Tetrahedron Letters,Vol.30,No.34,pp 4539-4542,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

ENANTIOSELECTIVE TOTAL SYNTHESIS OF (+)-(S)-DIHYDROPERIPHYLLINE

Takehiko Kaseda, Toyohiko Kikuchi, and Chihiro Kibayashi*

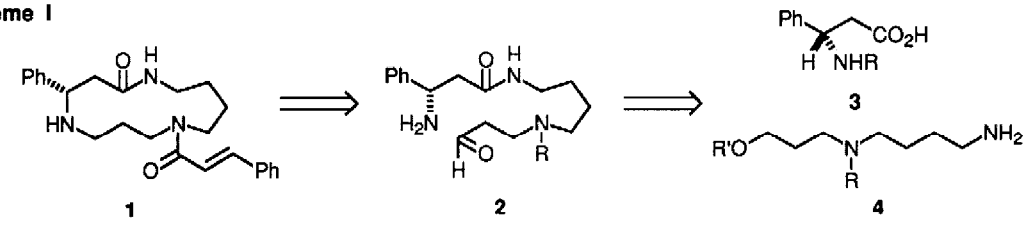
Tokyo College of Pharmacy, Horinouchi, Hachioji, Tokyo 192-03, Japan

Abstract: The first enantioselective total synthesis of (+)-(S)-dihydroperiphylline was achieved from (S)-ß-phenyl-ß-alanine, prepared by chelation controlled phenylation of the Schiff base, by a new route involving 13-membered lactam formation via iminium cyclization.

In 1977 a new type of spermidine alkaloids containing a 13-membered ring system typified by dihydroperiphylline (1) was isolated from the leaves of Peripterygia marginata by Husson and co-workers.[1] Although synthesis of racemic 1 has been reported,[2] no report on the enantiomeric synthesis of 1 has been published.[3] In this communication we report the first enantioselective total synthesis of (+)-(S)-dihydroperiphylline (1).

Our synthetic approach to 1 is retrosynthetically outlined in Scheme I, which relies on an effective new method for elaborating the 13-membered lactam via intramolecular iminium cyclization of the (S)-amino aldehyde 2. Accordingly, our first efforts were directed toward the enantioselective preparation of (S)-ß-phenyl-ß-alanine (3, R = H).

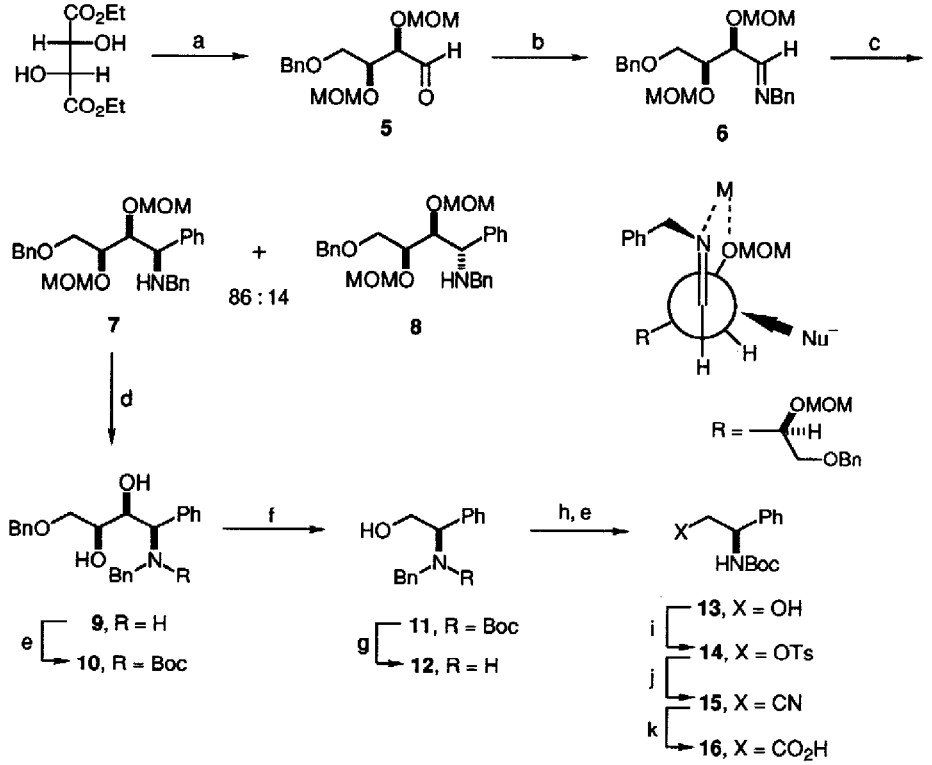
Scheme I



Nucleophilic addition to the Schiff base 6, prepared from the L-threose derivative 5[4] and benzylamine, with 2 equiv of phenyllithium in THF at -60 °C resulted in the preference formation (86:14) of the syn amine 7[5] (total yield of 7/8: 68% from 6). The observed stereochemistry is consistent with an α-chelation model (Scheme II) as reported previously from this laboratory.[4,6] Removal of the MOM groups (HCl/MeOH) and N-protection [$(Boc)_2O$] of the resultant diol 9 afforded 10 (63% from 7), which underwent glycol cleavage (HIO_4) followed by $NaBH_4$ reduction to give the alcohol 11 (66%). After removal of the Boc group (CF_3CO_2H), resulting 12 was converted to the N-protected amino alcohol 13 by debenzylation (H_2, $PdCl_2$) and N-protection [$(Boc)_2O$] in 72% yield from 11.[7] Compound 13 was subjected to tosylation, displacement (NaCN), and alkaline hydrolysis to afford enantiomerically pure N-Boc-(S)-ß-phenyl-ß-alanine (16) in 47% overall yield.

We next prepared the diamino unit as outlined in Scheme III. N-benzylation (PhCHO then $NaBH_4$) of 3-aminopropanol (17) followed by N-cyanopropylation generated 18 (60% overall yield), which was converted to the diamine 20 (66% from 18) via benzoylation and catalytic reduction. Condensation of the (S)-ß-phenyl-ß-alanine derivative 16 with the diamine 20 was achieved by using the Mukaiyama procedure[8] giving the (S)-amide 21 in 79% yield. Hydrogenolytic de-N-benzylation followed by N-benzyloxycarbonylation afforded 22

Scheme II

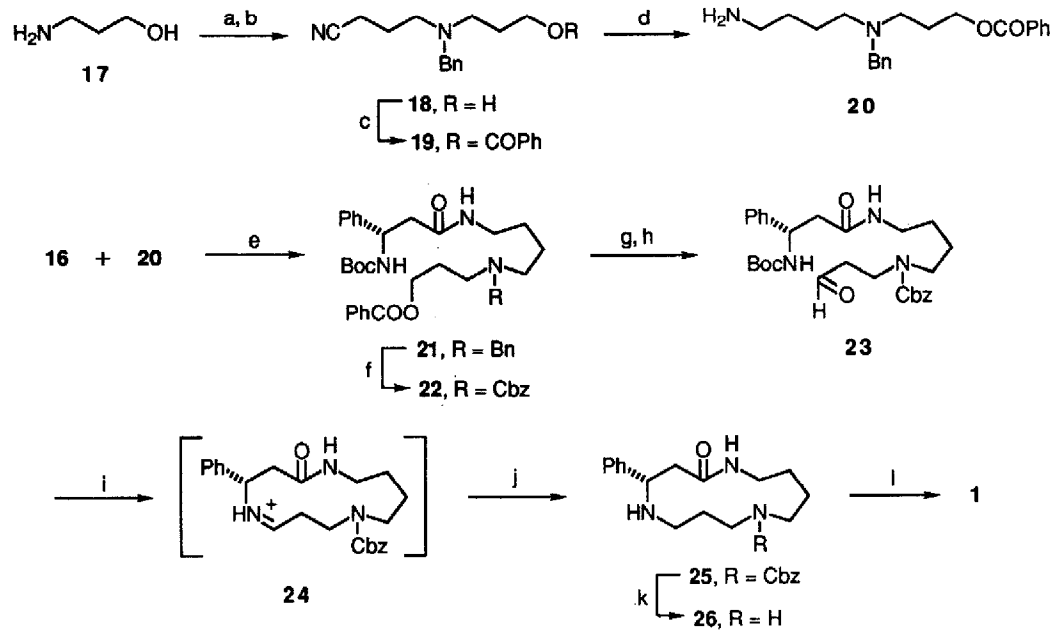


(a) Ref 4; (b) $PhCH_2NH_2$, Et_2O, 0 °C, 15 min; (c) PhLi, THF, -60 °C, 2 h; (d) concd. HCl, MeOH, reflux, 1 h; (e) $(Boc)_2O$, toluene, reflux, 2 h; (f) HIO_4, MeOH, 0 °C, 1 h, then $NaBH_4$, MeOH, r.t., 1 h; (g) CF_3CO_2H, CH_2Cl_2, r.t., 1.5 h; (h) H_2, $PdCl_2$, MeOH, 1 h; (i) TsCl, DMAP, CH_2Cl_2, r.t., 2 h; (j) NaCN, Me_2SO, 90 °C, 1 h; (k) 2N NaOH, EtOH, 90 °C, 3 h.

(90%) which was hydrolyzed under the alkaline conditions and then oxidized (PCC) to give the aldehyde **23** (78% from **22**). When the BOC group was removed by exposing to CF_3CO_2H at room temperature, the in situ cyclization to the 13-membered ring via iminium formation was performed to provide **24** which was subsequently converted to **25** (61% from **23**) by $NaBH_4$ reduction. In the previous synthesis, the crucial step for the construction of the 13-membered dihydroperiphylline ring system are based on the lactam formation via mixed anhydride method[9] and transamidation.[2] After removal of the benzyloxycarbonyl protective group (94%), **26** was siteselectively coupled with trans-cinnamic acid by using the Mukaiyama procedure (67%), furnishing (S)-dihydroperiphylline (1).

Synthetic **1** had spectral data (IR, ^1H NMR, and mass) identical with those published[1] for natural dihydroperiphylline and also with those of an authentic sample of (±)-1, but the optical rotation $[[\alpha]^{23}_D$ +3.5° (c 0.4, $CHCl_3$)] found for the synthetic material was quite different from that reported[1] for the natural product $[[\alpha]^{20}_D$ -21° (c 0.5, $CHCl_3$)]. In order to confirm the C-11 stereogenic center, synthetic **1** was converted to tetrahydroperiphylline (**27**) by catalytic hydrogenation (Scheme IV). Alternatively, **27** was prepared by

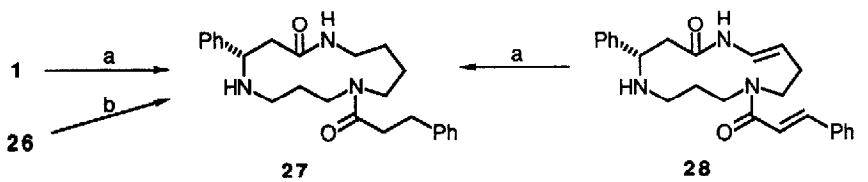
Scheme III



(a) PhCHO, benzene, reflux, 14 h, then $NaBH_4$, MeOH, r.t., 1 h; (b) $Cl(CH_2)_3CN$, Et_3N, toluene, reflux, 6 h; (c) PhCOCl, Et_3N, CH_2Cl_2, 0 °C → r.t., 1 h; (d) H_2, PtO, concd. HCl–EtOH, 3 h; (e) 2-chloro-N-methylpyridinium iodide, Et_3N, CH_2Cl_2, r.t., 1 h; (f) H_2, $PdCl_2$, MeOH, 3 h, then $PhCH_2OCOCl$, Et_3N, CH_2Cl_2, 0 °C → r.t., 1 h; (g) K_2CO_3, MeOH, r.t., 30 min; (h) PCC, CH_2Cl_2, r.t., 1 h; (i) CF_3CO_2H, CH_2Cl_2, r.t., 30 min; (j) $NaBH_4$, MeOH, r.t., 40 min; (k) H_2, $PdCl_2$, 40 min; (l) trans-PhCH=$CHCO_2H$, 2-chloro-N-methylpyridinium iodide, Et_3N, CH_2Cl_2, r.t., 1 h.

coupling **26** and phenylpropionic acid in the presence of Mukaiyama reagent. The synthetic **27** thus obtained was found to have the same optical rotation[5] and circular dichroism[5] as those for a sample derived from natural (-)-periphylline (**28**) by catalytic hydrogenation. Since the C-11 chirality of natural periphylline has been defined as S,[3] the above observations establish the 11-S configuration for synthetic (+)-dihydroperiphylline which is consistent with the fact that the ß-phenyl-ß-alanyl residue in natural products is usually found to belong to the S series.[10] These results strongly indicate that the originally reported optical rotation value (-21°) for natural dihydroperiphylline is erroneous and should be corrected to

Scheme IV



(a) H_2, PtO, MeOH, 1 h; (b) $Ph(CH_2)_2CO_2H$, 2-chloro-N-methylpyridinium iodide, Et_3N, CH_2Cl_2, r.t., 1 h.

+3.5°. Such an error of the optical rotation for the natural alkaloid appears to arise from contamination by periphylline [$[\alpha]_D^{20}$ -291° (c 1, $CHCl_3$)][1] which coexists with dihydroperiphylline in the same plant.[1] Indeed, because of the proximity of the spots on TLC, complete separation of the two alkaloids by chromatography seems to be difficult.

Acknowledgment We are indebted to Professor H. H. Wasserman of Yale University for providing a sample of (±)-dihydroperiphylline and also to Professor R. Hocquemiller of Paris-Sud University for natural (-)-periphylline.

References and Notes

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5. All products gave spectral data which were consistent with the assigned structures. Physical data for the main products are as follows. **7**: $[\alpha]_D^{22}$ -54.5° (c 0.5, EtOH). **9**: $[\alpha]_D^{23}$ -48.0° (c 0.5, EtOH). **11**: $[\alpha]_D^{23}$ -66.1° (c 1.7, EtOH). **12**: $[\alpha]_D^{22}$ -80.8° (c 0.5, EtOH). **13**: mp 141-142 °C; $[\alpha]_D^{22}$ -48.2° (c 0.4, EtOH). **14**: mp 150-152 °C; $[\alpha]_D^{23}$ -7.2° (c 0.4, EtOH). **15**: mp 122-124 °C; $[\alpha]_D^{25}$ -8.9° (c 0.3, EtOH). **16**: mp 129-131 °C; $[\alpha]_D^{23}$ -42.2° (c 0.5, EtOH). **21**: $[\alpha]_D^{24}$ -15.4° (c 0.2, $CHCl_3$). **22**: $[\alpha]_D^{20}$ -11.7° (c 0.6, $CHCl_3$). **23**: $[\alpha]_D^{22}$ -15.9° (c 1.4, $CHCl_3$). **25**: $[\alpha]_D^{23}$ +5.7° (c 0.7, $CHCl_3$). **26**: $[\alpha]_D^{22}$ -24.4° (c 0.6, $CHCl_3$). **1**: $[\alpha]_D^{23}$ +3.5° (c 0.4, $CHCl_3$); CD (c 0.1, MeOH) $\Delta\epsilon^{20}$ -3.6 (222), -3.1 (225). **27**: $[\alpha]_D^{23}$ +5.5° (c 0.9, $CHCl_3$); CD (c 2.4, MeOH) $\Delta\epsilon^{20}$ +0.13 (268), +0.13 (261), -3.8 (226).
6. For α-chelation controlled nucleophilic addition to α,ß-bis[(methoxymethyl)oxy] carbonyl compounds, see: (a) H. Iida, N. Yamazaki, and C. Kibayashi, J. Org. Chem., **1986**, 51, 3769. (b) H. Iida, N. Yamazaki, and C. Kibayashi, Ibid., **1986**, 51, 4245. (c) H. Iida, N. Yamazaki, and C. Kibayashi, Ibid., **1987**, 52, 1956. (d) N. Yamazaki and C. Kibayashi, J. Am. Chem. Soc., **1989**, 111, 1396.
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(Received in Japan 18 April 1989)