Highly Regio- and Enantioselective Catalytic Hydrogenation of Enamides in Conjugated Diene Systems: Synthesis and Application of γ,δ-Unsaturated Amino Acids

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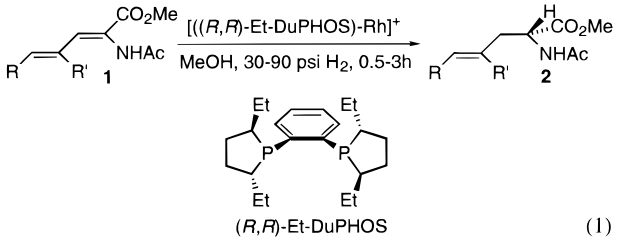
Abstract: An extremely efficient method has been found for the catalytic asymmetric hydrogenation of conjugated α,γ-dienamide esters using the Et-DuPHOS-Rh catalyst system. α,γ-Dienamide ester substrates were prepared via the Suzuki cross-coupling reaction and the Horner−Emmons olefination. Full conversion to the corresponding γ,δ-unsaturated amino acids with very high regio- and enantioselectivity was achieved after short reaction times. This new methodology was applied to the synthesis of the natural product bulgecinine from a prochiral dienamide ester.

Unsaturated amino acids are an important class of natural products that display an array of interesting biological properties.[1] Specifically, γ,δ-unsaturated amino acids not only have been synthetically challenging targets[2] but also have been isolated from a variety of natural sources[3] and have served as intermediates in the synthesis of complex amino acids and peptides.[4]

We recently have shown that Rh complexes bearing DuPHOS and BPE ligands are extremely effective catalysts in enantioselective hydrogenation of a variety of prochiral unsaturated substrates including enamide esters.[5] In work with enamido olefins it was demonstrated that an enamide double bond could be hydrogenated with complete regioselectivity over distal C=C double bonds.[5a] The enhanced reactivity of the enamide double bond has been attributed to the ability of this group to chelate to the catalyst metal center; this property is also believed to be critical for attainment of high enantioselectivity in rhodium-catalyzed hydrogenation reactions.[6] To the best of our knowledge no attempts have been made to reduce conjugated enamido esters. We now have developed a procedure that takes advantage of this feature and herein describe the hydrogenation of α,γ-dienamide esters to afford γ,δ-unsaturated amino acids with both high regioselectivity and high enantioselectivity. A demonstration of the use of this catalytic asymmetric method in the synthesis of the natural product (+)-bulgecinine is also included.



(1)

Results and Discussion

Substrate Preparation. Parallel synthetic routes were developed for the preparation of the α,γ-dienamide ester substrates **1**. Suzuki cross-coupling (route A) of (*Z*)-methyl 2-acetamido-3-bromoacrylate[7] (**3**) with a variety of vinyl boronic

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(1) (a) Shimohigashi, Y; English, M. L.; Stammer, C. H.; Costa, T. *Biochem. Biophys. Res. Commun.* **1982**, *104*, 583−590. (b) Jung, G. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1051. (c) Freud, S.; Jung, G.; Gutbrod, O.; Folkers, G.; Gibbons, W. A.; Allgaier, H.; Werner, R. *Biopolymers* **1991**, *31*, 803. (d) Jain, R.; Chauhan, V. S. *Biopolymers* **1996**, *40*, 105.

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(3) (a) Drinkwater, D. J.; Smith, P. W. G. *J. Chem. Soc. (C)* **1971**, 1305. (b) Letham, D. S.; Young, H. *Phytochemistry* **1971**, *10*, 23. (c) Davis, A. L.; Cavitt, M. B.; McCord, T. J.; Vickrey, P. E.; Shive, W. *J. Am. Chem. Soc.* **1973**, *95*, 6800. (d) Gellert, E.; Halpern, B.; Rudzats, R. *Phytochemistry* **1978**, *17*, 802. (e) Cramer, U.; Rehfeldt, A. G.; Spener, F. *Biochemistry* **1980**, *19*, 3074. (f) Baldwin, J. E.; Adlington, R. M.; Basak, A. *J. Chem. Soc., Chem. Commun.* **1984**, 1284. (g) Tsubotani, S.; Funabashi, Y.; Takamoto, M.; Hakoda, S.; Harada, S. *Tetrahedron* **1991**, *47*, 8079.

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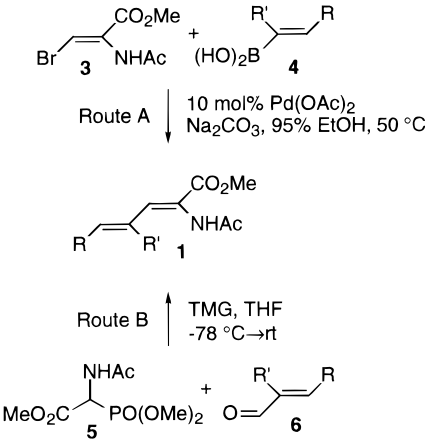
Scheme 1

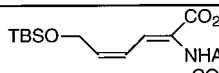
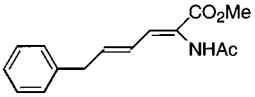
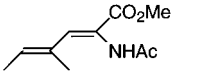
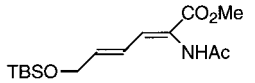
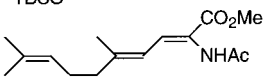
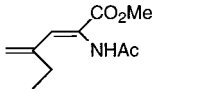
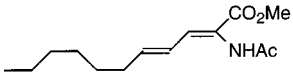
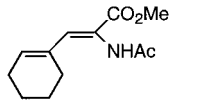
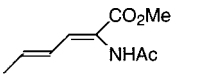
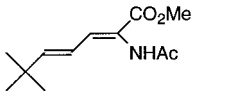
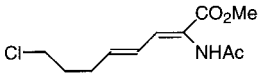
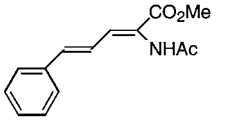


acids **4** furnished dienamide esters in good yields (Scheme 1).[8] The mild reaction conditions (10 mol % $Pd(OAc)_2$, Na_2CO_3, 95% EtOH at 50 °C) not only left the ester intact but also gave the cross-coupling product with complete retention of configuration about both C=C double bonds. Two limitations of this route were evident. The production of the boronic acids via Brown's hydroboration of alkynes limited us to *trans*-terminal (R′ = H) and symmetrically (R′ = R) substituted vinyl boronic acids.[9] Also, due to functional group incompatibilities, some substituted boronic acids were not accessible.

Horner−Emmons olefination[10] (route B) served as an alternative to the cross-coupling. The olefination reaction between phosphonate **5** and a series of unsaturated aldehydes **6** proceeded in THF at −78 °C → rt with tetramethylguanidine to give (*Z*)-dienamide esters in fair yields.[11] A greater diversity of functionalized dienamide esters could be made in this manner, but yields were generally lower when compared to the cross-couplings, especially in the preparation of γ-substituted enamido olefins (R′ ≠ H) such as **1f**,**h**. Overall the two methods for the preparation of the α,γ-dienamide esters were complementary and provided ready access to a variety of amino acid precursors. The results of both methods are summarized in Table 1.[12]

Hydrogenation Optimization Trials. The effects of ligand substitution, solvent, and pressure were investigated for the hydrogenation of dienamide **1d**. The achievement of high enantioselectivity is of obvious concern, but here, regioselectivity is also very important. The asymmetric hydrogenation of dienamide **1d** was initially examined under a standard set of reaction conditions (catalyst precursor = [(COD)Rh-DuPHOS]-OTf; S/C = 500; 90 psi initial pressure of H_2; MeOH; 25 °C; 2 h reaction time). The *i*-Pr-DuPHOS-Rh catalyst gave only moderate enantioselectivity (87.8% ee) and demonstrated little regioselectivity by reducing both double bonds. Upon moving to the less sterically congested Et- and Me-DuPHOS-Rh catalysts, the enantiomeric excesses increased significantly to >99% ee[13] and 97.9% ee, respectively. Matching the sterics of the ligand to that of the substrate also had a profound effect upon the regioselectivity of the hydrogenation. In the optimum case with Et-DuPHOS-Rh, the amount of overreduction product (i.e., the product of the reduction of both the enamide double bond and the γ,δ double bond) dropped to <0.5%.

Table 1. Results of the Preparation of **1** by the Suzuki Cross-Coupling Reactions

Entry	Product		% Yield (Method)[a]
1		(**1a**)	70 (B)
2		(**1b**)	94 (A)
3		(**1c**)	77 (A)
4		(**1d**)	68 (B)
5		(**1e**)	77 (B)
6		(**1f**)	18 (B)
7		(**1g**)	88 (A)
8		(**1h**)	17 (B)
9		(**1i**)	70 (B)
10		(**1j**)	72 (A)
11		(**1k**)	50 (A)
12		(**1l**)	55 (A)

[a] Method A: Pd(0)-catalyzed Suzuki cross-coupling between the bromoenamide **3** and the boronic acid **4**; method B: Horner−Emmons olefination with phosphonate **5** and unsaturated aldehyde **6**. For specific conditions, please see the Experimental Section.

Other common hydrogenation catalysts derived from BINAP, DIPAMP, BDPP, CHIROPHOS, DIOP, and PROPHOS[14] were found to be inferior to Et-DuPHOS-Rh, particularly in terms of regioselectivity, a challenge unique to these conjugated dienamide ester substrates. The results of the hydrogenation of **1i** to **2i** with different catalysts is shown in Table 2. Good enantioselectivity (90% ee) was obtained with [(COD)Rh(*R*,*R*)-DIPAMP]BF_4 (entry 4); however, a significant amount of

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(10) For a review see Maercker, A. *Org. React.* **1965**, *14*, 335−344.

(11) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 53.

(12) Configurations of all the starting materials and products of the coupling reactions were proven by NMR including NOE and NOESY experiments.

(13) Minor enantiomer not detected by GC analysis.

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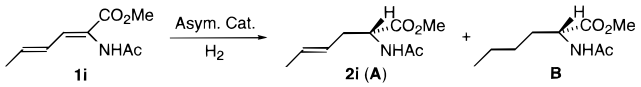
Table 2. Hydrogenation of **1i** to **2i** Using Different Catalysts[a]



1i 2i (A) B

entry	catalyst precursor	S/C	time (h)	convn (%)	% ee **A** (config.)	**A**:**B**[d]
1	[(COD)Rh(*S*,*S*)-Et-DuPHOS]SbF_6	500:1	2	100[b]	99.2 (*S*)	200:1
2	[(COD)Rh(*R*,*R*)-Me-DuPHOS]OTf	500:1	0.5	99	97 (*R*)	25:1
3	$RuBr_2$(*S*)-BINAP	1000:1	1	55	83 (*S*)	5:1
4	[(COD)Rh(*R*,*R*)-DIPAMP]BF_4	500:1	2	43	90 (*S*)	2:1
5	[(COD)Rh(*R*,*R*)-BDPP]OTf	1000:1	0.5	47	23 (*S*)	11:1
6	[(COD)Rh(*S*,*S*)-CHIRAPHOS]OTf	500:1	12	15	10 (*S*)	7:1
7	RhCl(*R*,*R*)-DIOP[c]	500:1	0.25	95	58 (*R*)	15:1
8	[(COD)Rh(*R*)-PROPHOS]OTf[c]	500:1	1	11	59 (*S*)	2:1
9	[(COD)Rh(*S*)-BINAP]OTf[c]	500:1	1	35	1 (*S*)	6:1

[a] All reactions performed in MeOH with an initial pressure of 90 psi of H_2. Analysis by chiral capillary GC on a Chrompak Chirasil-L-Val column followed passage through a short plug of silica. [b] Starting material could not be detected by GC analysis. [c] Catalyst precursor prepared in situ. [d] Enantiomeric purity of the overreduced material was not determined.

overreduced material (**B**) was produced after only 43% of the starting material had been consumed. By contrast, RhCl(*R*,*R*)-DIOP (entry 7) showed poor enantioselectivity (58%) but allowed less overreduction. Very high enantioselectivities were achieved with both the Me-DuPHOS-Rh and Et-DuPHOS-Rh catalysts after short reaction times (entries 2 and 1). With Me-DuPHOS, overreduction began to increase as the reaction approached completion. The superior regioselectivity of Et-DuPHOS was evidenced by negligible overreduced products even after the standard reaction time of 2 h (used to ensure complete conversion of starting material). Subtle forces are uniquely balanced during catalysis by Et-DuPHOS-Rh which combines high enantioselectivity and high regioselectivity in a remarkably efficient and useful reaction.

Hydrogenation of the enamido olefins was found to be sensitive to solvent. Low conversions of starting material were found in the Me-DuPHOS-Rh-catalyzed hydrogenations of **1d** in the following solvents (90 psi initial pressure of H_2; S/C = 500; 3 h reaction time): CH_3CN (5.8% conversion), hexane (5.6% conversion), toluene (8.1% conversion), and THF (54.2% conversion). In *i*-PrOH, excellent conversion and stereochemical induction (96.3% ee) were found; however, a significant amount of overreduction product was formed (28.4%). High conversions and enantioselectivities were achieved in MeOH (98.6% conversion, 97.9% ee) and C_6H_6 (98.8% conversion, 95.6% ee), while the overreduction material amounted to <0.5% for this substrate. Higher enantioselectivity combined with better substrate solubility made MeOH the solvent of choice.

Pressure variations were studied for the hydrogenation of **1i**, but little effect on reaction times or enantioselectivities was found. Using the Et-DuPHOS-Rh catalyst in MeOH, enantioselectivities varied by <0.5% ee over the pressure range 15−90 psi. However, for some substrates, regioselectivity could be improved at lower pressures because the rate of the overreduction reaction decreased while the desired α,β hydrogenation was not significantly affected.

High reaction rates and high selectivity observed in this work is believed to be due to chelation of the metal center by the enamide group of the substrate.[6] Carbamates would be more synthetically useful than the acetamides **1**, but neither the *N*-Boc nor *N*-CBZ derivatives of **1d** or **1i** were hydrogenated under the conditions described here. Similar results were observed with β,β-disubstituted carbamidoacrylates, where the reduced reactivity again was rationalized by the attenuated ability of the carbamoyl group to coordinate to the rhodium center.[5c,15]

Hydrogenation Results. The results of the asymmetric catalytic hydrogenations of several enamido olefins are shown in Table 3. Under our standard reaction conditions, we used the Et-DuPHOS-Rh catalyst at S/C = 500, initial pressures ranged from 30 to 90 psi of H_2, and 0.5−3 h was required to give full conversion of the substrate. In all cases, less than 2% overreduction was detected and the products were isolated in better than 95% yield. Enantiomeric excesses were determined by chiral capillary GC.[16] All substrates were reduced racemically[17] and intentionally overreduced for comparison to the asymmetric reductions. In most cases separate hydrogenations were run to prepare both enantiomeric products. Representative gas chromatograms are shown in Figure 1.

In application of this methodology to specific substrates several interesting observations were made. The amount of overreduction product varied but could be minimized by careful control of the S/C ratio, reaction time, and to a lesser degree initial hydrogen pressure. In all cases, hydrogenation of the enamide double bond preceded reduction of the distal double bond.[18] It was found that the distal double bond of trisubstituted γ,δ-olefins (compounds **1c**,**e**,**h**) did not undergo appreciable reduction even under forcing conditions (24 h reaction time and 90 psi initial pressure). By contrast overreduction was most facile and difficult to control in the hydrogenation of **1l**. Hydrogenation products **2c** and **2i** are examples of natural products isolated from the seed of *Aesculus californica*[19] and from steroid metabolism by *Pseudomonas testosteroni*,[20] respectively. Either the *R* or *S* products could be prepared using the catalyst of appropriate stereochemistry (entry 9).

(15) Burk, M. J.; Gross, M. F.; Martinez, J. P.; Straub, J. A. Unpublished results.

(16) A 25 m Chrompack Chirasil-L-Val column was used for determinations of enantiomeric excesses.

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(18) As the distal double bond of **2** was reduced, the enantiomeric excess of the monoreduced material (**2**) decreased showing moderate reverse substrate selectivity for the overreduction reaction (i.e., the major enantiomer of **2** was preferentially reduced causing the % ee of the monoreduced material to decrease). When the overreduction reaction was allowed to go to completion, the % ee of the resulting fully reduced material was identical with the initial % ee of **2**.

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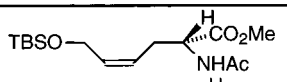
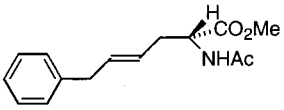
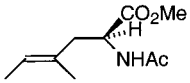
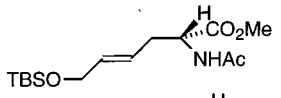
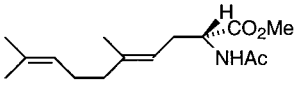
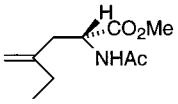
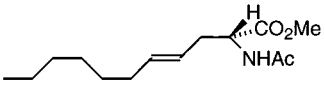
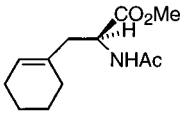
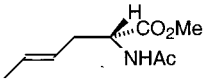
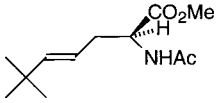
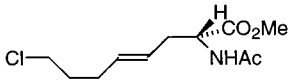
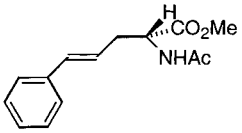
Table 3. Rh-Catalyzed Enantioselective Hydrogenation of α,β,γ,δ-Unsaturated Amino Acids[a]

Entry	Ligand	Product		% ee (Config.)[b]
1	(*R*,*R*)-Et-DuPHOS		(**2a**)	99.3 (*R*)
2	(*R*,*R*)-Et-DuPHOS		(**2b**)	98.2 (*R*)
3	(*S*,*S*)-Et-DuPHOS		(**2c**)	99.5 (*S*)
4	(*R*,*R*)-Et-DuPHOS		(**2d**)	>99[c] (*R*)
5	(*R*,*R*)-Et-DuPHOS		(**2e**)	>99[c] (*R*)
6	(*R*,*R*)-Et-DuPHOS		(**2f**)	97.8 (*R*)
7	(*R*,*R*)-Et-DuPHOS		(**2g**)	86.4 (*R*)
8	(*S*,*S*)-Et-DuPHOS		(**2h**)	99.5 (*S*)
9	(*R*,*R*)-Et-DuPHOS		(**2i**)	99.3 (*R*)
	(*S*,*S*)-Et-DuPHOS			99.2 (*S*)
10	(*S*,*S*)-Et-DuPHOS		(**2j**)	99.4 (*S*)
11	(*R*,*R*)-Et-DuPHOS		(**2k**)	98.9 (*R*)
12	(*R*,*R*)-Et-DuPHOS		(**2l**)	98.6 (*R*)

[a] Using S/C = 500, initial pressures from 30 to 90 psi, and 0.5−3 h reaction times in MeOH, less than 2% overreduction at 100% conversion was observed in all cases. For specific conditions, please see the Experimental Section. [b] Absolute configurations were assigned by comparing the sign of optical rotation of hydrolyzed (1 M NaOH) product with that of known *N*-acetyl amino acids, by analogy, and through comparison of sign of optical rotation and chiral GC elution order with configurationally defined samples. [c] The (*S*)-enantiomer could not be detected.

Bulgecinine Synthesis. A demonstration of the use of these γ,δ-unsaturated amino acids as chiral intermediates in synthesis presented itself in the bulgecin natural products.[21] Several syntheses of naturally occurring (−)-bulgecinine by halocyclization reactions have appeared,[4c−e,22] demonstrating 1,3-stereoinduction from the amino acid α-position. We hoped to be able to set all three stereogenic centers in this molecule based on asymmetric hydrogenation in the first catalytic synthesis of (+)-bulgecinine (Scheme 2).[4e,23]

The required α,β,γ,δ-unsaturated amino acid was prepared by Horner−Emmons olefination in 70% yield. Catalytic asymmetric hydrogenation using (*R*,*R*)-Et-DuPHOS-Rh at 60 psi required 2 h to give 99% of **2a** in 99.3% ee. Treatment with di-*tert*-butyl dicarbonate in THF followed by hydrazine in THF/MeOH (1:1) in a two-step one-pot procedure[24] gave 92% of the *N*-Boc derivative. The *tert*-butyldimethylsilyl ether was cleaved with HF-pyridine, and the methyl ester was hydrolyzed with LiOH to give **7** in a combined 76% yield for the three steps. Treatment of **7** with NBS effected a bromolactonization onto the extant double bond, giving the desired bromo-γ-lactone **8**[25] and its diastereomer in a 9:1 ratio.[26] The key intermediate **8** thus obtained was subjected to the conditions of Oppolzer[22] to afford (+)-bulgecinine in 80% yield (NMR spectroscopy).

(21) Imada, A.; Kintaka, K.; Nakao, M.; Shinagawa, S. *J. Antibiot.* **1982**, *35*, 1400.

(22) Oppolzer, W.; Moretti, R.; Zhou, C. *Helv. Chim. Acta* **1994**, *77*, 2363.

(23) (a) Yuasa, Y.; Ando, J. Shibuya, S. *J. Chem. Soc., Chem. Commun.* **1994**, 1383. (b) Yuasa, Y.; Ando, J. Shibuya, S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 793. (c) Schmeck, C.; Hegedus, L. S. *J. Am. Chem. Soc.* **1994**, *116*, 9927.

(24) Burk, M. J.; Allen, J. G. *J. Org. Chem.* **1997**, *62*, 7054.

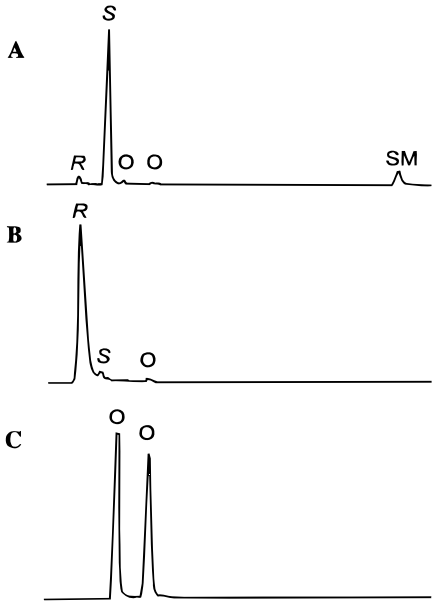
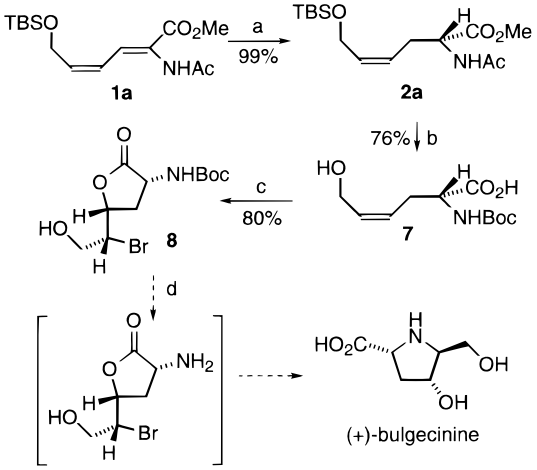


Figure 1. Representative gas chromatograms showing the separation of **2a** and the corresponding overreduced derivative using a 25 m chiral capillary Chirasil-L-Val column at 160 °C: (A) (*R*)- and (*S*)-**2a** after 2 h reduction with (*S,S*)-Me-DuPHOS-Rh (97% ee) showing 1.2% overreduction product (O) at 94% conversion of starting material (SM) **1a**; (B) (*R*)- and (*S*)-**2a** after 2 h reduction with (*R,R*)-Et-DuPHOS-Rh (99.3% ee) showing 0.5% overreduction at full conversion of starting material; (**C**) racemic overreduced product obtained with Rh-DiPFc.[17]

Scheme 2[a]



[a] Reagents and conditions: (a) [((*R,R*)-Et-DuPHOS)-Rh]OTf, S/C = 500/1, MeOH, 60 psi of H_2, 2 h (99.3% ee *R*); (b) (i) Boc_2O, DMAP, THF 24 h then N_2H_4, MeOH/THF (1:1) 4 h, 92%; (ii) HF-pyridine, CH_2Cl_2, 91%; (iii) 0.5 M LiOH/THF, 4:1, 91%; (c) NBS, THF, 0 °C, 5 min; (d) (i) TFA, CH_2Cl_2, 40 °C 3 h; (ii) 0.1 N $Ba(OH)_2$, room temperature, 3 h, ref 22, 80% by ^{1}H NMR spectroscopy for two steps.

Conclusion

A variety of α,*β*,*δ*,*γ*-unsaturated amino acids were prepared by Suzuki cross-coupling and Horner−Emmons olefination reactions. The first highly regio- and enantioselective catalytic hydrogenations of conjugated dienamide esters using the Et-DuPHOS-Rh catalyst were successfully demonstrated. Quantitative conversion of starting material was observed with short reaction times to give *γ*,*δ*-unsaturated amino acid products with better than 95% ee and less than 2% overreduction. The utility of these interesting intermediates was demonstrated with the formal asymmetric synthesis of (+)-bulgecinine.

Experimental Section

General Procedures. ^{1}H and ^{13}C NMR spectra were recorded on a General Electric QE-300 spectrometer at 300.15 and 75.48 MHz, respectively, in $CDCl_3$, and shifts are reported in parts per million downfield from TMS. High-resolution mass spectra were obtained using a JEOL JMS-SX102A spectrometer. Enantiomeric excess determinations were made by chiral capillary GC on a Chrompack Chirasil-L-Val column (25 m) in all cases. For TLC, system A was (petroleum ether:ethyl acetate); system B was ($CHCl_3$:acetone). Unspecified reagents were from commercial sources and used as obtained.

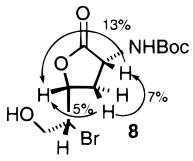
Substrate Preparations. Wittig Coupling (Method B) Sample Procedure for (2*Z*,4*Z*)-Methyl 2-Acetamido-6-((*tert*-butyldimethylsilyl)oxy)hexa-2,4-dienoate (1a). To a suspension of methyl 2-acetylamido-2-(dimethoxyphosphinyl)acetate[27] (2.1 g, 8.9 mmol) in THF (22 mL) at −78 °C was added tetramethylguanidine (1.4 mL, 11.8 mmol), and the mixture was stirred for 15 min. (*Z*)-4-((*tert*-Butyldimethylsilyl)oxy)-but-2-enal[28] (2.2 g, 10.7 mmol) was added, and the mixture was stirred for 2 h at −78 °C and 2 h at room temperature. The mixture was diluted with $CHCl_3$, washed with 1 N HCl, 1 N $CuSO_4$, and saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography on silica gel gave **1a** as a white solid (2.0 g, 70%): R_f 0.64 (1:1 system A); mp 124−125 °C (needles from PE:EA); ^{1}H NMR *δ* 0.07 (s, 6H), 0.89 (s, 9H), 2.13 (s, 3H), 3.78 (s, 3H), 4.44 (dd, 2H, J = 1.6, 4.2 Hz), 5.90−6.00 (m, 1H), 5.98 (dd, 1H, J = 11.5 Hz), 6.94 (br s, 1H), 7.42 (d, 1H, J = 11.7 Hz); ^{13}C NMR *δ* 18.2, 23.6, 25.8, 52.5, 60.4, 123.3, 123.7, 127.2, 138.8, 165.4, 168.4; HRMS calcd for $C_{15}H_{30}NO_4Si$ (M + H$^+$) *m*/*z* 316.1944, found 316.1936.

Suzuki Cross-Coupling (Method A) Sample Procedure[8] for (2*Z*,4*E*)-Methyl 2-Acetamido-6-phenylhexa-2,4-dienoate (1b). Under an inert atmosphere, (*Z*)-methyl 2-acetamido-3-bromoacrylate (0.3 g, 2.1 mmol), ((*E*)-3-phenyl-1-propenyl)boronic acid (0.5 g, 3.2 mmol), $Pd(OAc)_2$ (22 mg, 0.10 mmol), and Na_2CO_3 were combined. Degassed 95% EtOH (20 mL) was added, and the sealed vessel was heated at 50 °C with stirring for 4 h. The mixture was passed through plugs of $NaHCO_3$ and silica and concentrated in vacuo. Flash chromatography on silica gel gave **1b** as a white solid (0.36 g, 94%): R_f 0.45 (1:2 system A); mp 118−119 °C (needles from PE:EA); ^{1}H NMR *δ* 2.03 (s, 3H), 3.39 (d, 2H, J = 5.7 Hz), 3.65 (s, 3H), 6.00−6.30 (m, 2H), 6.95 (d, 1H, J = 9.9 Hz), 7.08−7.22 (m, 5H); ^{13}C NMR *δ* 23.0, 29.3, 39.3, 52.1, 122.3, 126.1, 126.2, 128.3, 133.4, 138.6, 141.8, 165.3, 169.0; HRMS calcd for $C_{15}H_{18}NO_3$ (M + H$^+$) *m*/*z* 260.1287, found 260.1288.

(2*Z*,4*E*)-Methyl 2-Acetamido-4-methylhexa-2,4-dienoate (1c). Obtained as a white solid by method A (0.68 g, 77%): R_f 0.22 (1:1 system A); mp 104.1−105.1 °C (needles from PE:EA); ^{1}H NMR *δ* 1.75 (d, 3H, J = 6.9 Hz), 1.83 (s, 3H), 2.09 (s, 3H), 3.75 (s, 3H), 5.97 (q, 1H, J = 6.9 Hz), 7.10 (s, 1H), 7.45 (s, 1H); ^{13}C NMR *δ* 13.0, 14.0, 22.6, 51.9, 120.3, 132.5, 136.7, 139.9, 166.1, 170.1; HRMS calcd for $C_{10}H_{16}NO_3$ (M + H$^+$) *m*/*z* 198.1138, found 198.1134.

(2*Z*,4*E*)-Methyl 2-Acetamido-6-(*tert*-butyldimethylsilyl)oxy)hexa-2,4-dienoate (1d). Obtained as a white solid by method B (5.2 g, 68%): R_f 0.46 (1:1 system A); mp 124−125 °C (needles from PE:EA); ^{1}H NMR *δ* 0.02 (s, 6H), 0.86 (s, 9H), 2.07 (s, 3H), 3.72 (s, 3H), 4.25 (m, 2H), 6.12 (dt, 1H, J = 15.2 Hz, J = 4.2 Hz), 6.35 (dd, 1H, J = J = 11.5 Hz), 7.05 (d, 1H, J = 11.4 Hz), 7.14 (br s, 1H); ^{13}C NMR *δ* 18.2, 23.2, 25.7, 52.3, 63.0, 122.6, 123.8, 133.1, 141.8, 165.4, 168.6; HRMS calcd for $C_{15}H_{30}NO_4Si$ (M + H$^+$) *m*/*z* 316.1944, found 316.1943.

(25) NOE experiments confirmed the relative stereochemistry; $[\alpha]^{20}_D$ = −45.8° (*c* = 0.81, MeOH), mp = 139−141 °C (CHCl3, hexanes). Oppolzer et al. (ref 22) found for (+)-**8** $[\alpha]^{28}_D$ = +45.6 (*c* = 0.815, MeOH), mp = 140−142 °C ($CHCl_3$, hexanes).



(26) Molecular mechanics calculations using the MacroModel 4.0 MM3 forcefield found $\Delta\Delta G_f$ = 2.15 kcal/mol for the two diastereomers.

(27) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 53−60.

(28) Roush, W. R.; Straub, J. A.; VanNieuwenhze, M. S. *J. Org. Chem.* **1991**, *56*, 1636−1648.

(2*Z*,4*E*)-Methyl 2-Acetamido-5,9-dimethyldeca-2,4,8-trienoate (1e). Obtained as a white solid by method B (3.1 g, 77%): R_f 0.35 (1:1 system A); mp 91.2−92.2 °C (needles from PE:EA); ^{1}H NMR δ 1.56, 1.64, 1.87 (3s, 3H ea.), 2.10−2.20 (m, 4H), 2.12 (s, 3H), 3.75 (s, 3H), 5.04 (br s, 1H), 5.93 (d, 1H, J = 14.9 Hz), 6.89 (br s, 1H), 7.34 (d, 1H, J = 11.8 Hz, H-3); ^{13}C NMR δ 14.1, 17.7, 23.5, 25.6, 26.4, 40.7, 52.3, 120.1, 123.4, 130.2, 132.5, 133.0, 150.6, 167.0, 168.6; HRMS calcd for $C_{15}H_{24}NO_3$ (M + H$^+$) m/z 266.1756, found 266.1745.

(2*Z*)-Methyl 2-Acetamido-4-ethylpenta-2,4-dienoate (1f). Obtained as a white solid by method B (0.15 g, 18%): R_f 0.67 (1:1 system A); mp 72−73 °C (needles from PE:EA); ^{1}H NMR δ 0.99 (t, 3H, 7.40 Hz), 2.04 (s, 3H), 2.20 (q, 2H, H=7.24 Hz), 3.74 (s, 3H), 5.23 (s, 2H), 6.86 (s, 1H), 7.14 (br s, 1H); ^{13}C NMR δ 12.7, 23.1, 27.5, 52.5, 119.6, 124.0, 134.1, 145.0, 165.7, 169.2; HRMS calcd for $C_{10}H_{16}NO_3$ (M + H$^+$) m/z 198.1130, found 198.1140.

(2*Z*)-Methyl 2-Acetamido-3-(1-cyclohexeneyl)prop-2-enoate (1 h). Obtained as a white solid (0.27 g, 17%): R_f 0.28 (1:2 system A); mp 145.5−146.4 °C (needles from EA:PE); ^{1}H NMR δ 1.45−1.65 (m, 4H), 1.95−2.40 (m, 4H), 2.04 (s, 3H), 3.70 (s, 3H), 6.10−6.15 (m, 1H), 6.99 (s, 1H), 7.09 (br s, 1H); ^{13}C NMR δ 21.3, 22.4, 23.1, 25.9, 26.4, 52.3, 120.2, 134.1, 139.1, 139.7, 166.2, 169.9; HRMS calcd for $C_{12}H_{17}NO_3$ (M + H$^+$) m/z 224.1287, found 224.1283.

(2*Z*,4*E*)-Methyl 2-Acetamidohexa-2,4-dienoate (1i). Separated a mixture of 4*E* and 4*Z* (97:3 4*E*:4*Z*, 2.0 g, 70%). 4*E* was obtained as a white solid by method B: R_f 0.33 (1:2 system A); mp 89.0−90.1 °C (needles from PE:EA); ^{1}H NMR δ 1.75 (d, 3H, J = 5.6 Hz), 2.02 (s, 3H), 3.69 (s, 3H), 5.95−6.30 (m, 2H), 6.92 (d, 1H, J = 10.1 Hz), 7.59 (br s, 1H); ^{13}C NMR δ 18.8, 23.0, 52.1, 121.3, 126.5, 134.2, 139.2, 165.4, 169.1; HRMS calcd for $C_9H_{13}NO_3$ (M + H$^+$) m/z 184.0974, found 184.0978.

(2*Z*,4*E*)-Methyl 2-Acetamido-5-*tert*-butylpenta-2,4-dienoate (1j). Obtained as a white solid by method A (0.73 g, 72%): R_f 0.29 (1:1 system A); mp 101.6−102.6 °C (needles from PE:EA); ^{1}H NMR δ 0.96 (s, 9H), 2.03 (s, 3H), 3.66 (s, 3H), 6.01 (dd, 1H, J = 3.9 Hz), 6.03 (s, 1H), 6.92 (dd, 1H, J = 3.3, 3.6 Hz), 7.73 (s, 1H); ^{13}C NMR δ 22.9, 28.8, 33.8, 52.0, 120.0, 121.9, 134.7, 154.8, 165.4, 169.2; HRMS calcd for $C_{12}H_{19}NO_3$ (M + H$^+$) m/z 225.1365, found 225.1372.

(2*Z*,4*E*)-Methyl 2-Acetamido-5-phenylpenta-2,4-dienoate (1l). Obtained as a white solid by method A (0.31 g, 55%): R_f 0.35 (9:1 system B); mp 179.4−180.2 °C (needles from EA); ^{1}H NMR δ 2.02 (s, 3H), 3.80 (s, 3H), 6.85−6.90 (m, 2H), 7.07 (br s, 1H), 7.20−7.50 (m, 6H); ^{13}C NMR δ 23.7, 52.5, 122.8, 123.7, 127.3, 128.6, 130.0, 132.7, 136.2, 140.0, 165.4, 168.7; HRMS calcd for $C_{14}H_{15}NO_3$ (M + H$^+$) m/z 254.1052, found 254.1045.

Substrate Hydrogenations. (2*R*,4*Z*)-Methyl 2-Acetamido-6-((*tert*-butyldimethylsilyl)oxy)hex-4-eneoate (2a). After 2 h reaction time at 60 psi initial pressure: R_f 0.44 (9:1 system B); t_R 7.36 min (160 °C, 30 psi, 99.3% ee); $[\alpha]^{20}_D$ −32.6° (c = 2.03, $CHCl_3$); ^{1}H NMR δ 0.02 (s, 6H), 0.84 (s, 9H), 1.95 (s, 3H), 2.40−2.60 (m, 2H), 3.68 (s, 3H), 4.12 (dd, 2H, J = 0.7, 6.2 Hz), 4.50−4.70 (m, 1H), 5.20−5.40 (m, 1H), 5.60−5.80 (m, 1H), 6.30 (br d, 1H, J = 7.1 Hz); ^{13}C NMR δ 18.3, 23.0, 25.8, 29.8, 51.5, 52.3, 59.0, 124.3, 133.3, 169.8, 172.2; HRMS calcd for $C_{15}H_{30}NO_4Si$ (M + H$^+$) m/z 316.1944, found 316.1940.

(2*R*,4*E*)-Methyl 2-Acetamido-6-phenylhex-4-eneoate (2b). After 0.5 h reaction time at 30 psi initial pressure: R_f 0.47 (1:2 system A); t_R 5.08 min (180 °C, 30 psi, 98.2% ee); $[\alpha]^{20}_D$ −61.1° (c = 1.01, $CHCl_3$); ^{1}H NMR δ 1.98 (s, 3H), 2.40−2.60 (m, 2H), 3.30−3.40 (m, 2H), 3.70 (s, 3H), 4.60−4.70 (m, 1H), 5.35−5.50 (m, 1H), 5.60−5.75 (m, 1H), 7.10−7.35 (m, 6H); ^{13}C NMR δ 13.6, 19.7, 23.0, 24.0, 35.2, 51.8, 52.3, 58.8, 124.8, 126.1, 128.4, 134.0, 140.1, 169.5, 172.4; HRMS calcd for $C_{15}H_{30}NO_4Si$ (M + H$^+$) m/z 262.1443, found 262.1438.

(2*S*,4*E*)-Methyl 2-Acetamido-4-methylhex-4-eneoate (2c). After 2 h reaction time at 90 psi initial pressure: R_f 0.33 (1:1 system A); t_R 4.28 min (135 °C, 20 psi, 99.5% ee); $[\alpha]^{20}_D$ +24.3° (c = 1.02, $CHCl_3$); ^{1}H NMR δ 1.61 (m, 6H), 2.00 (s, 3H), 2.29 (dd, 1H, J = 8.1, 16.5 Hz), 2.46 (dd, 1H, J = 5.7, 13.2 Hz), 3.73 (s, 3H), 4.60 (ddd, 1H, J = 7.8, 13.5 Hz), 5.24 (q, 1H, J = 6.0 Hz), 5.86 (br d, 1H, J = 6.0 Hz); ^{13}C NMR δ 13.4, 15.2, 22.8, 42.2, 50.7, 52.1, 123.1, 130.5, 167.8, 173.0; HRMS calcd for $C_{15}H_{30}NO_4Si$ (M + H$^+$) m/z 200.1287, found 200.1296.

(2*R*,4*E*)-Methyl 2-Acetamido-6-((*tert*-butyldimethylsilyl)oxy)hex-4-eneoate (2d). General Procedure. Methyl 2-acetamido-6-((*tert*-butyldimethylsilyl)oxy)hexa-2,4-dienoate (**1d**) (1.7 g, 5.4 mmol) and [(COD)Rh(*R*,*R*)-Et-DuPHOS]OTf (7.0 mg) were dissolved in MeOH (125 mL), and the vessel was charged with H_2 (90 psi). After 2 h the H_2 was vented and the solvent was evaporated. The crude material was passed through a short plug of silica with acetone before the optical purity was assayed by GC. Chromatography on silica gave pure **2d** (1.6 g, 95%): R_f 0.39 (1:2 system A); t_R 7.36 min (160 °C, 30 psi, >99% ee); $[\alpha]^{20}_D$ −45.8° (c = 1.25, $CHCl_3$); ^{1}H NMR δ 0.02 (s, 6H), 0.86 (s, 9H), 1.98 (s, 3H), 2.40−2.60 (m, 2H), 3.70 (s, 3H), 4.08 (dd, 2H, J = 1.2, 4.8 Hz), 4.60−4.70 (m, 1H), 5.40−5.60 (m, 2H), 5.60 (br d, 1H, J = 7.5 Hz); ^{13}C NMR δ 18.3, 23.1, 25.9, 34.8, 51.8, 52.3, 63.2, 123.7, 134.1, 169.6, 172.3; HRMS calcd for $C_{15}H_{30}NO_4Si$ (M + H$^+$) m/z 316.1944, found 316.1943.

(2*R*,4*E*)-Methyl 2-Acetamido-5,9-dimethyldeca-4,8-dienoate (2e). After 2 h reaction time at 90 psi initial pressure: R_f 0.42 (1:2 system A); t_R 8.97 min (180 °C, 30 psi, >99% ee); $[\alpha]^{20}_D$ −63.3° (c = 1.16, $CHCl_3$); ^{1}H NMR δ 1.56, 1.57 (2s, 6H), 1.65 (s, 3H), 1.90−2.20 (m, 2H), 1.97 (s, 3H), 2.40−2.60 (m, 2H), 3.70 (s, 3H), 4.55−4.70 (m, 1H), 4.90−5.10 (m, 2H), 6.00 (d, 1H, J = 7.4 Hz); ^{13}C NMR δ 16.0, 17.7, 23.1, 25.6, 26.4, 30.5, 39.7, 52.0, 52.2, 117.3, 123.8, 131.6, 134.0, 169.5, 172.6; HRMS calcd for $C_{15}H_{26}NO_3$ (M + H$^+$) m/z 268.1913, found 268.1907.

(2*R*)-Methyl 2-Acetamido-4-ethylpenta-4-enoate (2f). After 2 h reaction time at 60 psi initial pressure: R_f 0.27 (1:1 system A); t_R 5.70 min (120 °C, 20 psi, 97.8% ee); $[\alpha]^{20}_D$ −23.6° (c = 1.28, $CHCl_3$); ^{1}H NMR δ 1.00 (t, 3H, J = 7.4 Hz), 1.90−2.10 (m, 2H), 1.98 (s, 3H), 2.37 (dd, 1H, J = 8.2 Hz, J = 14.0 Hz), 2.54 (dd, 1H, J = 5.6 Hz, J = 14.0 Hz), 3.70 (s, 3H), 4.60−4.70 (m, 1H), 4.74 (s, 1H), 4.83 (s, 1H), 5.89 (d, 1H, J = 6.0 Hz); ^{13}C NMR δ 12.1, 23.0, 28.0, 39.0, 50.6, 52.3, 112.1, 146.0, 170.0, 172.9; HRMS calcd for $C_{10}H_{18}NO_3$ (M + H$^+$) m/z 200.1287, found 200.1291.

(2*S*)-Methyl 2-Acetamido-3-cyclohexenylpropanoate (2 h). After 2 h reaction time at 90 psi initial pressure: R_f 0.29 (1:2 system A); t_R 7.25 min (150 °C, 20 psi, 99.5% ee); $[\alpha]^{20}_D$ +29.8° (c = 2.01, $CHCl_3$); ^{1}H NMR δ 1.40−1.60 (m, 2H), 1.80−2.00 (m, 2H), 1.95 (s, 3H), 2.20−2.50 (m, 2H), 3.66 (s, 3H), 4.55−4.70 (m, 1H), 5.41 (br s, 1H), 5.98 (d, 1H, J = 7.2 Hz); ^{13}C NMR δ 22.0, 22.6, 22.9, 25.2, 27.7, 40.8, 50.6, 52.1, 125.6, 132.7, 169.7, 173.1; HRMS calcd for $C_{12}H_{20}NO_3$ (M + H$^+$) m/z 226.1443, found 226.1435.

(2*R*,4*E*)-Methyl 2-Acetamidohexa-4-enoate (2i). After 2 h reaction time at 90 psi initial pressure: R_f 0.41 (1:2 system A); t_R 4.18 min (120 °C, 20 psi, 99.3% ee); $[\alpha]^{20}_D$ −57.2° (c = 1.18, $CHCl_3$); ^{1}H NMR δ 1.62 (d, 3H, J = 6.1 Hz), 1.98 (s, 3H), 1.80−2.00 (m, 2H), 3.70 (s, 3H), 4.55−4.70 (m, 1H), 5.20−5.40 (m, 1H), 5.45−5.60 (m, 1H), 6.00 (br s, 1H); ^{13}C NMR δ 18.0, 23.1, 35.2, 51.9, 52.3, 124.3, 130.0, 169.6, 172.5; HRMS calcd for $C_9H_{16}NO_3$ (M + H$^+$) m/z 186.1130, found 186.1135.

(2*S*,4*E*)-Methyl 2-Acetamidohexa-4-enoate (*ent*-2i). After 2 h reaction time at 90 psi initial pressure: t_R 4.97 min (120 °C, 20 psi, 99.2% ee); $[\alpha]^{20}_D$ +62.0° (c = 0.99, $CHCl_3$); please see **2i** for other characterization data.

(2*S*,4*E*)-Methyl 2-Acetamido-5-*tert*-butylpent-4-eneoate (2j). After 1 h reaction time at 30 psi initial pressure: R_f 0.55 (1:2 system A); t_R 3.47 min (150 °C, 20 psi, 99.4% ee); $[\alpha]^{20}_D$ +61.4° (c = 1.03, $CHCl_3$); ^{1}H NMR δ 0.98 (s, 9H), 2.02 (s, 3H), 2.38−2.60 (m, 2H), 3.74 (s, 3H), 4.60−4.70 (m, 1H), 5.18 (ddd, 1H, J = 7.2, 15.6 Hz), 5.53 (d, 1H, J = 15.6 Hz), 6.02 (br d, 1H, J = 7.2 Hz); ^{13}C NMR δ 23.1, 29.4, 33.1, 35.5, 52.0, 52.2, 105.6, 117.8, 146.7, 169.5, 172.4; HRMS calcd for $C_{12}H_{22}NO_3Si$ (M + H$^+$) m/z 228.1600, found 228.1592.

(2*R*,4*E*)-Methyl 2-Acetamido-5-phenylpenta-4-enoate (2l). After 2 h reaction time at 90 psi initial pressure: R_f 0.30 (4:1 system B); t_R 5.04 min (180 °C, 30 psi, 98.6% ee); $[\alpha]^{20}_D$ −90.8° (c = 1.11, $CHCl_3$); ^{1}H NMR δ 1.93 (s, 3H), 2.50−2.80 (m, 2H), 3.67 (s, 3H), 4.60−4.75 (m, 1H), 5.96 (dt, 1H, J = 7.4 Hz, J = 15.7 Hz), 6.16 (br d, 1H, 7.5 Hz), 6.37 (d, 1H, J = 15.8 Hz), 7.10−7.30 (m, 5H); ^{13}C NMR δ 23.1, 35.7, 51.9, 52.4, 123.3, 126.1, 127.5, 128.5, 134.0, 136.6, 169.7, 172.3; HRMS calcd for (M + H$^+$) m/z 248.1287, found 248.1282.

(+)-Bulgecinine Synthesis. (2*R*,4*Z*)-2-(*tert*-Butoxycarbamido)-6-hydroxyhex-4-eneoic Acid (7). Acetamide **2a** (0.30 g, 1.0 mmol), BOC_2O (0.44 mL, 1.9 mmol), and DMAP (21.6 mg, 0.19 mmol) were stirred in THF (2.4 mL) 20 h at rt and then held at reflux 0.5 h. The reaction mixture was diluted with MeOH (2.4 mL) and cooled to 0 °C, and hydrazine (0.12 mL, 3.8 mmol) was added. After 5 h the mixture was poured into CH_2Cl_2, washed with 1 N HCl, $CuSO_4$, and $NaHCO_3$, dried ($MgSO_4$), and evaporated. Flash column chromatography on silica gel gave the pure *N*-Boc derivative (0.33 g, 92%) as a colorless oil: R_f 0.39 (9:1 system A); t_R 7.19 min (160 °C, 30 psi, >99% ee); $[\alpha]^{22}_D$ −10.6° (c = 2.21, $CHCl_3$); ^{1}H NMR δ 0.01 (s, 6H), 0.84 (s, 9H), 1.37 (s, 9H), 2.40−2.60 (m, 2H), 3.67 (s, 3H), 4.12 (d, 2H, J = 6.1 Hz), 4.30−4.40 (m, 1H), 5.15−5.20 (m, 1H), 5.20−5.40 (m, 1H), 5.60−5.70 (m, 1H); ^{13}C NMR δ 18.3, 25.9, 28.2, 30.2, 52.2, 52.8, 59.0, 124.3, 133.4, 155.2, 172.4; HRMS calcd for $C_{18}H_{36}NO_5Si$ (M + H^+) m/z 374.2363, found 374.2358. The *N*-Boc derivative (0.14 g, 0.38 mmol) in CH_2Cl_2 (3.8 mL) was cooled to 0 °C, HF-pyridine (22 μL, 70%) was added, and the mixture was stirred for 0.5 h. The reaction mixture was diluted with CH_2Cl_2 and washed with 1 N HCl and $NaHCO_3$, dried ($MgSO_4$), and evaporated. Flash column chromatography on silica gel gave the pure alcohol (91 mg, 92%) as a white solid: R_f 0.53 (1:2 system A); mp = 44−45 °C (from PE:EA); $[\alpha]^{22}_D$ −22.3° (c = 1.40, $CHCl_3$); ^{1}H NMR δ 1.40 (s, 9H), 1.91 (br s, 1H), 2.40−2.70 (m, 2H), 3.72 (s, 3H), 4.12 (d, 2H, J = 6.8 Hz), 4.30−4.40 (m, 1H), 5.20−5.30 (m, 1H), 5.40−5.50 (m, 1H), 5.70−5.80 (m, 1H); ^{13}C NMR δ 28.2, 30.3, 52.4, 53.0, 58.0, 126.1, 132.6, 155.3, 172.5; HRMS calcd for $C_{12}H_{22}NO_5$ (M + H^+) m/z 260.1498, found 260.1501. The alcohol methyl ester (0.12 g, 0.48 mmol) in THF (4.8 mL) was stirred at 0 °C with 0.5 M LiOH (1.2 mL) 0.75 h. The mixture was diluted with CH_2Cl_2 and acidified (48 μL of 12 M HCl), and the aqueous layer was saturated with NaCl. After the mixture was stirred for 1 h, the organic layer was separated off, washed with 1 N HCl, dried ($MgSO_4$), and evaporated. The residue was washed with (9:1 PE:EA) to give pure **7** (0.10 g, 91%) as an amorphous white solid: $[\alpha]^{22}_D$ −27.6° (c = 1.08, $CHCl_3$); ^{1}H NMR δ 1.42 (s, 9H), 1.50−1.70 (br m, 2H), 4.10−4.30 (m, 2H), 4.30−4.40 (m, 1H), 5.40−5.60 (m, 1H), 5.70−5.80 (m, 1H), 6.47 (br s, 2H); ^{13}C NMR δ 28.3, 29.9, 53.1, 57.9, 80.4, 126.5, 132.0, 155.7, 175.3; HRMS calcd for $C_{11}H_{20}NO_5$ (M + H^+) m/z 246.1341, found 246.1330.

(2*R*,4*R*,5*R*) 5-Bromo-2-(*tert*-butoxycarbamido)-6-hydroxyhexano-4-lactone (8). The acid **7** (76 mg, 0.33 mmol) was dissolved in THF (3.3 mL) and treated with recrystallized NBS (65 mg, 0.36 mmol) at 0 °C for 5 min. The reaction mixture was diluted with CH_2Cl_2, washed with 1 N HCl and $NaHCO_3$, dried ($MgSO_4$), and evaporated. The residue was purified by chromatography to give pure **8** (86 mg, 80%): R_f 0.43 (1:2 system A); mp = 139−141 °C (from $CHCl_3$:hexanes), $[\alpha]^{22}_D$ −45.8°, $[\alpha]^{22}_{578}$ −46.9°, $[\alpha]^{22}_{546}$ −53.2°, $[\alpha]^{22}_{436}$ −88.8°, $[\alpha]^{22}_{365}$ −137.3° (c = 0.81, MeOH); ^{1}H NMR δ 1.42 (s, 9H), 2.20 (dd, 2H, J = 11.5 Hz), 2.30 (br s, 1H), 2.78−2.95 (m, 1H), 3.90−4.00 (m, 2H), 4.10−4.20 (m, 1H), 4.40−4.50 (m, 1H), 4.65−4.75 (m, 1H), 5.23 (br s, 1H); ^{13}C NMR δ 28.2, 33.8, 50.8, 55.1, 63.5, 80.9, 155.4, 173.9; HRMS calcd for $C_{11}H_{19}BrNO_5$ (M + H^+) m/z 324.0447, found 324.0445.

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Supporting Information Available: Representative NMR spectra and gas chromatograms for compounds **1** and **2** including the formal synthesis of (+)-bulgecinine (29 pages). See any current masthead page for ordering and Internet access instructions.

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