1606, 1257 cm^{-1}; LRMS (FAB^+) calcd for $C_{16}H_{15}FN_2O_2$ ($[M+H]^+$): 287.3, found: 287.2 ($[M+H]^+$).

4.4. Synthesis of dihydropyridinone 12

To a solution of silane (*S*,*S*)-**3** (141 mg, 0.449 mmol) in dichloromethane (2.5 mL) was added hydrazone **11** (86 mg, 0.30 mmol). After 3 min, Danishefsky's diene (155 mg, 0.900 mmol) was added. After 30 min, the reaction mixture was quenched by the addition of 1 N HCl (2 mL) and the resulting mixture was stirred for 5 min. The mixture was extracted with dichloromethane (3×10 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by flash chromatography (2:3 hexanes/EtOAc) provided the product as a yellow oil (87 mg, 82% yield). Analysis by chiral HPLC (Daicel Chiralpak OD, 87:13 hexane/ethanol, 1.0 mL/min, 254 nm) gave 84% ee for the product. $[\alpha]_D^{22}$ +184.9 (*c* 1.4, $CHCl_3$); ^1H NMR (400 MHz, CD_3OD) δ 7.55 (br s, 1H, N–*H*), 7.51 (dd, *J*=8.8, 5.7 Hz, 1H, Ar–*H*), 7.36–7.33 (m, 2H, Ar–*H*), 7.31 (d, *J*=8.1 Hz, 1H, OCC═C*H*), 7.00 (dt, *J*=8.0, 2.5 Hz, 1H, Ar–*H*), 6.86–6.82 (overlap, 3H, Ar–*H*), 5.59 (dd, *J*=14.7, 4.7 Hz, 1H, NC*H*–Ar), 5.28 (dd, *J*=8.2, 1.4 Hz, 1H, C═C*H*N). 3.81 (s, 3H), 2.88 (dd, *J*=17.6, 15.2 Hz, 1H, Ar–CC*H*HCO), 2.63 (ddd, *J*=17.2, 4.5, 1.2 Hz, 1H, Ar–CCH*H*CO), 2.26 (s, 3H, Ar–C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.4, 167.2, 163.4, 162.4 (d, *J*=248.0 Hz), 158.4, 139.5 (d, *J*=8.5 Hz), 132.2, 129.4, 128.8 (d, *J*=8.7 Hz), 123.9, 118.2 (d, *J*=22.3 Hz), 114.4, 114.3 (d, *J*=22.3 Hz), 102.5, 61.4, 55.8, 45.0, 19.5; IR (thin film) 3247, 2969, 1652, 1607, 1579, 1500, 1256 cm^{-1}.

4.5. Synthesis of 13

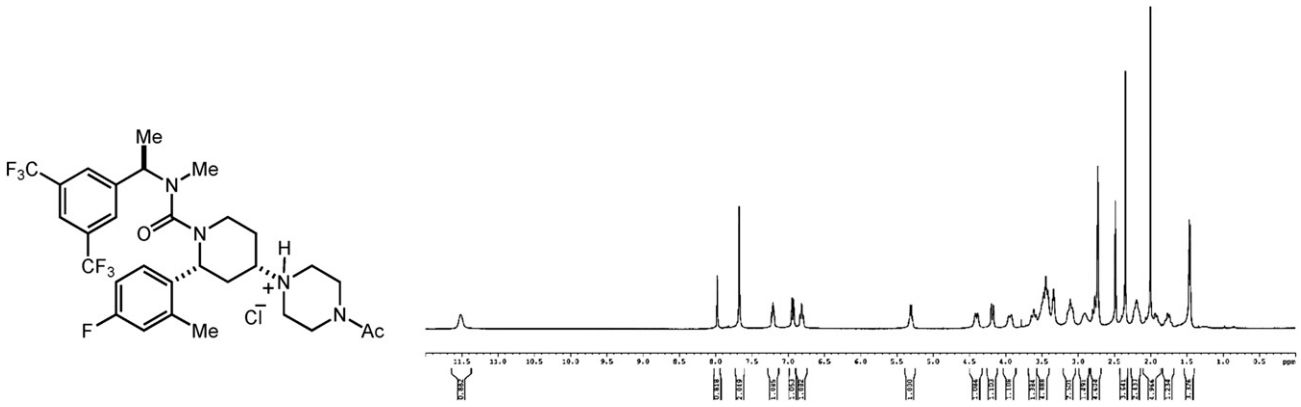
To a glass liner equipped with a stir bar was added a solution of **12** (422 mg, 1.19 mmol) in methanol (12 mL). Diisopropylethylamine (0.4 mL), 1-acetylpiperazine (305 mg, 2.38 mmol), and 20% $Pd(OH)_2/C$ (42 mg) were added. The glass liner was then placed into a Parr bomb, and the gas inlet/pressure gage assembly was screwed onto the bomb apparatus. The bomb was charged to 200 psi with H_2 and slowly vented to 160 psi. The bomb was then immersed in an oil bath heated to 60 °C. After 48 h, the oil bath was removed and after the apparatus had cooled to room temperature it was vented. The residue was diluted with methanol (15 mL) and filtered through a pad of Celite. After concentration, the resulting viscous yellow oil was purified via flash chromatography (1:9 MeOH/EtOAc to 3:7 MeOH/EtOAc) to afford **13** contaminated with silica gel. The mixture was treated with EtOAc, filtered, and concentrated to afford **13** (300 mg, 54% yield) as a yellow oil. (The minor diastereomer was isolated as well in this fashion and that isolation allowed us to determine a dr for the reaction of ~7:1.) The relative stereochemistry of **13** was proven to be cis based on ^1H NMR COSY and NOESY analysis. Data for **13**: $[\alpha]_D^{22}$ −1.88 (*c* 0.4, $CHCl_3$); ^1H NMR (400 MHz, CD_3OD) δ 7.60–7.56 (m, 1H, Ar–*H*), 7.27–7.23 (m, 2H, Ar–*H*), 6.76–6.67 (overlap, 4H, Ar–*H*), 4.45 (br d, *J*=11.7 Hz, 1H, Ar–C*H*N), 3.68 (s, 3H, Ar–OC*H*$_3$), 3.55–3.50 (m, 4H, C*H*$_2$NCOC*H*$_2$), 3.13–3.07 (m, 1H, NNC*H*H), 2.95–2.93 (m, 1H, NNCH*H*), 2.54–2.44 (m, 4H, C*H*$_2$NC*H*$_2$), 2.32 (s, 3H, Ar–C*H*$_3$), 2.25 (m, 1H, NC*H*CH$_2$CH–Ar), 2.03–2.0 (overlap, 6H, NCOC*H*$_3$, NNCH$_2$C*H*H, NNCH$_2$CH*H*, Ar–CHC*H*H), 1.64 (br t, *J*=11.8 Hz, 1H, Ar–CHCH*H*); ^{13}C NMR (75 MHz, CD_3OD) δ 170.5, 167.5, 162.8, 161.7 (d, *J*=245.4 Hz), 137.6, 137.0, 129.0, 126.0, 116.2 (d, *J*=21.5 Hz), 113.6, 112.6 (d, *J*=20.4 Hz), 58.8, 56.6, 54.8, 51.4, 50.5, 50.0, 47.7, 42.0, 37.0, 27.5, 20.1, 18.5; IR (thin film) 3228, 2958, 2923, 2860, 2361, 1629, 1500, 1450, 1248 cm^{-1}; LRMS (FAB^+) calcd for $C_{26}H_{33}FN_4O_3$ ($[M+H]^+$): 469.6, found: 469.3 ($[M+H]^+$).

4.6. Synthesis of casopitant

To a cooled (−78 °C) solution of **13** (30 mg, 0.064 mmol) in degassed methanol (1 mL) was added SmI_2 (3.2 mL of a 0.1 M solution in THF, 0.32 mmol). The cooling bath was removed and the mixture was allowed to warm to room temperature (~20 min) and the reaction was then quenched by exposure to air for ~2 min. The resulting mixture was concentrated and diluted with EtOAc (5 mL) and 1 N NaOH (3 mL). The mixture was extracted with EtOAc (3×10 mL). The combined organic phases were washed with brine (2×2 mL), dried over Na_2SO_4, filtered, and concentrated. The resulting viscous yellow oil was co-evaporated with dichloromethane (2×1 mL). To a solution of the residue in dichloromethane (0.5 mL) was added diisopropylethylamine (0.1 mL) and the resulting mixture was cooled to 0 °C. A solution of triphosgene (39 mg, 0.13 mmol) in dichloromethane (0.5 mL) was then added, and the resulting reaction mixture was allowed to warm to ambient temperature over the course of ~15 min. A solution of amine **16** (54 mg, 0.20 mmol) in dichloromethane (0.5 mL) was then added. The reaction flask was fitted with a reflux condenser and the mixture was heated at reflux for 48 h (oil bath, external temperature 50 °C). After being allowed to cool to room temperature, the reaction was quenched by the addition of aq satd $NaHCO_3$ (2 mL) and the mixture was then extracted with dichloromethane (3×5 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by flash chromatography (1:5:100 NEt_3/EtOH/EtOAc) afforded casopitant as an oil (23 mg, 58%) as well as a small amount of a diasteromer. Data for casopitant: $[\alpha]_D^{22}$ −4.1° (*c* 0.3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H, Ar–*H*), 7.58 (s, 2H, Ar–*H*), 7.15 (dd, *J*=8.7, 6.2 Hz, 1H, Ar–*H*), 6.84 (dd, *J*=10.0, 2.8 Hz, 1H, Ar–*H*), 6.78 (dt, *J*=9.5, 2.8 Hz, 1H, Ar–*H*), 5.56 (q, *J*=7.1 Hz, 1H, NC*H*CH$_3$), 4.29 (dd, *J*=11.8, 2.5 Hz, 1H, Ar–C*H*N), 3.64–3.53 (m, 2H, C*H*$_2$OCNC*H*$_2$), 3.44 (br t, *J*=4.7 Hz, 2H, C*H*HOCNC*H*H), 3.38–3.35 (m, 1H, OCNC*H*HCH$_2$), 2.86 (t, *J*=12.8 Hz, 1H, OCNCH*H*CH$_2$), 2.73 (s, 1H, NC*H*$_3$), 2.58–2.50 (overlap, 5H, C*H*$_2$NC*H*$_2$, *H*CNCH$_2$), 2.44 (s, 3H, NOC*H*$_3$), 2.07 (s, 1H, Ar–C*H*$_3$), 2.00–1.93 (overlap, 2H, C*H*HCH–Ar, OCNCH$_2$C*H*H), 1.69–1.57 (m, 1H, OCNCH$_2$CH*H*), 1.53–1.46 (m, 1H, CH*H*CH–Ar), 1.43 (d, *J*=7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 165.4, 161.1 (d, *J*=243.2 Hz), 143.8, 138.2, 137.0 (d, *J*=7.7 Hz), 131.9 (q, *J*=35.1 Hz), 127.1, 125.9 (d, *J*=7.7 Hz), 123.2 (q, *J*=272.0 Hz), 121.3 (q, *J*=4.1 Hz), 117.1 (d, *J*=22.9 Hz), 112.7 (d, *J*=20.7 Hz), 61.5, 56.4, 52.0, 49.4, 49.0, 48.6, 46.5, 41.6, 36.8, 29.7, 27.7, 21.2, 19.4, 15.5; IR (thin film) 2943, 2829, 2342, 1649, 1434, 1370, 1279, 1169, 1126 cm^{-1}; LRMS (FAB^+) calcd for $C_{30}H_{35}F_7N_4O$ ($[M+H]^+$): 616.6, found: 617.4 ($[M+H]^+$).

4.7. Identity of casopitant

A list of signals in the ^1H NMR spectrum of the HCl salt of casopitant in DMSO-d_6 has been published.[4] In order to confirm our synthesis of casopitant, we prepared the HCl salt of our synthetic material, and took its ^1H NMR spectrum in DMSO-d_6, and found complete agreement with the published data. Our spectrum is reproduced here:



Acknowledgements

This work was supported by a grant from the National Science Foundation (CHE-08-09659). S.K.L. is a National Science Foundation Graduate Research Fellow and U.K.T. is a National Institutes of Health Postdoctoral Fellow (F32 GM077937). We thank Boehringer-Ingelheim for a Graduate Fellowship to N.R.P.

References and notes

1. (a) Hattori, K.; Yamamoto, H. *Tetrahedron* **1993**, *49*, 1749; (b) Bromidge, S.; Wilson, P. C.; Whiting, A. *Tetrahedron Lett.* **1998**, *39*, 8905; (c) Kobayashi, S.; Komiyama, S.; Ishitani, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 979; (d) Kobayashi, S.; Kusakabe, K.; Komiyama, S.; Ishitani, H. *J. Org. Chem.* **1999**, *64*, 4220; (e) Kobayashi, S.; Kusakabe, K.; Ishitani, H. *Org. Lett.* **2000**, *2*, 1225; (f) Yamashita, Y.; Mizuki, Y.; Kobayashi, S. *Tetrahedron Lett.* **2005**, *46*, 1803; (g) Yao, S.; Johannsen, M.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 3121; (h) Yao, S.; Saaby, S.; Hazell, R. G.; Jørgensen, K. A. *Chem.—Eur. J.* **2000**, *6*, 2435; (i) Josephson, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4018; (j) García Mancheño, O.; Gómez Arrayás, R.; Carretero, J. C. *J. Am. Chem. Soc.* **2004**, *126*, 456; (k) Akiyama, T.; Tamura, Y.; Itoh, J.; Morita, H.; Fuchibe, K. *Synlett* **2006**, 141; (l) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4796; (m) Newman, C. A.; Antilla, J. C.; Chen, P.; Predeus, A. V.; Fielding, L.; Wulff, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 7216; (n) Shang, D.; Xin, J.; Liu, Y.; Zhou, X.; Liu, X.; Feng, X. *J. Org. Chem.* **2008**, *73*, 630.
2. (a) Berger, R.; Rabbat, P. M. A.; Leighton, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 9596; (b) Berger, R.; Duff, K.; Leighton, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 5686; (c) Shirakawa, S.; Berger, R.; Leighton, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 2858; (d) Shirakawa, S.; Lombardi, P. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 9974; (e) Notte, G. T.; Leighton, J. L. *J. Am. Chem. Soc.* **2008**, *130*, 6676; (f) Valdez, S. C.; Leighton, J. L. *J. Am. Chem. Soc.* **2009**, *131*, 14638.
3. (a) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400; (b) Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15.
4. Alvaro, G.; Di Fabio, R.; Maragni, P.; Tampieri, M.; Tranquillini, M. E. PCT Int. Appl. WO0232867, 2002.
5. This was revealed by completion of the synthesis as described in Scheme 4, which involves urea formation with enantiomerically pure amine **16**. An approximately 1:1 mixture of diastereomers was obtained from this reaction.
6. This was confirmed by the completion of the synthesis as described in Scheme 4.
7. (a) Burk, M. J.; Martinez, J. P.; Feaster, J. E.; Cosford, N. *Tetrahedron* **1994**, *50*, 4399; (b) Ding, H.; Friestad, G. K. *Org. Lett.* **2004**, *6*, 637.
8. Kanai, M.; Yasumoto, M.; Kuriyama, Y.; Inomiya, K.; Katsuhara, Y.; Higashiyama, K.; Ishii, A. *Org. Lett.* **2003**, *5*, 1007.
9. Hodges, R.; Martin, J.; Hammil, N. A.; Houson, I. N. PCT Int. Appl. WO 2006067395.