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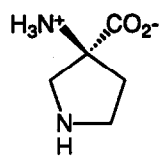
Asymmetric Synthesis of S-(-)-Cucurbitine

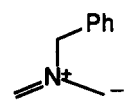
Robert M. Williams* and Glenn J. Fegley
Department of Chemistry, Colorado State University
Fort Collins, Colorado 80523

Abstract: *The asymmetric synthesis of (S)-(-)-cucurbitine in greater than 98 % ee is described. The key step of the synthesis involves 1,3-dipolar cycloaddition of azomethine ylide (1)[1] to α,β-dehydrolactone (3) to give pyrrolidine (6) as a single diastereomer.*

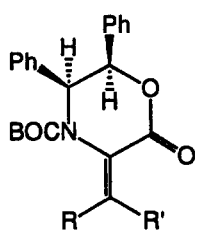
Cucurbitine is a naturally occurring amino acid found in the seeds of several *Cucurbita* (pumpkin) species and is known to inhibit the growth of immature *Schistosoma japonicum.* It was first isolated from *Cucurbita moschata* by Fang and coworkers[2] and the absolute stereochemistry was later determined to be of the (S)-configuration.[3] To date there exists only two racemic syntheses[4] and one enantiospecific synthesis[5] of the title compound. The enantiospecific synthesis of (-)-cucurbitine was accomplished by a method involving 1,3-dipolar cycloaddition of azomethine ylide (**1**) (derived from N-benzyl-N-(methoxymethyl)trimethylsilylmethylamine) to diethyl methylenemalonate. Subsequent pig liver esterase-catalyzed hydrolysis of the pro-(R) ester group followed by conversion of the free carboxylate to an amino group via the Curtius rearrangement, provided the cucurbitine nucleus. The maximum observed enantiomeric excess for the esterase hydrolysis reaction was only 10%.



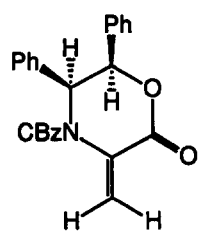
S-(-)-Cucurbitine



1



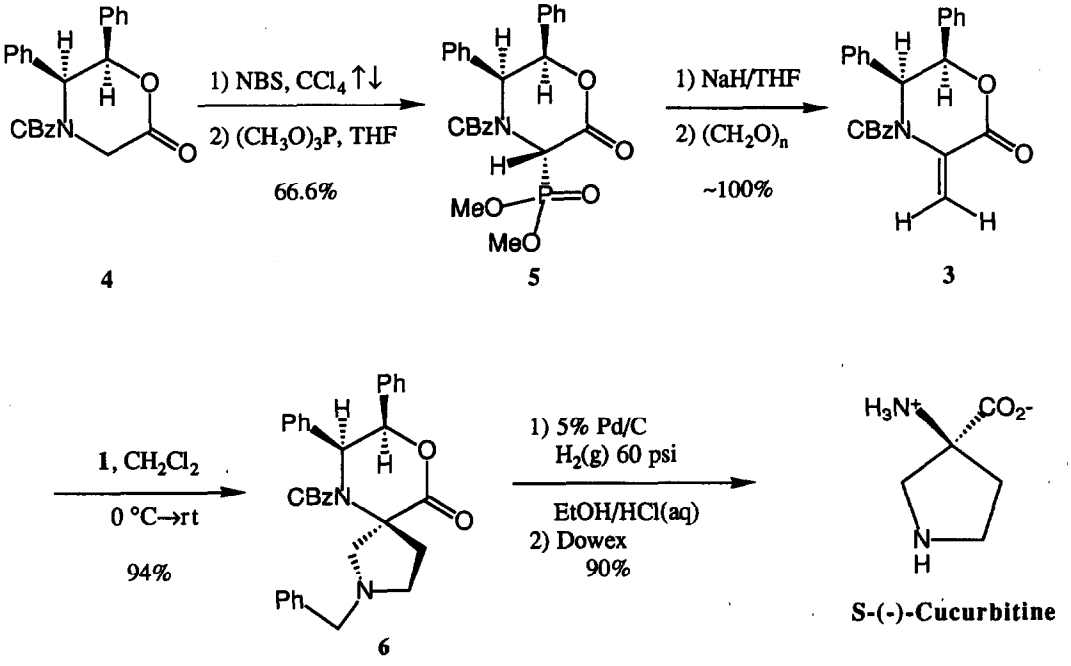
2a: R = R' = ^{2}H
2b-d: R = H; R' = Me, Et, Ph



3

Considering the general lack of successful asymmetric syntheses of cucurbitine and structurally related derivatives, we decided to apply the axially chiral dehydroalanine amino acid methodology [6] to this challenging problem. Recently we reported the asymmetric syntheses of 1-aminocyclopropane-1-carboxylic derivatives utilizing the axially chiral nonracemic α,β-dehydrolactone derivatives (**2a-d**).[7] As an extension to this methodology, compounds **2a-d** can potentially serve as suitable substrates for the development of other stereoselective cycloaddition processes (i.e. dipolar cycloadditions and Diels-Alder transformations). For the synthesis of cucurbitine we elected to study the 1,3-dipolar cycloaddition of azomethine ylide (**1**) to α,β-dehydrolactone derivative (**3**), since deprotection to the requisite amino acid would only require a one-step hydrogenolysis of the newly formed cycloadduct (Scheme 1).

SCHEME 1



Thus, the stereoselective synthesis of (S)-(-)-cucurbitine is as follows: Lactone (**4**) was readily converted to phosphonate ester (**5**) in 67% yield and subsequently to α,β-dehydrolactone (**3**, quantitative) as described earlier[7] for the synthesis of the corresponding N-t-BOC-protected analogues. Treatment of **3** with **1** (generated in situ from 5.0 equiv of N-benzyl-N-(methoxymethyl)[(trimethyl)silyl]methylamine and 0.2 equiv TFA)[1a] in CH_2Cl_2 between 0 °C and room temperature, provided pyrrolidine (**6**) in 94% yield after crystallization of the crude product from EtOH. Compound (**6**) was obtained as a single diastereomer as determined by examination of

the ^1H NMR of the crude product.[8] Finally, (S)-(-)-cucurbitine was obtained in 90% by treating an EtOH solution of **6** with 0.1 equiv 5% Pd/C, 3.0 equiv HCl(aq), and H_2(g) at 60 psi for 12 hours. [9] The free amino acid was obtained by sequentially eluting an aqueous solution of the crude HCl salt on a C_{18} sep-pak cartridge and a Dowex cationic ion exchange column. The optical purity of the synthetic cucurbitine was determined by optical polarimetry and Mosher amide analysis and are consistent with reported data. It is interesting to note that the high degree of facial selectivity for the azomethine ylide addition to **3** contrasts our previous diazomethane cycloadditions with similar olefin substrates.[7] We believe this is an inherent result of the slower reacting and thus more discriminating azomethine ylide (**1**). Additional studies involving the syntheses of novel cucurbitine derivatives from the Cbz-protected analogues of **2b-d** and of Diels-Alder cycloadducts from these same α,β-dehydrolactone precursors are presently under study and will be reported in due course.

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References and Footnotes

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8. Spectroscopic data for the compounds described herein are as follows: **(3S,5S,6R)-4-(Benzyloxycarbonyl)-3-(dimethoxyphosphoryl)-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (5):**
^1H NMR (300 MHz)($CDCl_3$)δTMS: 3.60-3.98(6H, m), 4.91(1H, 1/2 ABq, J = 12.3 Hz), 5.01(1H, 1/2 ABq, J = 12.3 Hz), 5.20(d, J = 3.1 Hz) and 5.29(d, J = 3.3 Hz)(1H), 5.48-5.66(1H, m), 6.35(d, J = 3.1 Hz) and 6.40(d, J = 3.1 Hz)(1H), 6.52-7.40(15H, m); IR(NaCl, neat)υ: 3059, 3038, 2857, 1956, 1886, 1760, 1715, 1498, 1453, 1403, 1352, 1297, 1267, 1186, 1111, 1051, 1031 cm^{-1};
Anal.(recrystallized from EtOH) Calc'd for $C_{26}H_{26}NO_7P$: C, 63.03%; H, 5.29%; N, 2.83%. Found: C, 63.17%; H, 5.49%; N, 2.76%; $[\alpha]^{25}_D$ = - 25.5 ° (c = 1.0, CH_2Cl_2); mp = 165-166 °C.
(5S,6R)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-methylidene-2,3,5,6-tetrahydro-1,4-oxazin-2-one (3):
^1H NMR(300 MHz)($CDCl_3$)δTMS: 5.04(1H, 1/2 ABq, J = 12.3 Hz), 5.13(1H, 1/2 ABq, J = 12.3 Hz), 5.41(1H, d, J = 2.7 Hz), 5.81(1H, d, J = 2.8 Hz), 6.30(1H, s), 6.52(1H, broad s), 6.66(2H, d, J = 7.4

Hz), 6.99-7.31(13H, m); IR(KBr)υ: 3088, 3061, 3030, 2986, 2939, 2892, 1742, 1718, 1607, 1457, 1395, 1353, 1284, 1272, 1256, 1172, 1086, 1070 cm^{-1}; Anal.(recrystallized from EtOH) Calc'd for $C_{25}H_{21}NO_4$: C, 75.17%; H, 5.30%; N, 3.51%. Found: C, 75.34%; H, 5.54%; N, 3.49%; $[\alpha]^{25}_D$ = -89.4 ° (c = 1.0, CH_2Cl_2); mp = 152-153.5 °C.

(5S,7S,8R)-2-Benzyl-6-(benzyloxycarbonyl)-7,8-diphenyl-9-oxa-2,6-diazaspiro[4.5]decan-10-one (6):

^1H NMR(300 MHz)(373 K, Cl_2DCCl_2) δ TMS: 2.59-2.67 (1H,m); 3.02-3.14 (3H, m); 3.23 (1H, 1/2 ABq, J=9.9 Hz); 3.33 (1H, 1/2 ABq, J = 9.9 Hz); 3.70 (1H, 1/2 ABq, J=13.3 Hz); 3.76 (1H, 1/2 ABq, J = 13.3 Hz); 5.10 (1H, 1/2 ABq, J = 12.5 Hz); 5.16 (1H, 1/2 ABq, J = 12.5 Hz); 5.43 (1H, d, J = 2.8 Hz); 5.68 (1H, d, J = 2.8 Hz); 6.66 (2H, d, J = 7.3 Hz); 7.01-7.32 (18 H, m). IR(KBr)υ: 3087, 3062, 3032, 2938, 2821, 2807, 1744, 1708, 1497, 1455, 1390, 1342, 1277, 1209, 1178, 1127, 1084, 1065cm^{-1}; Anal.(recrystallized from EtOH) Calc'd for $C_{34}H_{32}N_2O_4$: C, 76.67%; H, 6.06%; N, 5.26%. Found: C, 76.82%, H, 6.17%; N, 5.16%; $[\alpha]^{25}_D$ = + 50.5 ° (c = 1.0 CH_2Cl_2); mp = 178-180 °C.

(S)-(-)-Cucurbitine:

^1H NMR(300 MHz)(D_2O)δ(HOD at 4.64 ppm): 1.83-1.93(1H, m), 2.16-2.26(1H, m), 3.02(1H, 1/2 ABq, J = 12.2 Hz), 3.33(2H, apparent t, J = 7.5 Hz), 3.45(1H, 1/2 ABq, J = 12.2 Hz); IR(KBr)υ: 3285, 3061-2380, 2156, 1602, 1388, 1258, 1087, 908 cm^{-1}. Anal.(recrystallized from H_2O/EtOH) Calc'd for $C_5H_{10}N_2O_2$: C 46.14; H 7.74; N 21.52. Found: C 46.37; H 7.84; N 21.31 ; $[\alpha]^{25}_D$ = -19.96° (c = 1.02, H_2O) lit.[2,3] $[\alpha]^{25}_D$ = - 19.76° (c = 9.31, H_2O) ; mp = 239-241 °C (dec).

9. Experimental procedure for azomethine ylide addition and hydrogenation:
To a 0 °C solution containing **3** (735.0 mg, 1.84 mmol, 1.0 equiv), N-benzyl-N-(methoxymethyl)-N-[(trimethylsilyl)methyl]amine (3.1 g, 12.88 mmol, 7.0 equiv), and CH_2Cl_2 (10 mL) was added TFA (28.4 μL, 0.37 mmol, 0.2 equiv) dropwise via syringe. After 15 min the mixture was warmed to room temperature and stirred an additional 3h. Evaporation of solvent and crystallization of the crude product provided 916.1 mg (93.5%) **6** as a white amorphous solid.

A mixture of **6** (400.0 mg, 0.75 mmol, 1.0 equiv), 5% Pd/C (160.0 mg, 0.08 mmol, 0.1 equiv), 2M HCl (1.13 mL, 2.25 mmol, 3.0 equiv), and EtOH (20 mL) was thoroughly degassed and pressurized to 60 psi H_2(g) for 12 h. At this time the reaction was again degassed and the catalyst was removed via vacuum filtration using Whatman No. 42 filter paper. The resulting filtrate was concentrated to dryness providing 289.2 mg white solid consisting of bibenzyl and cucurbitine·2HCl. Bibenzyl was removed by triturating the solid mixture with pentane. The crude amino acid was then dissolved in H_2O (~ 1 mL) and sequentially eluted on a C_{18} sep-pak cartridge and a small column packed with Dowex® 50x2-400 ion-exchange resin, using H_2O and 0.1M $NH_4^+OH^-$, respectively. Concentration of the fractions collected provided 89.0 mg (90%) cucurbitine as a white crystalline solid.

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