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Asymmetric Synthesis of *cis*-2,5-Disubstituted Pyrrolidine, the Core Scaffold of β_3-AR Agonists

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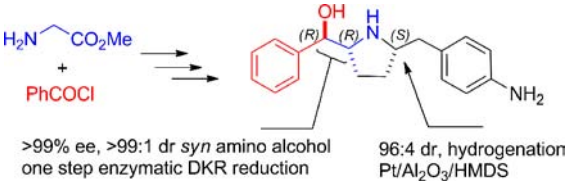
ABSTRACT



A practical, enantioselective synthesis of *cis*-2,5-disubstituted pyrrolidine is described. Application of an enzymatic DKR reduction of a keto ester, which is easily accessed through a novel intramolecular N→C benzoyl migration, yields *syn*-1,2-amino alcohol in >99% ee and >99:1 dr. Subsequent hydrogenation of cyclic imine affords the *cis*-pyrrolidine in high diastereoselectivity. By integrating biotechnology into organic synthesis and isolating only three intermediates over 11 steps, the core scaffold of β_3-AR agonists is synthesized in 38% overall yield.

β_3 adrenergic receptor (β_3-AR) agonists represent a new class of agents that may provide advantages over current therapies for the treatment of overactive bladders. Pyrrolidine **1**, recently reported by Merck laboratories, is the core scaffold of a novel class of potent and selective human β_3-AR agonists.[1] In comparison with these acyclic β-hydroxylamine β_3-AR agonists,[1] a pyrrolidine moiety incorporated to link the C2,C5 substituents significantly improves the selectivity and potentially the metabolic stability of drug candidates but raises the chemical complexity of accessing the evolved generation of β_3-AR agonist drug candidates.

To support the drug development program, an efficient synthesis of **1** suitable for large-scale preparation was required. The key synthetic challenge in preparing pyrrolidine scaffold **1** is the effective and practical establishment of three contiguous stereogenic centers. In particular, the unique structure of **1** possesses an *R*,*R* (C1′, C2) stereochemistry setup,[2] while the (C2, C5) substituted groups in the pyrrolidine ring are in a *cis* relationship. Several

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(1) (a) Morriello, G. J.; Wendt, H. R.; Bansal, A.; Salvo, J. D.; Feighner, S.; He, J.; Hurley, A. L.; Hreniuk, D. L.; Salituro, G. M.; Reddy, M. V.; Galloway, S. M.; McGettigan, K. K.; Laws, G.; McKnight, C.; Doss, G. A.; Tsou, N. N.; Black, R. M.; Morris, J.; Ball, R. G.; Sanfiz, A. T.; Streckfuss, E.; Struthers, M.; Edmondson, S. D. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1865–1870. (b) Edmonson, S. D.; Berger, R.; Chang, L.; Colandrea, V. J.; Hale, J. J.; Harper, B.; Kar, N. F.; Kopka, I. E.; Li, B.; Morriello, G. J.; Moyes, C. R.; Sha, D.; Shen, D.-M.; Wang, L.; Wendt, H.; Zhu, C. PCT Int. Appl. WO025690, 2011. (c) Berger, R.; Chang, L.; Edmonson, S. D.; Goble, S. D.; Harper, B.; Kar, N. F.; Kopka, I. E.; Li, B.; Morriello, G. J.; Moyes, C. R.; Shen, D.-M.; Wang, L.; Wendt, H.; Zhu, C. PCT Int. Appl. WO123870, 2009.

(2) For example, to prepare the less potent C1′(*R*), C2(*S*) epimers through a Pd-catalyzed cycloamination, see: Lemen, G. S.; Wolfe, J. P. *Org. Lett.* **2010**, *12*, 2322–2325. Applying a similar protocol for the preparation of **1** afforded unsatisfactory results.

(3) For recent review, see: (a) Schultz, D. M.; Wolfe, J. P. *Synthesis* **2012**, *44*, 351–361.

(4) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C. *J. Am. Chem. Soc.* **2006**, *128*, 3538–3539.

(5) For recent examples to prepare *cis*-2,5-disubstituted pyrrolidines, see: (a) Babij, N. R.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2012**, *51*, 4128–4130. (b) Hong, Z.; Liu, L.; Sugiyama, M.; Fu, Y.; Wong, C.-H. *J. Am. Chem. Soc.* **2009**, *131*, 8352–8353. (c) Kuwano, R.; Kashiwabara, M.; Ohsumi, M.; Kusano, H. *J. Am. Chem. Soc.* **2008**, *130*, 808–810. (d) Zhang, S.; Xu, L.; Miao, L.; Shu, H.; Trudell, M. L. *J. Org. Chem.* **2007**, *72*, 3133–3136. (e) Weihofen, R.; Dahnz, A.; Tverskoy, O.; Helmchen, G. *Chem. Commun.* **2005**, 3541–3543. (f) Aggarwal, V. K.; Astle, C. J.; Rogers-Evans, M. *Org. Lett.* **2004**, *6*, 1469–1471. (g) Brenneman, J. B.; Martin, S. F. *Org. Lett.* **2004**, *6*, 1329–1331.

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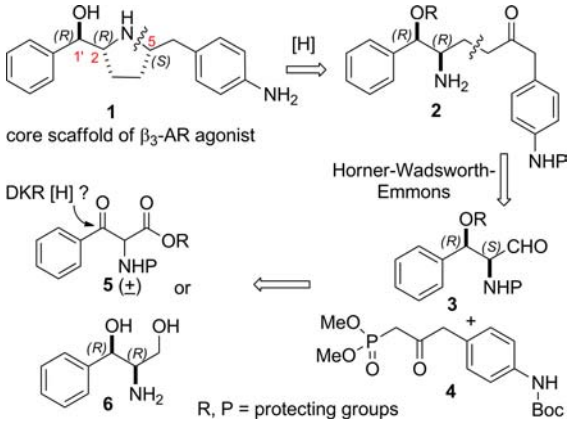
protocols[2−5] for the asymmetric synthesis of 2,5-disubstituted pyrrolidines have been developed recently. However, practical preparation of optically active *cis*-2,5-disubstituted pyrrolidines such as **1** still remains a challenging task to date. In fact, the central problem of the initial syntheses[1] of **1** essentially lies in the tortuous nature of setting the desired stereochemistry via chiral auxiliaries[1a,b] or not readily available chiral starting materials.[1a,b] We envisioned that a straightforward approach to prepare *cis*-pyrrolidine **1** (Scheme 1) could be accomplished through an intramolecularly induced asymmetric reduction of the corresponding pyrrolidine imine intermediate derived from amino ketone precursor **2** with the C1′,C2 stereogenic centers established already. On the basis of stereofacial bias of the pyrrolidine, in principal, high *cis* C2,C5 selectivity should be achievable by optimizing proper reduction conditions and/or by modifying the R group of **2** to amplify the capability of asymmetric induction.

Scheme 1. Retrosynthetic Analysis of Pyrrolidine **1**

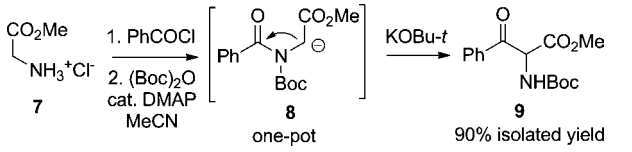


Further, a retro-synthetic disconnection of ketone **2** leads to a *syn* 1,2-amino alcohol aldehyde **3** and phosphonate **4**.[6] In comparison with the previous synthesis,[1] the application of a Horner−Wadsworth−Emmons reaction can offer a significant convergence to access pyrrolidine **1**. However, a literature survey showed that methodologies to establish a *syn* stereochemistry relationship of 1,2-amino alcohols in an open-chain system, such as **2** (R = H), have been lacking, while the corresponding undesired *anti* 1,2-amino alcohols can be easily prepared enantioselectively.[7]

Several approaches to prepare precursor **3** were explored. The use of amino diol **6**, which has the desired C1′ and C2 stereochemistry, is not feasible for large-scale preparation[8,9] because **6** is not commercially readily available in large quantities. Alternatively, we envisioned that an effective preparation of *syn* 1,2-amino alcohol could be possible via an selective asymmetric ketone reduction of the corresponding enantiomer *ent*-(*S*)-**5** as a fast epimerization of **5** can be achieved under dynamic kinetic resolution (DKR) conditions (Scheme 1).

For this synthetic strategy, a one-pot through-process was first developed to prepare the desired α-amino *β*-keto ester **9** (Scheme 2). Treatment of glycine ester **7** with benzoyl chloride under Schotten−Baumann reaction conditions at 0 °C, in the presence of Na_2CO_3 or Et_3N, gave the corresponding benzamide in >95% assay yield. The aqueous phase was discarded; the organic layer was solvent switched to dry MeCN and treated with $(Boc)_2O$ in the presence of a catalytic amount of DMAP to afford **8**. Without workup, the reaction stream in the same pot was directly treated with a solution of *t*-BuOK in THF at 0−5 °C. As such, **8** was rearranged to **9** through an intramolecular nucleophilic attack on the amide carbonyl group, a Chan-type N→C benzoyl migration,[10] effectively affording the desired keto ester **9**. Thus, ester **9** was directly isolated from aqueous *i*-PrOH in 90% yield over three steps.

Scheme 2. Through-Process to Keto Ester **9**



With **9** in hand, we started to explore the opportunities to prepare the desired *syn*-1,2-amino alcohol **10**. Studies showed that a fast epimerization of ketone **9** could be easily achieved with a weak base such as Et_3N. However, DKR hydrogenation of racemic **9** in the presence of Noyori's Ru-BINAP catalyst, which, to our knowledge,[7] is the only reported method for the asymmetric preparation of *syn*-1,2-amino alcohol analogues of **10** through a reduction of α-amino-*β*-keto esters at the time,[11] resulted in an extremely slow reaction with low conversion under various conditions.[7]

In parallel, we also investigated the preparation of **10** via an enzymatic DKR reduction. If the desired enzymatic reactivity converting **9** to **10** (even with low conversion) could be realized through screening, we were confident that we could evolve/develop the initial proof-of-concept result to a practical process through enzyme evolution, given the recent development and success on enzyme engineering technology.[12]

(6) Maloney, K. M.; Chung, J. Y. L. *J. Org. Chem.* **2009**, *74*, 7574–7576.

(7) (a) Liu, Z.; Schultz, C. S.; Sherwood, C. A.; Krska, S.; Dormer, P. G.; Desmond, R.; Lee, C.; Cherer, E. C.; Shpungin, J.; Cuff, J.; Xu, F. *Tetrahedron Lett.* **2011**, *52*, 1685–1688. (b) Seashore-Ludlow, B.; Villo, P.; Häcker, C.; Somfai, P. *Org. Lett.* **2010**, *12*, 5274–5277and references cited therein.

(8) To support the early development work, a process to prepare aldehyde **12** from **6** was also developed.[9]

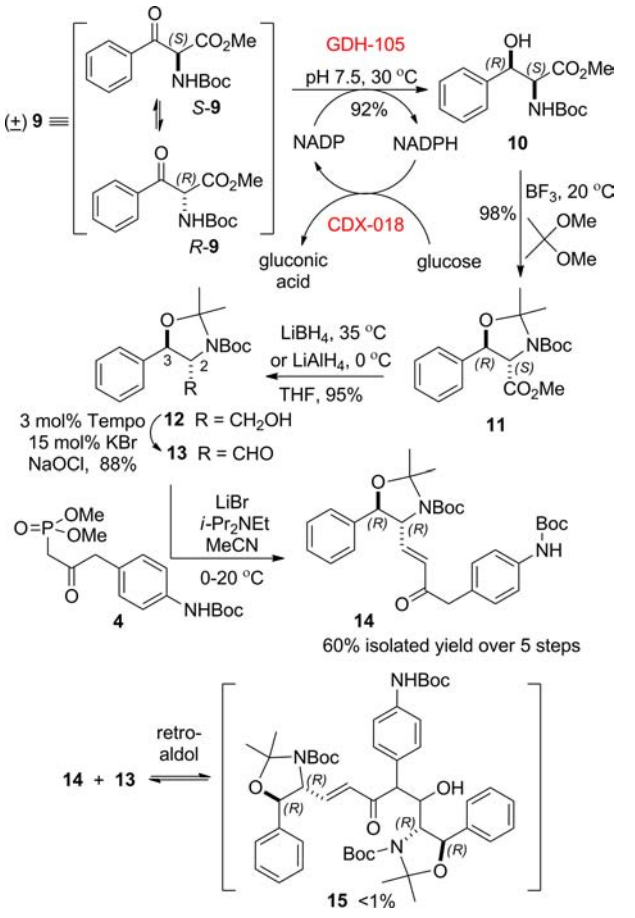
(9) For more detailed discussion, see the Supporting Information.

(10) (a) Farran, D.; Parrot, I.; Toupet, L.; Martinez, J.; Dewynter, G. *Org. Biomol. Chem.* **2008**, *6*, 3989–3996. (b) Hara, O.; Ito, M.; Hamada, Y. *Tetrahedron Lett.* **1998**, *39*, 5537–5540.

(11) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, T.; Akutagawa, S.; Sayo, N.; Saito, T. *J. Am. Chem. Soc.* **1989**, *111*, 9134–9135.

(12) For an excellent example, see: Savile, K. C.; Janey, J. M.; Mundorff, E. C.; Moore, J. C.; Tam, S.; Jarvis, W. R.; Colbeck, J. C.; Krebber, A.; Fleitz, F. J.; Brands, J.; Devine, P. N.; Huisman, G. W.; Hughes, G. J. *Sciences* **2010**, *329*, 305–309.

Scheme 3. Through-Process to Enone **15** via Enzymatic DKR



To this end, screening of enzymatic DKR reduction identified that several enzymes promoted the desired reaction to produce **10**. Preliminary results showed that methyl ester **9** gave higher dr selectivity than the corresponding ethyl ester.

The attainment of the catalytic cycle for the desired enzymatic DKR reduction required the use of coenzyme NADP and CDX-901, both of which, by consuming glucose to gluconic acid, deliver the hydride source to selectively reduce *ent*-(*S*)-**9** to give the desired **10**. Enzymes[13] KRED-130 and CDX-901 were initially selected for further optimization. Although promising results were obtained on a laboratory scale to give **10** in 99% ee and 90% assay yield, the stability and reactivity of the enzymes on large-scale runs were not ideal and resulted in incomplete conversion. However, this issue was overcome by employing the evolved enzymes GDH-105 and CDX-018,[13] which were also evolved to withstand higher concentration of organic solvent desired for improving the solubility of **9** and therefore the volume productivity. After optimization, the highly enantioselective enzymatic DKR reduction was carried out by treating **9** in an aqueous DMSO phosphate buffer in the presence of glucose, a catalytic amount of NADP, and enzymes GDH-105 and CDX-018 at 30 °C. NaOH (2 N) was added to neutralize the gluconic acid formed during the reaction and to maintain the reaction pH at 7.5 to accomplish a fast epimerization of **9**, thereby achieving >98% conversion within 2 days. It is also worth noting that the use of *i*-PrOH−*t*-BuOMe for extractive workup resulted in a clear phase separation that overcame the potential emulsion caused by enzyme protein. As such, **10** was obtained in 92% assay yield with >99% ee and >99:1 dr selectivity. Thus, the *syn* stereochemistry of **10**, which is generally not readily prepared through a chemical reduction, was established through a powerful enzymatic DKR reduction of racemic substrate **9**. The integration of biotechnology into classical organic synthesis is an alternative and useful tool to solve synthetic problems.

To convert *syn*-amino alcohol **10** to aldehyde **13**, which thereby allowed us to extend the desired functionality for the preparation of **1** through a Horner−Wadsworth−Emmons reaction (Scheme 1), acetonide **11** was prepared in the presence of 10 mol % of $BF_3 \cdot OEt_2$ and dimethoxypropane in toluene/acetone (Scheme 2). The use of a small amount of toluene streamlined the process, such that the conversion from **9** to **14** was performed without isolating any intermediates. Reduction of ester **11** with either 1.3 equiv of $LiBH_4$ or 0.7 equiv of $LiAlH_4$ gave **12** in 95% assay yield. Subsequent TEMPO/bleach oxidation was carried out in a biphasic mixture of aqueous MeCN/toluene in the presence of $NaHCO_3$ and 15 mol % of KBr at <10 °C to afford aldehyde **13** without any ee loss in 88% assay yield. The aqueous phase was discarded, and the wet crude reaction stream of aldehyde **13** was directly used "as is" in the subsequent step.

Appropriately mild conditions[14] were identified to promote the desired Horner−Wadsworth−Emmons reaction. In the presence of 3 equiv of LiBr and 3 equiv of Hunig's base, the coupling of phosphonate **5**[6] and aldehyde **12** proceeded smoothly in MeCN to give **14** in 89% assay yield. The use of either LiCl or <3 equiv of LiBr led to a lower conversion and yield. Interestingly, byproduct **15**, which competitively formed up to ~12% through a reversible aldol condensation of **14** and aldehyde **13**[15] within initial several hours, was eventually converted to the desired **14** in >99% conversion[16] upon aging the reaction at 20 °C overnight (Scheme 3). After aqueous workup, enone **14** was crystallized from aqueous *i*-PrOH in 80% yield and >98% purity. Thus, starting from keto ester **9**, enone **14** was prepared in 60% yield over five steps without isolating any intermediates.

Hydrogenation of **14** (5 wt % of 10% Pd−C, 20 psi H_2, THF, 20 °C, 2 h) gave ketone **16** cleanly (Scheme 4). The use of THF avoided hydrogenolysis cleavage of the benzylic C−O bond. With compound **16** in hand, we set forward for global deprotection. However, initial

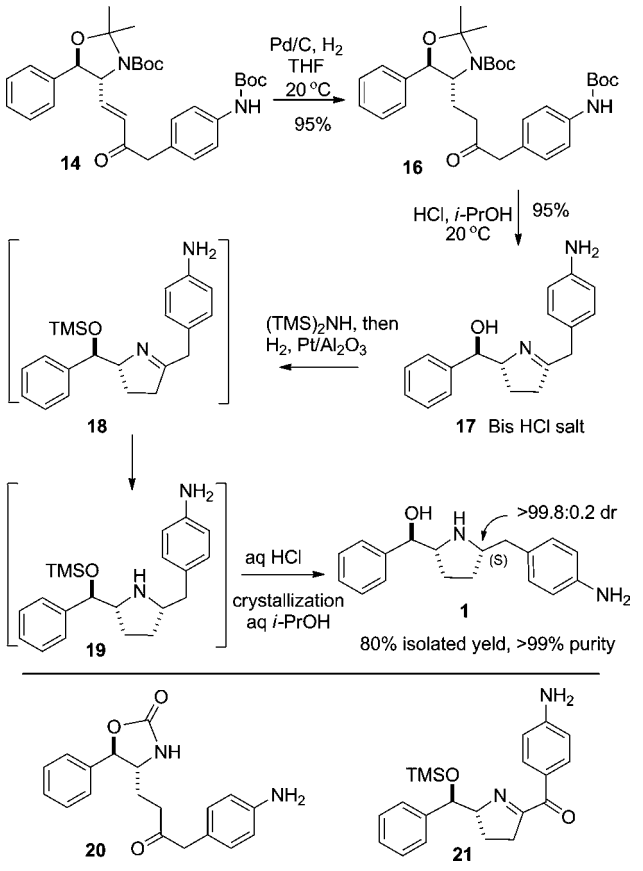
(13) In collaboration with Codexis Inc., USA.

(14) (a) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183–2186. (b) Rathke, M. W.; Nowak, M. *J. Org. Chem.* **1985**, *50*, 2624–2626.

(15) Since Horner−Wadsworth−Emmons coupling is irreversible, **13** liberated via a retro-aldo reaction can be fully consumed to yield **14**.

(16) For examples, see: (a) Lygo, B.; Beynon, C.; McLeod, M. C.; Roy, C. E.; Wade, C. E. *Tetrahedron* **2010**, *66*, 8832–8836. (b) Ahn, K. H.; Kwon, G. J.; Choi, W.; Lee, S. J.; Yoo, D. J. *Bull. Korean Chem. Soc.* **1994**, *15*, 825–827.

Scheme 4. Deprotection and Hydrogenation



treatment of **16** with TFA resulted in the desired imine **17** along with 20−25% of cyclic carbamate byproduct **20**. Further studies showed that complete global deprotection followed by spontaneous dehydration−cyclization was best carried out in *i*-PrOH−HCl. After 24 h at ambient temperature, imine **17** bis-HCl salt monohydrate was directly isolated from *i*-PrOH−*i*-PrOAc in 95% yield and >97% purity.

To complete the construction of the core skeleton desired for a novel class of β_3 adrenergic receptor agonists, diastereoselective reduction of imine **17** was highly desired. Preliminary results showed the reduction applying hydride methods gave unsatisfactory selectivity; we therefore focused our efforts on hydrogenation of **17**. Among the various catalysts/conditions[9] examined, Raney Ni gave 96:4 dr selectivity (*cis*:*trans*) in MeOH at 75 °C/40 psi H_2 (Table 1, entry 7). However, 100 wt % of Raney Ni was required in order to achieve >95% conversion in 20 h. In addition, the use of aqueous MeOH instead of dry MeOH resulted in lower dr selectivity.[9]

A survey of the literature[1,16] suggested that increasing the bulkiness of the substitute group of the C2 stereogenic center in the pyrroline ring, which can be achieved by masking the OH group in **18**, could improve the *cis*-selectivity. Thus, bis-HCl salt monohydrate **17** was treated with 2.1 equiv of $(Me_3Si)_2NH$ in THF to give the corresponding

Table 1. Selected Initial Results of Hydrogenation of Imine[a]

entry	substrates	catalysts	solvents	conv[b] (%)	cis/trans[b]
1	**17**	Pd/C	*i*-PrOH	64	60:40
2		Pd/C	EtOH	93	56:44
3		Rh/Al_2O_3	MeOH	94	61:39
4		Ru/C	*i*-PrOH	61	84:16
5		PtO_2	EtOH	69	66:33
6		Pt/Al_2O_3	*i*-PrOH	>99	84:16
7		Raney Ni[c]	MeOH	>99	96:4[c]
8	**18**	Pt/Al_2O_3	THF	>99	96:4
9		Rh/Al	THF	72	98:2
10		Pd/C	THF	78	91:9
11		Pd/Al	THF	37	95:5

[a] Unless otherwise mentioned, all reactions were carried out at 25 °C, 15−40 psi H_2 with 10−25 wt % of catalyst loading. [b] Determined by HPLC analysis.[9] [c] 75 °C, 40 psi H_2, 100 wt % of Raney Ni.

TMS-protected imine **18** quantitatively, which set a new stage for screening hydrogenation conditions in an attempt to improve the *cis* selectivity. Interestingly, under the basic conditions, imine **17** was readily oxidized upon exposure to air to give ketone **21**; notwithstanding, maintaining an inert atmosphere was straightforward on the plant scale. Finally, several suitable catalysts/conditions were identified to prepare **1** in high diastereoselectivity (Table 1, entry 8). Given overall considerations in terms of reaction rate, conversion, and impurity profile, Pt/Al_2O_3 was selected for further optimization. In practice, the in situ TMS-silylated imine **18** was directly subjected to hydrogenation in the presence of 5 wt % of 5% Pt/Al_2O_3 at 20−25 °C/40 psi H_2 for 12 h to give the corresponding amine **19** (*cis*/*trans* = 96:4). After aqueous HCl workup, the desired *cis*-pyrrolidine **1** hemihydrate was crystallized from aqueous *i*-PrOH in 80% yield and >99% purity. The undesired *trans* diastereomer was cleared to <0.2%.

In summary, an efficient asymmetric synthesis of *cis*-2,5-disubstituted pyrrolidine **1** has been developed. This practical synthesis features the application of enzymatic DKR reduction to establish the two stereogenic centers of *syn* phenyl 1,2-amino alcohol in >99% ee and >99:1 dr in one step. Effective hydrogenation of chiral cyclic imine affords pyrrolidine **1** in high *cis* diastereoselectivity. Starting from inexpensive glycine ester and only isolating 3 intermediates, the core scaffold of β_3-AR agonists is prepared in 38% yield over 11 steps. This synthesis is amenable to the preparation of various analogues of **1**.

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Supporting Information Available. Experimental procedure/data and discussion including an alternative synthesis of **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.