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An Enantioselective Synthesis of (*S*)-(+)-3-Aminomethyl-5-methylhexanoic Acid via Asymmetric Hydrogenation

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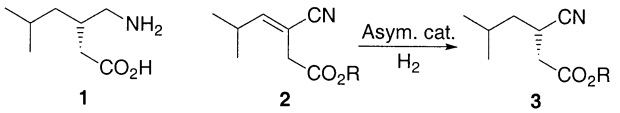
Abstract: A concise enantioselective synthesis of (*S*)-(+)-3-aminomethyl-5-methylhexanoic acid (**1**, Pregabalin) has been developed. The key step is the asymmetric hydrogenation of a 3-cyano-5-methylhex-3-enoic acid salt **2** with a rhodium Me-DuPHOS catalyst, providing the desired (*S*)-3-cyano-5-methylhexanoate **3** in very high ee. Subsequent hydrogenation of the nitrile **3** with a heterogeneous nickel catalyst provides Pregabalin **1** in excellent overall yield and purity.

(*S*)-(+)-3-Aminomethyl-5-methylhexanoic acid (**1**, Pregabalin) is a potent anticonvulsant related to the inhibitory neurotransmitter γ-aminobutyric acid.[2] Since the biological activity resides in the (*S*)-enantiomer, an enantioselective synthesis is required. During the initial development of Pregabalin **1** several routes were examined in considerable detail.[3] The preferred process to emerge from these studies starts with the condensation of diethyl malonate and isobutyraldehyde. After a further 4 steps, resolution with (*S*)-(+)-mandelic acid provides (*S*)-Pregabalin **1** in 25−29% overall yield. Although this route is cost-effective, the use of a late-stage resolution without the opportunity to efficiently recycle the off-isomer is inefficient and there was clearly scope for developing a more economical process. Asymmetric catalytic hydrogenation of a suitable prochiral precursor such as **2** was identified as a potential route to **1** via intermediate **3**.



1 **2** **3**

Considerable precedent exists for the asymmetric hydrogenation of β-substituted itaconic acid derivatives. Rhodium−phosphine complexes generally provide the desired 2-substituted succinates with high enantioselectivity.[4] In particular, hydrogenation of itaconate salts with Rh-DuPHOS catalysts provides significant rate enhancement, increases the selectivity, and allows mixtures of geometrical isomers to be hydrogenated to a single product. This is in sharp contrast to previous catalyst systems for which considerable differences were noted for the different geometrical isomers. Chiral ruthenium complexes have also found some application, but in general these are less effective than rhodium complexes, and require higher catalyst loading, higher temperatures, and longer reaction times.[5] There are surprisingly few reports on the asymmetric hydrogenation of acrylonitrile derivatives. In one example, (*Z*)-*N*-(1-cyano-2-phenylvinyl)benzamide was hydrogenated in the presence of [(*R,R*)-(DIPAMP)Rh(COD)]BF_4, giving the desired product in 89% ee. However, the reaction was less selective and considerably slower than the hydrogenation of the corresponding acrylic acid.[6]

Thus, while there was no direct precedent for the hydrogenation of this class of compounds we had considerable confidence that a suitable catalyst could be identified for this reaction. Herein we report a succinct synthesis of Pregabalin **1**, utilizing a rhodium-catalyzed asymmetric hydrogenation to furnish the key intermediate **3** in high yield and excellent enantiomeric excess.[7]

The required precursor for the hydrogenation reaction was readily prepared following a literature procedure for similar compounds, summarized in Scheme 1.[8] Baylis−Hillman reaction between isobutyraldehyde and acrylonitrile furnished hydroxy nitrile **4**.[9] This was then converted to the ethyl carbonate **5** (the reaction also works with the corresponding acetate), which was used directly in a palladium-catalyzed carbonylation to give 3-cyano-5-methylhex-3-enoic acid ethyl ester (**2a**) as a 3.5:1 (*Z*/*E*) mixture of isomers (83%, Scheme 1). Initial attempts at using the crude product from this reaction in the hydrogenation step failed, presumably due to residual impurities. The ester was further purified by vacuum distillation. The other hydrogenation substrates, *tert*-butylammonium and potassium salts **2b** and **2c**,

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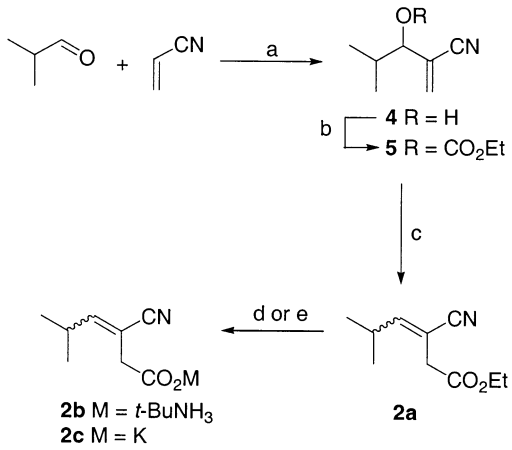
SCHEME 1[a]



[a] Reagents and conditions: (a) DABCO, H_2O, 2,6-di-*tert*-butyl-4-methylphenol, 50 °C, 97%; (b) $ClCO_2Et$, pyridine, CH_2Cl_2, rt, 95%; (c) $Pd(OAc)_2$, PPh_3, EtOH, CO (300 psi), 50 °C, 83%; (d) **2b** (i) LiOH, H_2O, THF, rt; (ii) HCl; (iii) *tert*-$BuNH_2$, EtOAc, 89%; (e) **2c** KOH, MeOH, 45 °C, 88%.

TABLE 1. Asymmetric Hydrogenation of 3-Cyano-5-methylhex-3-enoic Acid Ethyl Ester 2a

entry[a]	precatalyst	temp (°C)	conv (%)[b]	ee (%)[b,c]
1	[(*R*,*R*)-(Me-DuPHOS)Rh(COD)]BF_4	rt	10	8 (*S*)
2	[(*R*,*R*)-(Me-BPE)Rh(COD)]OTf	rt	54	10 (*R*)
3	[(*R*,*R*)-(Me-DuPHOS)Rh(COD)]BF_4	55	100	19 (*R*)
4	[(*R*,*R*)-(Et-DuPHOS)Rh(COD)]BF_4	55	100	42 (*R*)
5	[(*R*,*R*)-(^{i}Pr-DuPHOS)Rh(COD)]BF_4	55	79	44 (*S*)
6	[(*R*,*R*)-(Me-BPE)Rh(COD)]OTf	55	100	13 (*R*)
7	[(*R*,*R*)-(Et-BPE)Rh(COD)]BF_4	55	100	13 (*R*)
8	[(*S*,*S*)-(^{i}Pr-BPE)Rh(COD)]BF_4	55	67	<2
9	[(*R*,*R*)-(Me-FerroTANE)Rh(COD)]BF_4	rt	51	37 (*S*)
10	[(*R*,*R*)-(Et-FerroTANE)Rh(COD)]BF_4	rt	41	7 (*S*)

[a] 1 mmol of substrate in 5 mL of methanol was hydrogenated with 10 μmol of precatalyst in a glass lined stainless steel pressure vessel with hydrogen at 90 psi. [b] Conversion and enantiomeric excess were determined by GC (see Experimental Section). [c] The absolute stereochemistry was established by conversion to Pregabalin.

were readily prepared from the ester by standard methods. In both cases, mixtures of geometrical isomers were obtained in approximately the same ratio as observed for ester **2a**. The *tert*-butylammonium salt **2b** could also be prepared directly from the crude ester **2a** (62%), removing the need for vacuum distillation.

Efforts were initially focused on the asymmetric hydrogenation of the ethyl ester **2a**. A range of chiral rhodium complexes were examined under typical hydrogenation conditions (Table 1). Although the hydrogenation reactions proceeded slowly at room temperature, upon heating to 55 °C complete conversion was achieved for the majority of catalyst systems examined. Unfortunately, the enantiomeric excess obtained for this substrate was disappointingly low.

In contrast, however, the hydrogenation of *tert*-butylammonium salt **2b** not only proceeded rapidly at room temperature (reaction complete in under 15 min with some catalysts) but also gave the product with excellent enantioselectivity (Table 2).

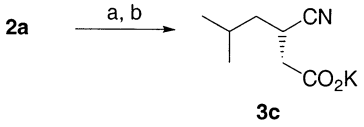
From this initial screen, three precatalysts were clearly outstanding in terms of both high reactivity and selectivity, namely [(Me-DuPHOS)Rh(COD)]BF_4, [(Et-DuPHOS)-Rh(COD)]BF_4, and [(*R*,*R*)-(Me-FerroTANE)Rh(COD)]BF_4 (entries 1, 2, and 7). In all cases the (*R*,*R*)-enantiomer of the catalyst provided the desired (*S*)-enantiomer of the product. A similar screen of catalysts was also conducted for the potassium salt **2c**, with comparable results being obtained in terms of rate and selectivity. These screening reactions were conducted at a molar substrate-to-catalyst ratio (S/C) of 100:1. For this to be an economically viable route, comparable rates and selectivity would need to be achieved at much lower S/C ratios. After some scale-up work, [(*R*,*R*)-(Me-DuPHOS)Rh(COD)]BF_4 was selected as the best catalyst for further development due to a combination of rate and selectivity at reduced catalyst loading. Under slightly modified reaction conditions the hydrogenation of **2b** with [(*R*,*R*)-(Me-DuPHOS)Rh(COD)]-BF_4 was demonstrated at a molar S/C of 2700/1, which corresponds to a substrate to catalyst w/w ratio of 1000/1. The reaction was complete in 4 h and the crude product was obtained in 97.7% e.e.

TABLE 2. Asymmetric Hydrogenation of *tert*-Butylammonium 3-Cyano-5-methylhex-3-enoate 2b

entry[a]	precatalyst	react. time	conv (%)[b]	ee (%)[b]
1	[(*R*,*R*)-(Me-DuPHOS)Rh(COD)]BF_4	15 min[c]	100	95.0 (*S*)
2	[(*R*,*R*)-(Et-DuPHOS)Rh(COD)]BF_4	15 min[c]	100	97.4 (*S*)
3	[(*R*,*R*)-(^{i}Pr-DuPHOS)Rh(COD)]BF_4	6 h	72	24.0 (*R*)
4	[(*R*,*R*)-(Me-BPE)Rh(COD)]OTf	45 min[c]	100	83.3 (*S*)
5	[(*R*,*R*)-(Et-BPE)Rh(COD)]BF_4	45 min[c]	100	81.0 (*S*)
6	[(*S*,*S*)-(*i*Pr-BPE)Rh(COD)]OTf	6 h	59	8.0 (*S*)
7	[(*R*,*R*)-(Me-FerroTANE)Rh(COD)]BF_4	20 min[c]	100	95.4 (*S*)
8	[(*R*,*R*)-(Et-FerroTANE)Rh(COD)]BF_4	20 min[c]	100	84.6 (*S*)

[a] 1 mmol of substrate in 5 mL of methanol was hydrogenated with 10 μmol of precatalyst in a glass-lined stainless steel pressure vessel with hydrogen at 90 psi at room temperature. [b] Conversion and enantiomeric excess were determined by GC (see Experimental Section). [c] Time within which hydrogen uptake had ceased.

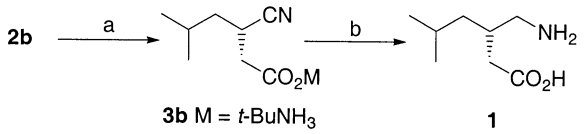
SCHEME 2[a]



[a] Reagents and conditions: (a) KOH, H_2O, MeOH; (b) [(*R*,*R*)-(Me-DuPHOS)Rh(COD)]BF_4, H_2 (45 psi), 55 °C, 99% conversion, 96.6% ee.

To circumvent the need to isolate 3-cyano-5-methylhex-3-enoic acid or a salt, ethyl ester **2a** was hydrolyzed with potassium hydroxide in a mixture of methanol and water to give a solution of potassium salt **2c**. Addition of a solution of the precatalyst, [(*R*,*R*)-(Me-DuPHOS)Rh(COD)]-BF_4 (S/C 2000/1), followed by hydrogenation gave potassium (*S*)-3-cyano-5-methylhexanoate (**3c**) in 96.6% ee (Scheme 2). An important point to note is that this reaction is conducted in a mixed methanol−water solvent system (presumably the water assists in the hydrolysis), demonstrating the utility of the Rh-DuPHOS catalyst under partially aqueous conditions. While this is a more direct approach, the drawback of this procedure is that any residual ethyl ester **2a** that may be present will be hydrogenated to the *opposite* enantiomer of the product **3**, thus reducing the enantiomeric excess. The rate of reaction was also somewhat slower under these reaction

SCHEME 3[a]



[a] Reagents and conditions: (a) [(*R*,*R*)-(Me-DuPHOS)Rh(COD)]-BF_4, H_2 (45 psi), MeOH, 55 °C, 100% conversion, 97.7% ee; (b) (i) Sponge Ni, KOH, H_2 (50 psi), H_2O, EtOH; (ii) AcOH, 61% (two steps), 99.8% ee.

conditions. Thus, the favored process is to prepare the *tert*-butylammonium salt **2b** from the purified ethyl ester **2a**, followed by asymmetric hydrogenation to *tert*-butylammonium salt **3b** (Scheme 3). This process has been scaled up to multi-killogram quantities without significant difficulties (see Supporting Information).

The final step in the synthesis of (*S*)-(+)-3-aminomethyl-5-methylhexanoic acid (**1**), the reduction of the nitrile group, was accomplished via a heterogeneous hydrogenation of the *tert*-butylammonium salt **3b** over sponge nickel. The crude product was crystallized from a mixture of ethanol, water, and acetic acid to give Pregabalin **1** in 61% yield and 99.8% ee (Scheme 3).

The much higher reactivity and selectivity observed for the asymmetric hydrogenation of salts **2b** and **2c** compared to the ethyl ester **2a** is due to enhanced coordination between the substrate and the catalyst. It is well established that the bisphosphine rhodium catalysts of this type are most effective when the substrate is able to behave as a bidentate ligand **7** (Scheme 4).[10] In the presence of the strongly coordinating nitrile ligand this chelating binding mode is disrupted. The $^{31}P\{^1H\}$ NMR spectrum of the complex formed between the catalytic intermediate [(*R*,*R*)-(Me-DuPHOS)Rh($CD_3OD)_2$]-BF_4 (**6**) and *tert*-butylammonium salt **2b** shows a dynamic mixture of species, characterized by complex and broadened signals. Within this is a pair of double doublets at δ 79.3 and 88.6 ppm (J_{PP} = 34 Hz, J_{PRh} = 149 Hz) which can be assigned to the rhodium chelate **7**. The spectroscopic data for this complex are similar to those previously reported for an analogous vinyl acetate complex.[10] Upon treatment with hydrogen, the olefin is reduced and the $^{31}P\{^1H\}$ NMR spectrum collapses to a doublet at δ 95.4 ppm (J_{PRh} = 171 Hz), assigned to the bis-(*S*)-3-cyano-5-methylhexanoate complex **8** as the $^{31}P\{^1H\}$ NMR spectrum is almost identical with that of [(*R*,*R*)-(Me-DuPHOS)Rh($NCCH_3)_2$]BF_4 [δ 95.3 (d, J_{PRh} = 175 Hz)]. It is proposed that the small standing concentration of **7** in the reaction mixture (ca. 10%) serves as a conduit through which all the hydrogenation substrate is converted to product. The relatively low reactivity observed in this reaction compared to, for example, itaconic salts[4c] or amido itaconates[11] is attributed to the low levels of the reactive intermediate **7** in the reaction mixture. Similar observations, where a minor component of a mixture gives rise to the major product, are well established in the asymmetric hydrogenation of prochiral olefins by chiral bisphosphine rhodium complexes.[12]

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In conclusion we have demonstrated a six-step synthesis of (*S*)-(+)-3-aminomethyl-5-methylhexanoic acid (**1**) that delivers the product in high yield and excellent enantiopurity. The synthetic sequence described is as short as the previously preferred route,[3] but potentially provides significant improvements in cost of goods, waste reduction, and throughput.

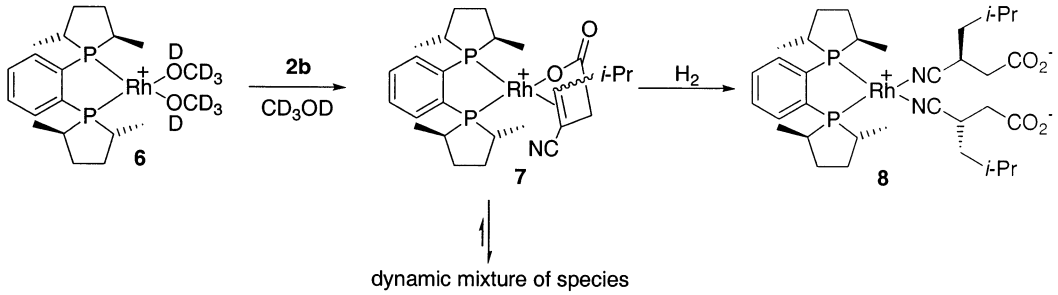
Experimental Section

***tert*-Butylammonium 3-Cyano-5-methyl-hex-3-enoate (2b).** Ethyl ester **2a** (20.0 g, 110 mmol, see Supporting Information) and lithium hydroxide hydrate (13.0 g, 310 mmol) were suspended in a mixture of tetrahydrofuran (75 mL) and water (25 mL). The slurry was vigorously stirred for 4 h at room temperature. The mixture was acidified to pH 2 (HCl, 3 N) and extracted into ethyl acetate (3 × 150 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give crude 3-cyano-5-methylhex-3-enoic acid: IR (film) ν_{max} 2222, 1714 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (major isomer) 1.09 (3H, d, J = 7.0 Hz), 2.91 (1H, dheptet, J = 10.0, 7.0 Hz), 3.25 (2H, br), 6.16 (1H, d, J = 10.0 Hz), (minor isomer) 1.05 (3H, d, J = 6.7 Hz), 2.63 (1H, dheptet, J = 10.0, 6.7 Hz), 3.31 (2H, s), 6.40 (1H, d, J = 10.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (major isomer) 22.1, 31.9, 39.0, 104.6, 116.9, 159.7, 175.4 (minor isomer) 21.9, 28.9, 34.2, 104.8, 119.5, 159.1, 175.0. *m*/*z* 152 (M − H), 305 (2M − H). The acid was dissolved in ethyl acetate (400 mL) and a solution of *tert*-butylamine in ethyl acetate (20 mL) was added. The temperature of the solution rose by approximately 10 °C as the salt **2b** precipitated as a white crystalline solid. The product was collected by filtration and dried in vacuo (22.15 g, 89%): mp 161 °C; IR (KBr) ν_{max} 2216, 1557 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ (major isomer) 1.09 (6H, d, J = 6.5 Hz), 1.37 (9H, s), 2.81 (1H, dheptet, J = 10.0, 6.5 Hz), 3.04 (2H, d, J = 1 Hz), 6.13 (1H, d, J = 10.0 Hz), (minor isomer) 1.05 (6H, d, J = 6.5 Hz), 1.37 (9H, s), 2.74 (1H, dheptet, J = 10.1, 6.5 Hz), 3.11 (2H, s), 6.25 (1H, d, J = 10.1 Hz); ^{13}C NMR (CD_3OD, 100 MHz) δ (major isomer) 22.7, 28.3, 33.0, 44.1, 52.9, 110.3, 119.2, 157.3, 177.1, (minor isomer) 22.1, 28.3, 29.7, 38.8, 52.9, 110.8, 122.1, 157.0, 176.5; *m*/*z* 74 (tBuNH$_3^+$), 305 (2M + H).

Representative Procedure for Hydrogenation Screening Reactions. A solution of ethyl ester **2a** (0.19 mL, 1.0 mmol) in methanol (4 mL) was placed in a glass-lined 50-mL PARR microreactor modified with an injection septum and valve. The vessel was heated to an internal temperature of 55 °C. A hydrogen atmosphere was established and a solution of [(*R*,*R*)-(^{i}Pr-DuPHOS)Rh(COD)]BF_4 (7.2 mg, 10 μmol) in methanol (1 mL) was added via syringe. The vessel was pressurized with hydrogen to 100 psi and stirred overnight. The pressure was then released and the solvent was removed in vacuo. ^1H NMR analysis showed approximately 80% conversion to **3a**, GC analysis showed 86.4% conversion, 43.8% ee (*S*): IR (film) ν_{max} 2242, 1738 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.96 (3H, d, J = 6.8 Hz), 0.98 (3H, d, J = 6.5 Hz), 1.29 (3H, t, J = 7.1 Hz), 1.34 (1H, ddd, J = 13.4, 9.4, 5.0 Hz), 1.64 (1H, ddd, J = 13.8, 10.9, 4.7 Hz), 1.87 (1H, m), 2.53 (1H, dd, J = 16.6, 6.9 Hz), 2.69 (1H, dd, J = 16.3, 7.3 Hz), 3.06 (1H, m), 4.20 (2H, q, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.5, 21.6, 23.2, 25.7, 26.2, 26.5, 37.5, 41.1, 61.6, 121.5, 170.1. Screening reactions at room temperature were carried out via a modified procedure. The liner was charged with a stir bar, the substrate, and catalyst. The vessel was assembled and a hydrogen atmosphere established as described above. Methanol was added via the septum, the vessel was again purged before pressurizing to the reaction pressure and stirring was then initiated.

***tert*-Butylammonium (*S*)-3-Cyano-5-methylhexanoate (3b).** A pressure reactor was charged with a solution of *tert*-butylammonium salt **2b** (125.8 g, 0.56 mol) in methanol (1 L). A hydrogen atmosphere was established and the vessel was heated to 45 °C. A solution of [(*R*,*R*)-(Me-DuPHOS)Rh(COD)]-BF_4 (0.125 g, 0.206 mmol) in methanol (15 mL) was added via syringe. The vessel was charged with hydrogen to 65 psi and the reaction was stirred at 45 °C until hydrogen uptake ceased

SCHEME 4. Proposed Mechanism for the Hydrogenation of *tert*-Butylammonium Salt 2b



(4 h). The solvent was removed in vacuo to give the product as a white crystalline solid (125 g, 99%), GC analysis showed >99% conversion, 97.7% ee: mp 148 °C dec; $[\alpha]^{25}_D$ −16.8° (*c* 1.2, MeOH); IR (KBr) ν_{max} 2238, 1557 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 0.98 (3H, d, J = 5.8 Hz), 1.00 (3H, d, J = 6.1 Hz), 1.37 (9H, s), 1.41 (1H, ddd, J = 13.4, 9.4, 5.0 Hz), 1.59 (1H, ddd, J = 13.8, 10.9, 5.1 Hz), 1.83 (1H, m), 2.39 (1H, dd, J = 15.2, 6.9 Hz), 2.49 (1H, dd, J = 15.5, 7.9 Hz), 3.10 (1H, m); ^{13}C NMR (CD_3OD, 100 MHz) 22.2, 23.9, 27.9, 28.3, 28.7, 42.2, 42.6, 52.9, 124.2, 177.7; *m*/*z* 74 (tBuNH$_3^+$), 309 (2M + H).

Potassium (*S*)-3-Cyano-5-methylhexanoate (3c) (in situ generation of salt). A pressure reactor was charged with a solution of ethyl ester **2a** (10.8 g, 59.7 mmol) in methanol (100 mL) and water (18 mL). A solution of potassium hydroxide in methanol (5 M, 11.7 mL, 58.4 mol) was added, a nitrogen atmosphere was established, and the vessel was heated to 55 °C and held at this temperature for 2 h. A hydrogen atmosphere was established and a solution of [(*R*,*R*)-(Me-DuPHOS)Rh(COD)]-BF_4 (0.018 g, 0.030 mmol) in methanol (20 mL) was added via syringe. The vessel was charged with hydrogen to 60 psi and the reaction was stirred at 55 °C until hydrogen uptake ceased (5 h). The solvent was removed in vacuo to give the product as a white crystalline solid (11.2 g, 99%), GC analysis showed >99% conversion, 97.7% ee: mp 102 °C dec; $[\alpha]^{25}_D$ −20.6° (*c* 1.1, MeOH); IR (KBr) ν_{max} 2240, 1580 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 0.98 (3H, d, J = 6.6 Hz), 1.00 (3H, d, J = 6.6 Hz), 1.41 (1H, ddd, J = 13.5, 9.7, 5.2 Hz), 1.58 (1H, ddd, J = 15.2, 10.7, 4.8 Hz), 1.84 (1H, m), 2.39 (1H, dd, J = 15.2, 6.9 Hz), 2.49 (1H, dd, J = 15.2, 7.6 Hz), 3.11 (1H, m); ^{13}C NMR (CD_3OD, 100 MHz) 22.2, 23.8, 27.9, 28.7, 42.2, 42.5, 124.6, 178.0; *m*/*z* 154 (M), 309 (2M + H).

(*S*)-3-Aminomethyl-5-methylhexanoic Acid (1). A solution of *tert*-butylammonium salt **3b** (8.0 g, 35.0 mmol) in water (15 mL) and ethanol (11 mL) was added to nickel sponge (A-7000, 5 g, water wet), followed by potassium hydroxide (91% flake, 2.2 g, 35.6 mmol), and the resulting slurry was shaken under 50 psi of hydrogen overnight. The mixture was filtered (Supercel) and the cake was rinsed with water (20 mL) and ethanol (7 mL). Acetic acid (4.1 mL, 71.6 mmol) was added to the combined filtrates which were then heated to 70 °C, then cooled slowly to room temperature over several hours, followed by aging for 6 h at 0−5 °C. The product was collected by filtration, rinsed with propan-2-ol (50 mL), and dried under vacuum to give **1** as a white crystalline solid (3.4 g, 61%, 99.8% ee), identical with that prepared previously.[3] Anal. Calcd for $C_8H_{17}NO_2$: C, 60.35; H, 10.76; N, 8.80. Found: C, 60.59; H, 10.78; N, 8.80.

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Supporting Information Available: Experimental details for the synthesis of **4**, **5**, **2a**, **2c**, and **3c** and for the multikillogram conversion of **2b** to **1**, copies of the ^{31}P NMR spectra of **6**−**8**, and ^1H and ^{13}C NMR spectra of **2a**−**c**, **3a**−**c**, 3-cyano-5-methylhex-3-enoic acid, and 3-cyano-5-methyl-hexanoic acid. This material is available free of charge via the Internet at http://pubs.acs.org.

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