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A Practical Synthesis for the Core Structure of a Family of Selective Prostaglandin D_2 Receptor Antagonists

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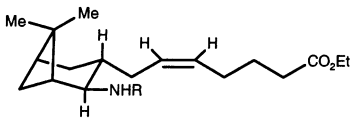
A convergent synthesis was developed for the production of the core structure of prostaglandin D_2 receptor antagonists for the treatment of allergic rhinitis. The key steps in this synthesis were a highly diastereoselective alkylation of (+)-nopinone, a chemo- and stereoselective reduction of an oxime to an amine, and a well-controlled reduction of an aminoalkyne to a (*Z*)-olefin.

Introduction

Prostaglandin D_2 (PGD_2) is the major cyclooxygenase metabolite of arachidonic acid produced by mast cells in response to antigen challenge.[1] It has been proposed that excess production of PGD_2 causes the inflammation commonly observed in allergic diseases such as allergic rhinitis, asthma, and atopic dermatitis.[2] Efforts to develop a PGD_2 receptor antagonist have identified the class of compounds bearing the core structure **1** as promising leads in the alleviation of various allergic disorders.[3] In this paper, the full details of the development of a highly convergent, efficient synthesis of **1** are disclosed.



1 R = H
2a R = Boc
2b R = SO_2Ar
2c R = C(O)R

The previously published synthesis of **1** utilized (+)-myrtenol as the source of the pinane core structure and involved several steps which were not amenable to a scalable process.[4] In addition, the synthesis required a protection/deprotection sequence of the amine through **2** and multiple operations to incorporate the side chain. The primary goal in redesigning the synthesis was to develop a streamlined, convergent route to **1** (Scheme 1). Retrosynthetically, we envisioned that **1** could be derived from ketoalkyne **3**, which was the product of the alkylation of (+)-nopinone (**4**) with a propargyl halide such as **5**.[5] This strategy was attractive because the synthesis was highly convergent, and the starting materials were either commercially available in bulk or readily prepared on kilogram scale.

Discussion

Alkylation of (+)-Nopinone. Our initial efforts were focused on the alkylation of the enolate of (+)-nopinone (**4**) with a model propargyl bromide **5a**. We quickly discovered that the temperature of the reaction had a dramatic effect on the yield and selectivity of the alkylation (Table 1). At higher temperatures, the yields were respectable, but the diastereoselectivity was poor (72:28), favoring the desired, kinetically preferred product **6a**.[6] Conversely, as the temperature was decreased, the diastereomeric ratios were as high as 99:1 favoring **6a**, but the yields dropped to as low as 15%.

These results indicated a highly diastereoselective, kinetically controlled alkylation to afford **6a** at low temperature, which was competitive with epimerization to the thermodynamically favored product **7a** at higher temperatures. To access **6a** in good yield, the reactivity

(1) Lewis, R, A.; Soter, N. A.; Diamond, P. T.; Austen, K. F.; Oates, J. A.; Roberts, L. J. *J. Immunol.* **1982**, *129*, 1627−1631.

(2) (a) Matsuoka, T.; Hirata, M.; Tanaka, H.; Takahashi, Y.; Murata, T.; Kabashima, K.; Sugimoto, Y.; Kobayashi, T.; Ushikubi, F.; Aze, Y.; Eguchi, N.; Urade, Y.; Yoshida, N.; Kimura, K.; Mizoguchi, A.; Honda, Y.; Nagai, H.; Narumiya, S.; Kato, M.; Watanabe, M.; Vogler, B.; Awen, B.; Masuda, Y.; Tooyama, Y.; Yoshikoshi, A. *Science* **2000**, *287*, 2013−2016. (b) Charlesworth, E. N.; Kagey-Sobotka, A.; Schliemer, R. P.; Norman, P. S.; Lichtenstein, L. M. *J. Immunol.* **1991**, *149*, 671−676. (c) Proud, D.; Sweet, J.; Stein, P.; Settipane, R. A.; Kagey-Sobotka, A.; Freidlander, M.; Lichtenstein, L. M. *J. Allergy Clin. Immunol.* **1990**, *85*, 896−905. (d) Murray, J. J.; Tonnel, A. B.; Brash, A. R.; Roberts, L. J.; Gosset, P.; Workman, R.; Capron, A.; Oates, J. *N. Engl. J. Med.* **1986**, *315*, 800−804.

(3) Tsuri, T.; Honma, T.; Hiramatsu, Y.; Mitsumori, S.; Inagaki, M.; Arimura, A.; Yasui, K.; Asanuma, F.; Kishino, J.; Ohtani, M. *J. Med. Chem.* **1997**, *40*, 3504−3507.

(4) Seno, K.; Hagashita, S. *Chem. Pharm. Bull.* **1989**, *37*, 1524−1533.

(5) Alkylation of ketones with this propargyl halide have been extensively utilized in prostaglandin syntheses: (a) Chen, S.; Janda, K. D. *J. Am. Chem. Soc.* **1997**, *119*, 8724−8725. (b) Sato, T.; Shima, H.; Otera, J. *J. Org. Chem.* **1995**, *60*, 3936−3937. (c) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 4718−4726. (d) Corey, E. J.; Niimura, K.; Hashimoto, S.; Hamada, Y. *Tetrahedron Lett.* **1986**, *27*, 2199−2202. (e) Binns, M. R.; Haynes, R. K.; Lambert, D. E.; Schober, P. A. *Tetrahedron Lett.* **1985**, *26*, 3385−3388.

(6) Diastereomer **6a** (stereochemistry determined by ^{1}H NMR) was treated under thermodynamic equilibration with NaOEt in EtOH to yield **7a** (stereochemistry confirmed by ^{1}H NMR) as the major product. The diastereomeric ratio of **6a**:**7a** was determined to be 15:85 by HPLC.

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SCHEME 1

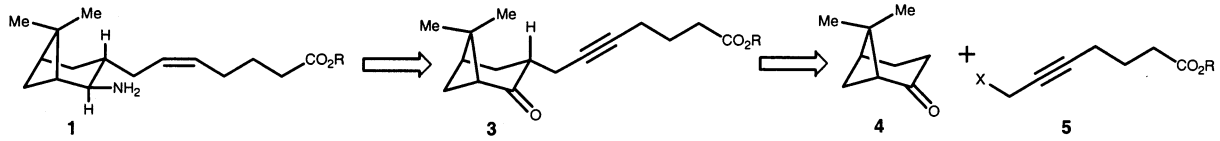
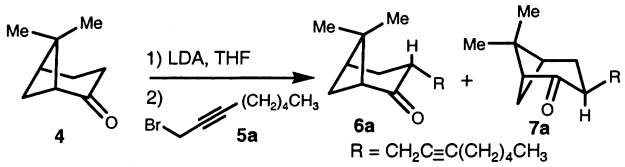


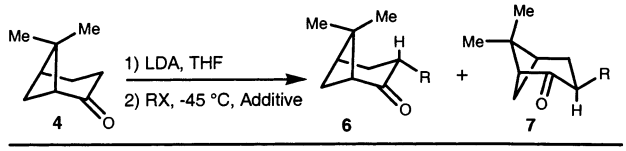
TABLE 1. Effect of Temperature on Diastereoselectivity and Yield[a]

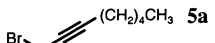
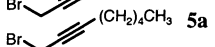
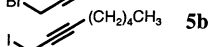
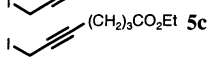


temp (°C)	conversion (%)[b]	**6a**:**7a**[c]
0	85	72:28
−25	68	90:10
−35	50	96:4
−45	30	99:1
−55	15	99:1

[a] All reactions were carried out in THF (1.2 M in substrate), using 1.05 equiv of LDA and 1.05 equiv of **5a**. [b] Conversion was determined 1.5 h after addition of **5a** (HPLC). [c] Diastereoselectivity was determined by HPLC.

TABLE 2. Diastereoselective Nopinone Alkylation with Carbon Electrophiles[a]



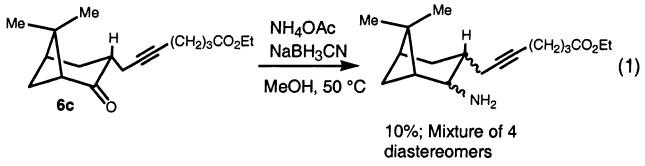
RX	Additive	% yield[b]	**6** : **7**[c]
 **5a**	none	30	98:2 (**6a**:**7a**)
 **5a**	1 equiv DMPU	89	99:1 (**6a**:**7a**)
 **5b**	none	90	99:1 (**6b**:**7b**)
 **5c**	none	90	99:1 (**6c**:**7c**)

[a] All reactions were carried out in THF (1.2 M in substrate), using 1.05 equiv of LDA and 1.05 equiv of RX. [b] Assay yield of the reaction was determined by HPLC. [c] Diastereoselectivity was determined by HPLC and stereochemistry was determined by ^{1}H NMR.

of the enolate or the electrophile needed to be increased such that the alkylation would occur at −45 °C. When the alkylation with **5a** was performed with 1 equiv of DMPU at −45 °C, a high yield and high diastereoselectivity were observed (90% yield, 99:1, **6a**:**7a**).[7]

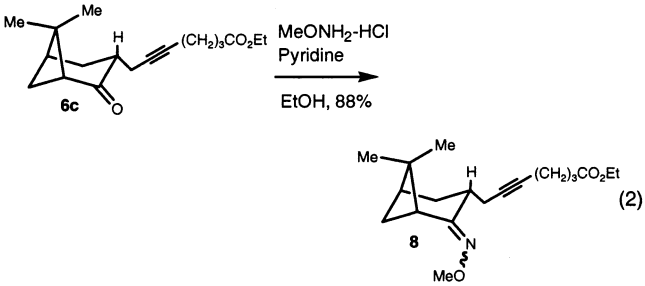
Alternatively, when the more reactive propargyl iodide **5b** (Table 2) was used in the alkylation in the absence of DMPU, the same high yield and diastereoselectivity was obtained (90% yield, 99:1 **6a**:**7a**). In every case, the reaction was quenched at low temperature (−45 °C) with trifluoroacetic acid (TFA) to avoid epimerization to the thermodynamically favored product.[8] These optimized conditions were then applied to the alkylation of (+)-nopinone with propargyl iodide **5c**,[9] affording alkylated adduct **6c** with the same results that were observed in the model system (90% yield, 99:1 **6c**:**7c**). This alkylation proved to be quite general, affording high yields and excellent diastereoselectivities for a variety of carbon and heteroatom electrophiles.[10]

Reductive Amination. With alkylated adduct **6c** in hand, our efforts were focused on methodology suitable to convert the ketone to a primary amine. Reductive amination with ammonium acetate and $NaBH_3CN$ was very sluggish and the chemoselectivity was solvent dependent. For example, only reduction of the ketone to the alcohol was observed in THF; however, in MeOH, reductive amination occurred in very low conversion (10%) and poor diastereoselectivity (eq 1). Other amines were also investigated with similar difficulties in effecting reductive amination. We concluded that the low reactivity of the ketone could be attributed to the steric environment around the reacting center.[11]



(1)

Although the one-step reductive amination procedure was unsuccessful, the two-step approach (oxime formation, reduction) was considered a reasonable alternative. The methyl oxime **8** was formed in good yield (88%, eq 2); however, conditions for the reduction of **8** to the amine were not anemable to the functionality present in the side chain. Hydrogenation conditions selectively reduced the alkyne before the oxime, and hydride reagents ($LiAlH_4$, DiBAL-H) reduced the ester first. Milder conditions (Zn/TFA,[12] $MoO_3/NaBH_4$[13]) afforded no reaction.



(2)

Whereas **8** was chemically inert to $MoO_3/NaBH_4$, oxime **9** was reduced to the amine under these conditions in

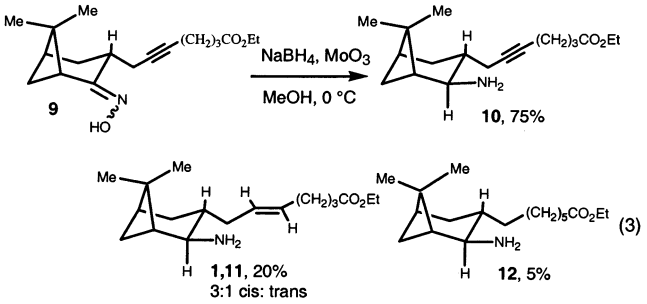
(7) Other additives (HMPA, TMEDA) were also investigated but none were as effective as DMPU. Alkylation is complete within 1.5 h at −45 °C. Lower temperatures afforded sluggish reactions.

(8) When the reaction was quenched by direct addition of aqueous acid, some epimerization to the thermodynamically favored product was always observed. In contrast, the reaction can be quenched by direct addition of trifluoroacetic acid (TFA) to the reaction solution at −45 °C or by reverse quench of the reaction solution at −45 °C into a 1:1 mixture of MTBE:satd $NH_4Cl_{(aq)}$ with no epimerization.

(9) Prepared according to the method of Corey and Sachdev: Corey, E. J.; Sachdev, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 8483−8484.

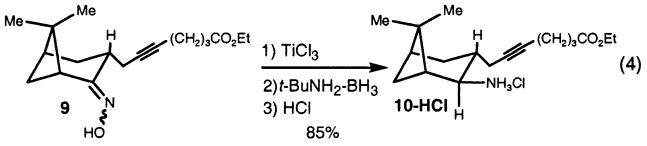
(10) Campos, K.; Lee, S.; Journet, M.; Kowal, J.; Cai, D.; Larsen, R.; Reider, P. *Tetrahedron Lett.* **2002**, *43*, 6957−6959.

less than 1 h (eq 3). Additionally, partial reduction of the alkyne was also observed (25%, 3:1:1 cis:trans:alkane). The lability of **9** provided the necessary reactivity that was required to successfully reduce the oxime in a chemoselective fashion.



(3)

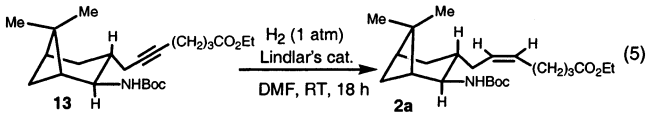
It is well-documented that $TiCl_3$ is an excellent reagent for the mild reduction of N−O bonds.[14] This reagent has been used in conjuction with a mild reducing agent to effect the reduction of oximes to amines in a one-pot procedure.[14,15] Treatment of substrate **9** under typical conditions ($NaBH_3CN$, $TiCl_3$, MeOH) afforded complete conversion to the aminoalkyne product **10** with good diastereoselectivity (98:2) and, as expected, no reduction of the alkyne. Due to the safety concerns and costliness of handling a cyanide-containing waste stream on large scale, we sought an alternative reducing agent to $NaBH_3CN$.[16] When $NaBH(OAc)_3$ was substituted for $NaBH_3CN$ as the reducing agent, only reduction of the N−O bond was observed, delivering the imine; however, using *t*-$BuNH_2$-BH_3 instead of $NaBH_3CN$ cleanly produced aminoalkyne **10**, which was then isolated by crystallization as the HCl salt in 85% overall yield.



(4)

Hydrogenation. On the basis of literature precedent, the partial hydrogenation of the aminoalkyne was performed with Lindlar's catalyst.[17] The starting material was completely consumed in less than 1 h with low catalyst loadings (10 wt %); however, analysis of the reaction mixture showed a significant amount of both the trans isomer **11** (8.5%) and the fully reduced product **12** (14%). Lower catalyst loadings (6 wt %) did slow the rate of hydrogenation; however, the amount of alkane was still at an unacceptably high level (6%) by the time that the starting material had been completely consumed. Since the rejection of **12** was very difficult in the purification of the final drug, we sought a process for the well-controlled hydrogenation of aminoalkyne **10**.

Reduction of the alkene intermediates could be overcome via protection of the primary amine moiety with a carbonyl-containing protecting group. The Boc-protected amine **13** could be reduced with Lindlar's catalyst in acetone by using low catalyst loading (6 wt %) to produce the desired *N*-protected aminoalkene **2a** with only 0.5% of the alkane impurity. This result suggested that the unprotected amine functionality was playing a role in the overreduction pathway.[18]



(5)

Closer investigation of the hydrogenation of **10** at lower catalyst loadings (4 wt %) revealed that overreduction was only significant after the alkyne was completely consumed.[19] Although it is theoretically possible to stop the hydrogenation at a point where **10** is consumed and **12** has not been formed in appreciable amounts, this solution is irreproducible, unreliable, and poorly controlled. A more reliable solution to the problem was to attempt to control overreduction through the use of an additive.

The fact that the rate of reduction of **1** only becomes significant after complete consumption of **10** suggests that the preassociation of the catalyst surface is stronger to **10** than to **1**.[20] One might expect, based on this model, that the most suitable additive to attenuate the reactivity of **1** would be a bidentate ligand to compete for catalyst surface association. As expected, monodentate amines such as pyridine or quinoline were ineffective at preventing overreduction (Table 3);[21] however, a number of bidentate amines were highly effective, reducing the amount of **12** to ≤0.7%.[22] Of the diamines investigated,

(11) For an excellent review of reductive amination of a variety of ketones see: Abdel-Magid, A.; Carson, K.; Harris, B.; Maryanoff, C. A.; Shah. R. *J. Org. Chem.* **1996**, *61*, 3849−3862.

(12) Scolastico, C.; Conca, E.; Prati, L.; Guanti, G.; Banfi, L.; Berti, A.; Farina, P.; Valcavi, U. *Synthesis* **1985**, 850−855.

(13) Ipaktschi, J. *Chem. Ber.* **1984**, *117*, 856−858.

(14) Hoffman, C.; Tanke, R. S.; Miller, M. J. *J. Org. Chem.* **1989**, *54*, 3750−3751 and references cited therein.

(15) Leeds, J. P.; Kirst, H. A. *Synth. Commun.* **1988**, *18*, 777−782.

(16) Additional safety concerns were raised regarding the potential hazard of using $NaBH_3CN$ under acidic conditions on large scale ($TiCl_3$ comes as a 20% solution in aqueous HCl).

(17) Lindlar, H.; Dubuis, R. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, pp 880−883.

(18) Significant overreduction has been observed with other substrates containing unprotected amines. (a) Lindel, T.; Hochguertel, M. *Tetrahedron Lett.* **1998**, *39*, 2541−2544. (b) Sagi, G.; Oetvoes, L.; Ikeda, S.; Andrei, G.; Snoeck, R.; De Clerq, E. *J. Med. Chem.* **1994**, *37*, 1307−1311. (c) Merino, P.; Castillo, E.; Franco, S.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1759−1769. (d) Cliff, M. D.; Pyne, S. G. *J. Org. Chem.* **1997**, *62*, 1023−1032.

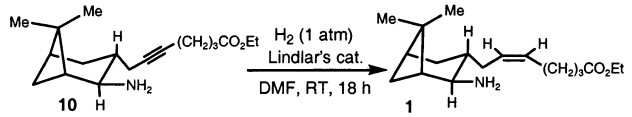
(19) With only 4 wt % catalyst, the hydrogenation was complete in less than 2 h. At the end of the reaction, the ratio of **4b**:**4c**:**4d** was 94:4:2; however, by the time that the ratio had been determined by HPLC (25 min), the ratio had already changed to 91:5:4.

(20) The preassociation of an amine to a catalyst surface (Pd/C) has been previously reported to account for surprising selectivities in olefin hydrogenations. See: Thompson, H. W.; Wong, J. K. *J. Org. Chem.* **1985**, *50*, 4270−4276. This is in accord with the relative coordination strength of an alkyne to palladium versus that of an olefin. Typically, the metal−carbon bonds in alkyne complexes are 0.1 Å shorter than those with their olefin counterparts. (a) Redhouse, A. D. In *The Chemistry of the Metal−Carbon Bond*; Hartley, F. R., Patai, S., Eds.; John Wiley and Sons: New York, 1982; Vol. 1, Chapter 1, pp 18−20. (b) Davies, J. A. In *Comprehensive Organometallic Chemistry*; Puddephatt, R. J., Ed.; Pergamon Press: New York, 1986; Vol. 9, Chapter 6, pp 293−320.

(21) Diphenylphosphinoethane was used as a catalyst poison as well (0.1 mol %); however, this was too effective a poison, affording no hydrogenation over 24 h.

(22) The hydrogenations were complete in 2−3 h; however, to test the robustness of the process, the reactions were allowed to stir for 18 h with no increase in the amount of the aminoalkane impurity. The catalyst level could be increased up to 10 wt % with very little change in the amount of overreduction observed (4 wt % 0.7% alkane; 10 wt % 0.9% alkane).

TABLE 3. Semihydrogenation of Aminoalkyne 10 with Amine Additives[a]



entry	additive	**1**:**11**:**12**[c]
1	pyridine	70:20:10
2	quinoline	80:13:7
3	ethylenediamine	97.6:2.0:0.4
4	propylenediamine	96.7:2.5:0.8
5	1,10-phenanthroline	97.0:2.5:0.5
6	diethylenetriamine	97.3:2.3:0.4

[a] All reactions were carried out in DMF (0.5 M in substrate) at rt. [b] Ratio of products determined by HPLC analysis.

ethylenediamine (EDA) afforded the least overreduction and *Z*/*E* isomerization, providing the desired cis aminoalkene **1** in >97% yield with only 2% isomerization to the trans isomer **11** and 0.4% overreduction to **12**.[23] This methodology was demonstrated to be effective for a variety of aminoalkynes of varying tether length between the amine and alkyne functionalities.[24]

For ease of handling, **1** was readily crystallized from pure heptane as the HCl salt to afford material that is >98 area % pure by HPLC. We were delighted to find that the enantiomeric excess of the crystallized material had been upgraded from 92% (technical grade β-pinene) to 99%. This intermediate can be readily coupled with a variety of sulfonylating and acylating agents to form the family of PGD_2 receptor antagonists **2** in good yield and high enantiomeric excess.

Summary

In conclusion, a highly convergent synthesis of **1** has been described that has significant advantages over previous routes with respect to ease of scale-up and convergence, allowing for the production of a variety amide derivatives from the same common intermediate. These studies have also resulted in the development of methodology for a highly diastereoselective alkylation of (+)-nopinone, a mild, chemo- and stereoselective reduction of an oxime, and a well-controlled semihydrogenation of aminoalkynes.

Experimental Section

NMR spectra (^{1}H, ^{13}C) were recorded with $CDCl_3$ as solvent. The reactions and products were assayed by HPLC with water and acetonitrile as eluting solvents. Diisopropylamine, ethylenediamine, and all solvents were used without further purification. Titanium trichloride was used as a 20% solution in 3% aqueous HCl. Hydrogenations were run in a pressurized vessel, degassed by vacuum, and then purged with hydrogen.

Ethyl 7-[(1*R*,3*R*,5*S*)-6,6-Dimethyl-2-oxobicyclo[3.1.1]-hept-3-yl]hept-5-ynoate (6c). A 50-L round-bottom flask was charged with dry THF (12 L) and diisopropylamine (2.23 L, 15.9 mol) and cooled to −30 °C. *n*-Butyllithium (2.4 M/Hex, 6.34 L, 15.2 mol) was added over 45 min while maintaining the temperature below −10 °C. The solution was aged for 10 min and (1*R*)-(+)-nopinone (2.00 kg, 92% optically pure, 14.5 mol, neat) was added over 45 min while keeping the temperature below −10 °C. After complete addition, the solution was aged for 30 min and cooled to −50 °C. The iodo-ester sidechain **5c** (4.25 kg assay, 15.2 mol) was added over 1.5 h while keeping the temperature between −48 and −45 °C. Upon complete addition, the reaction mixture was aged for 1.5 h at −45 °C. Trifluoroacetic acid (1.68 L, 21.7 mol) was then added over 1 h maintaining the temperature below −45 °C. The reaction mixture was then allowed to warm to −10 °C and transferred into a mixture of ethyl acetate (20.0 L) and 3% aqueous L-tartaric acid (20.0 L). The layers were separated and the organic was washed with water (2 × 20.0 L). The organic layer was concentrated to an orange oil that was used directly in the next step. Assay yield = 3.90 kg (92%). A sample of **6c** was purified by flash chromatography (90:10 hexane: ethyl acetate) to afford an analytically pure sample. [α_D^{23}] +62.7 (*c* 0.10, 92% ee, CCl_4); IR (film) 2976, 2938, 2872, 1734, 1710, 1456−997 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 4.12 (q, 2H, J = 7.2 Hz), 2.65−2.49 (m, 5H), 2.39 (t, 2H, J = 7.8 Hz), 2.28−2.17 (m, 4H), 1.98−1.93 (m, 1H), 1.78 (quint, 2H, J = 7.3 Hz), 1.58 (d, 1H, J = 9.6 Hz), 1.33 (s, 3H), 1.25 (s, 3H), 0.91 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.1, 18.1, 22.0, 24.0, 24.3, 25.7, 28.1, 33.0, 40.3, 40.9, 42.4, 58.0, 60.2, 78.6, 80.6, 173.1, 213.6; TLC R_f 0.35 (80% hexane, 20% EtOAc); separation of diastereomers was accomplished by HPLC analysis (Waters Symmetry C_{18}, 0.1% $HClO_4$:MeCN, 20:80) to show a diastereomeric ratio of 99:1 (**6c**:**7c**). Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02. Found: C, 74.27; H, 8.62.

Ethyl 7-[(1*R*,2*E*,*Z*,3*R*,5*S*)-2-(Hydroxyimino)-6,6-dimethylbicyclo[3.1.1]hept-3-yl]hept-5-ynoate (9). A 50-L round-bottom flask was charged with **6c** (3.90 kg assay, 13.4 mol), ethanol (13.0 L), and water (6.4 L). Sodium acetate trihydrate (3.63 kg, 26.7 mol) was added followed by hydroxylamine hydrochloride (1.86 kg, 26.7 mol). The reaction mixture was then heated to 50 °C (homogeneous) for 5 h. (**Note**: It is well-known that hydroxylamine hydrochloride should be stored away from any heat source due to the significant differential scanning calorimetry (DSC) exotherm at ~100 °C. Operational Hazards Evaluation of the oxime formation showed that a reaction temperature of 50 °C was suitable for the preparation of the oxime on multikilogram scale.) The reaction was cooled to room temperature and pumped into toluene (20.0 L) and water (20.0 L). The layers were separated and the organic layer was washed with water (2 × 20.0 L). The organic layer was then concentrated to an orange oil comprised of a mixture of *E*,*Z* isomers of the oxime that was used directly in the next step. Assay yield 3.67 kg (90%). IR (film) 3241(br), 2933(br), 2871, 1734, 1653, 1457, 1371, 1159, 1028, 948 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 4.14 (q, 2H, J = 7.1 Hz), 2.59−2.55 (m, 1H), 2.49−2.38 (m, 5H), 2.28−2.20 (m, 4H), 2.15−2.06 (m, 2H), 2.01−1.94 (m, 1H), 1.89−1.77 (m, 2H), 1.51 (d, 1H, J = 10.4 Hz, major isomer), 1.39 (d, 1H, J = 1.6 Hz, minor isomer), 1.34 (s, 3H, minor isomer), 1.28 (s, 3H, major isomer), 1.26 (t, 6H, J = 7.0 Hz), 0.85 (s, 3H, minor isomer), 0.77 (s, 3H, major isomer); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.1, 18.2, 21.5, 24.1, 24.9, 25.4, 25.6, 28.6, 30.8, 33.1, 40.8, 41.6, 48.2, 60.2, 79.4, 80.0, 165.4, 173.2; TLC (85% petroleum ether, 15% EtOAc); $R_{f(\text{major})}$ 0.27; $R_{f(\text{minor})}$ 0.20; separation of *E* and *Z* isomers was accomplished by HPLC analysis (Waters Symmetry C_{18}, 0.1% $HClO_4$:MeCN, 20:80) to show a 58:42 mixture of isomers. Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59. Found: C, 70.63; H, 8.97; N, 4.71.

Ethyl 7-[(1*R*,2*R*,3*R*,5*S*)-2-Amino-6,6-dimethylbicyclo-[3.1.1]hept-3-yl]hept-5-ynoate HCl Salt (10-HCl). To a solution of aqueous $TiCl_3$ (32 L, 20% in 3% HCl, 44.8 mol) at 25 °C was added sodium acetate (17.4 kg, 44.8 mol) with stirring until complete dissolution was achieved. The solution was cooled to 0 °C, and oxime **9** (3.90 kg, 12.8 mol) was added as a solution in 32 L of ethanol while maintaining a temper-

(23) Ethylenediamine has been reported to be a catalyst poison for other Pd catalysts. (a) Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron Lett.* **2000**, *41*, 5711−5714. (b) Enders, D.; Schankat, J. *Helv. Chim. Acta* **1995**, *78*, 970−992. (c) Savoia, D.; Trombini, C.; Umani-Ronchi, A.; Verardo, G. *J. Chem. Soc., Chem. Commun.* **1981**, 540−541.

(24) Campos, K. R.; Cai, D.; Journet, M.; Kowal, J. J.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2001**, *66*, 3634−3635.

ature of 0 °C. After the mixture was stirred for 1 h at 0 °C, borane *tert*-butylamine complex (2.23 kg. 25.6 mol) was charged over 10 min, keeping the temperature below 10 °C. The resulting solution was aged for 30 min, and then diluted with 64 L of ethyl acetate. The layers were separated, and the organic layer was washed with saturated ammonium chloride (32 L). The organic layer was neutralized with 1 M Na_2CO_3 until the pH of the aqueous solution was around 8. The organic layer was washed once more with water and then concentrated,the solvent was switched to isopropyl acetate (13 L), and the mixture was azeotropically dried. The resulting solution of free base in isopropyl acetate was treated with HCl in diethyl ether (2.0 M, 7.70 L) and aged for 30 min. The reaction mixture was concentrated to remove ether and any excess HCl, and the reaction volume was adjusted to 20 L with additional isopropyl acetate. The reaction mixture was seeded with the desired product followed by an addition of *n*-heptane (20 L) over 1 h. After thge solution was stirred for 1 h, the slurry was filtered, and the cake was washed with a 1:1 mixture of isopropyl acetate and *n*-heptane (6 L). The cake was dried to afford **10-HCl** as a crystalline solid (4.59 kg, 3.90 kg assay, 85% isolated yield). Mp 137.5−138.5 °C; $[\alpha_D^{23}]$ +44.7 (*c* 0.01, CCl_4); IR (film) 2906 (br), 2877(br), 1734, 1602, 1505, 1376, 1151 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 4.14 (q, 2H, J = 7.1 Hz), 3.60−3.53 (m, 1H), 2.71−2.62 (m, 1H), 2.51−2.35 (m, 5H), 2.28−2.21 (m, 4H), 1.99−1.96 (m, 1H), 1.81 (quint, 2H, J = 7.2 Hz), 1.50 (m, 1H), 1.29 (s, 3H), 1.27 (t, 3H, J = 7.2 Hz), 1.23 (s, 3H), 1.09 (br d, 1H, J = 9.6 Hz); ^{13}C NMR **(**400 MHz, $CDCl_3$) δ 14.1, 18.2, 22.9, 24.1, 25.9, 26.8, 30.0, 31.4, 33.2, 37.5, 40.6, 44.6, 57.4, 60.2, 76.6, 78.1, 81.2, 173.1; separation of diastereomers was accomplished by HPLC analysis (Supelcosil ABZ Plus, 0.1% $HClO_4$:MeCN, 20:80) to show a diastereomeric excess of 94%. Anal. Calcd for $C_{18}H_{30}ClNO_2$: C, 65.93; H, 9.22; N, 4.27. Found: C, 65.94; H, 9.14; N, 4.26.

Ethyl (5*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-2-Amino-6,6-dimethylbicyclo[3.1.1]hept-3-yl]hept-5-enoate HCl Salt (1-HCl). To an extractor containing isopropyl acetate (18 L) and the aminoalkyne HCl salt **10-HCl** (4.59 kg, 3.90 kg assay, 11.9 mol) was added Na_2CO_3 (1 M, 14 L). The mixture was stirred for 1 h, then the phases were separated. The organic layer was washed with Na_2CO_3 (1 M, 6.9 L), then with H_2O (14 L). The organic layer was concentrated to yield **10** as an oil (3.43 kg assay by HPLC, 98%). The crude material was diluted with DMF (9.4 L) followed by ethylenediamine (0.480 L, 7.19 mol), and then Lindlar's catalyst (5 wt % Pd on $CaCO_3$ poisoned with lead, 65 g). The reaction was subjected to hydrogen atmosphere (40 psi) for 6 h. The mixture was filtered over solka floc, and the filter bed was washed with 70:30 *n*-heptane:ethyl acetate (5 L). The filtrate was diluted with 70:30 *n*-heptane:ethyl acetate (20 L), washed once with 1.7% $NH_4Cl_{(aq)}$ (35 L), and washed twice with water (26 L). The organic solution was distilled at constant volume (∼20 L) with pure *n*-heptane until the Kf of the solution was <500 μg/mL. The reaction mixture was cooled to 0 °C, and HCl in Et_2O (2.2 M, 6.4 L) was added. Upon complete addition, the reaction was allowed to warm to RT and aged for 10 min. The mixture was distilled at constant volume (∼35 L) with pure *n*-heptane to remove excess diethyl ether and HCl. During the distillation, the HCl salt begins to precipitate. The mixture was heated to 60 °C or until complete dissolution of solid, and then allowed to cool to rt. After being stirred for 4 h, the resulting slurry was filtered to yield **1-HCl** as a crystalline solid (3.52 g, 3.46 kg assay, 94% isolated yield). Mp 90.9−91.8 °C; $[\alpha_D^{23}]$ +31.5 (*c* 0.012, CCl_4); IR (film) 2994−2869, 1730, 1598, 1509 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 5.53−5.43 (m, 2H), 4.12 (q, 2H, J = 7.2 Hz), 3.37 (m, 1H), 2.54−2.48 (m, 1H), 2.41−2.38 (m, 2H), 2.31 (t, 2H, J = 7.8 Hz), 2.25−2.12 (m, 4H), 1.70 (quint, 2H, J = 7.4 Hz), 1.50 (m, 1H), 1.26 (s, 3H), 1.25 (t, 3H, J = 7.2 Hz), 1.22 (s, 3H), 0.84 (br d, 1H, J = 9.2 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) 14.2, 23.0, 24.8, 26.7, 26.8, 30.6, 32.2, 33.7, 34.2, 36.4, 37.4, 40.8, 44.9, 58.6, 60.1, 127.2, 131.5, 172.5; separation of diastereomers was accomplished by GC analysis HP-35 (cross-linked 35% PhME Siloxane) to show a purity of 98.8% (0.5% **11**, 0.2% **12**). Anal. Calcd for $C_{18}H_{32}ClNO_2$: C, 65.53; H, 9.78; N, 4.25. Found: C, 65.57; H, 9.64; N, 4.20.

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