Pergamon

Tetrahedron Letters 40 (1999) 8805–8809

TETRAHEDRON LETTERS

Asymmetric palladium annulation: formal synthesis of (+)-huperzine A †

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Received 1 September 1999; accepted 30 September 1999

Abstract

A new formal stereoselective synthesis of (+)-huperzine A **1** was achieved using as a key step a palladium mediated annulation between 2-methylene-1,3-propanediol diacetate and (1*R*,2*S*)-2-phenylcyclohexanol derived β-ketoester **14**.

Keywords: alkaloids; palladium; cyclisation.

(−)-Huperzine A **1** isolated from *Huperzia serrata*,[1] a plant used in Chinese folk medicine, is a potent reversible inhibitor of acetylcholinesterase and is currently under clinical trials for the treatment of Alzheimer's disease.[2] This particular biological activity induced several synthetic studies which culminated with two total syntheses by Qian[3] and Kozikowski.[4] The main difficulty in the synthesis of huperzine A **1** lies in the presence of a 1,3,3-bicyclic framework. From the common β-keto ester **2**, two strategies have been used for the construction of this skeleton (Scheme 1). The first one is a particular case of the Robinson annulation already used by Raphael[5] in a synthetic approach to Lycopodium alkaloids following path a. The second strategy (path b) is an application of palladium-catalysed bicycloannulation with 2-methylene-1,3-propanediol diacetate first studied by Gravel[6] on a model system. The first synthesis of (−)-huperzine A **1** was described by Kozikowski[7] using the Michael-aldol annulation (path a) with a (−)-8-phenyl menthol derived chiral auxiliary. A diastereomeric excess of 80% was obtained in this reaction. However, the yield of the following elimination step was modest. A different approach using a chiral base was more recently studied by Terashima.[8] The best result was observed with one equivalent of (−)-cinchonidine which afforded compound (+)-**4** (R*=Me) with an enantiomeric excess of 64%. The same group also developed an asymmetric palladium-catalysed bicycloannulation following path b.[8] A modified chiral ferrocenyl ligand previously developed by Hayashi[9] afforded (+)-**5** (R*=Me) in 64% ee. A rather similar result was obtained by He and Bai[10] who prepared compound **5** in 52% ee with another modified Hayashi catalyst.

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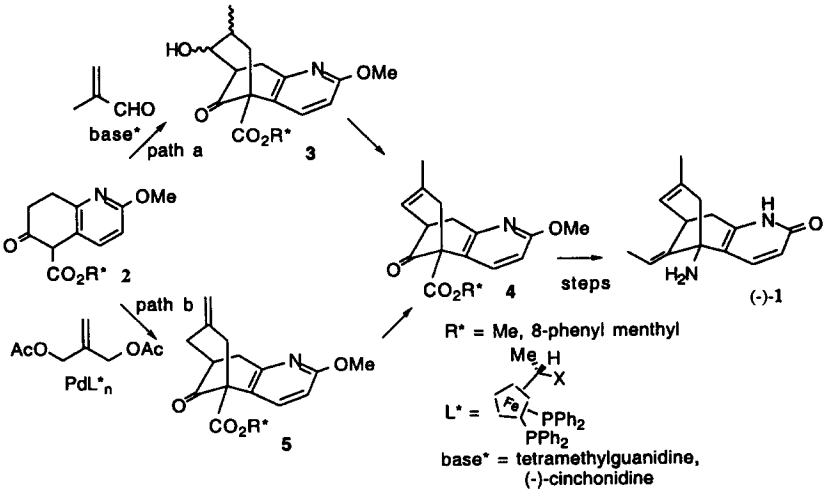
† Dedicated to Professor P. Sinaÿ on the occasion of his 62nd birthday.

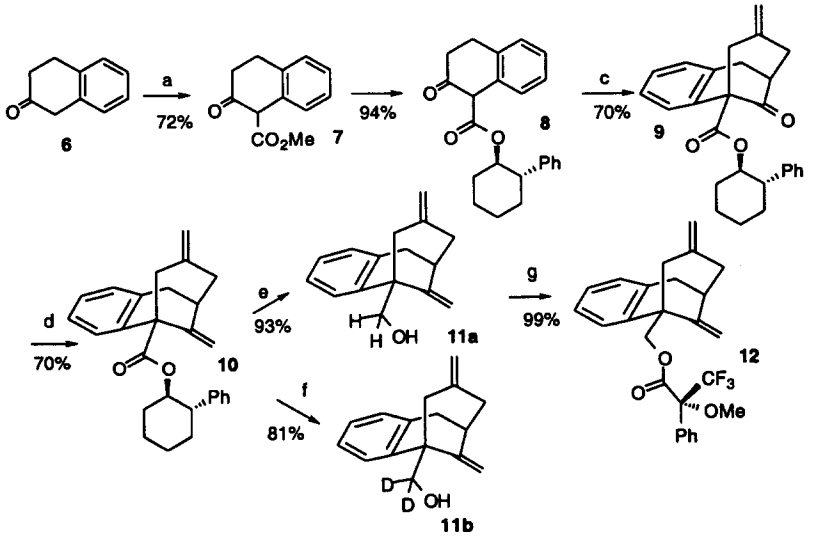
0040-4039/99/$ - see front matter
PII: S0040-4039(99)01874-2



Scheme 1.

In connection with the development of a new straightforward route to β-keto ester **2** (R*=Me),[11] we report in the present paper an efficient formal asymmetric synthesis of (+)-huperzine A **1** using the palladium annulation route and the (1*R*,2*S*)-2-phenylcyclohexanol derived keto ester **14**.

Two series of compounds were prepared to study the asymmetric palladium annulation. The benzenic β-keto ester **7** obtained in one step from the commercially available β-tetralone **6**, was first chosen as a model for this reaction (Scheme 2). Transesterification of ester **7** with (1*R*,2*S*)-2-phenylcyclohexanol[12] under acidic catalysis afforded ester **8** in 94% yield.

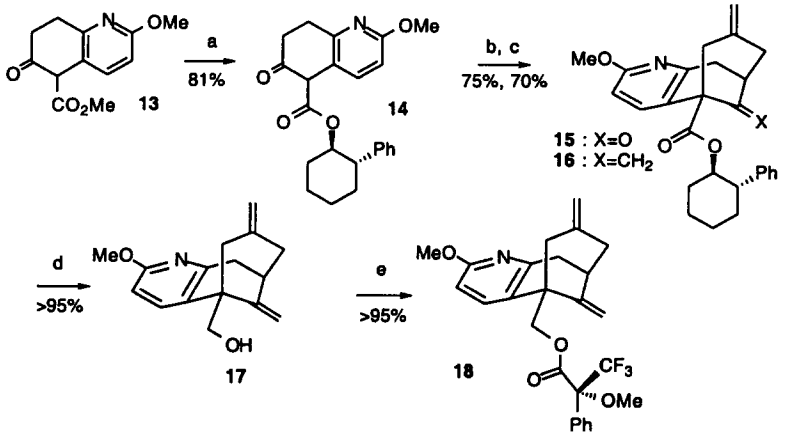


Scheme 2. (a) KH, $(MeO)_2CO$ (excess), rfx; (b) (1*R*,2*S*)-2-phenylcyclohexanol, C_6H_6, Dean–Stark, 30 h, rfx; (c) $Pd(PPh_3)_4$, 0.05 equiv., 2-methylene-1,3-propanediol diacetate, 1.1 equiv., TMG, 1.1 equiv., 1,4-dioxane, 14 h, 20°C; (d) (1) $MePPh_3^+Br^-$, *n*-BuLi, THF, 30 min, 20°C; (2) **9**, THF, 90 min, 0°C; (e) $LiAlH_4$, 1 equiv., 1 h, 20°C; (f) $LiAlD_4$, 1.5 equiv., 30 min, 20°C; (g) (1) (*R*)-(+)-Mosher acid, 1.9 equiv., C_7H_{16}, $(COCl)_2$, 3.8 equiv., DMF, cat., 1 h, 20°C; (2) (*R*)-(+)-Mosher acid chloride, 1.9 equiv., **11a**, DMAP, 3.8 equiv., CH_2Cl_2, 15 min, 20°C

1,1,3,3-Tetramethyl guanidine as the base and 1,4-dioxane as solvent were selected following the Kozikowski's palladium annulation conditions.[13] However, tetrakis(triphenylphosphine)palladium was

used instead of palladium diacetate in the presence of triphenylphosphine. When the reaction was performed at room temperature for 14 h, the tricyclic product **9** was isolated in 70% yield with an optical rotation of –60.4 (C=0.46, $CHCl_3$). In refluxing dioxane,[13] **9** was obtained in 65% yield with a reduced value of the optical rotation: –47.9. The direct measure of the diastereomeric excess was not possible at this stage and further transformations were necessary. Accordingly, the unstable β-keto ester **9**[14] was reacted with methylenetriphenylphosphorane affording ester **10**.[15] This compound was then reduced either with $LiAlH_4$ or $LiAlD_4$ affording, respectively, alcohols **11a** and **11b**. Alcohol **11a** was in turn nearly quantitatively esterified with the (*R*)-(+)-Mosher acid in the presence of oxalyl chloride giving rise to ester **12**. At this stage three different measures of the diastereomeric excess were used. ^{19}F NMR and GC of ester **12** showed that the diastereomeric excess of this compound was higher than 99%.[16] Whereas, the enantiomeric purity of alcohol **11b** was measured using Courtieu's method (^2H NMR in the presence of polybenzyl-L-glutamate)[17] and gave the same enantiomeric excess value for this compound.[18]

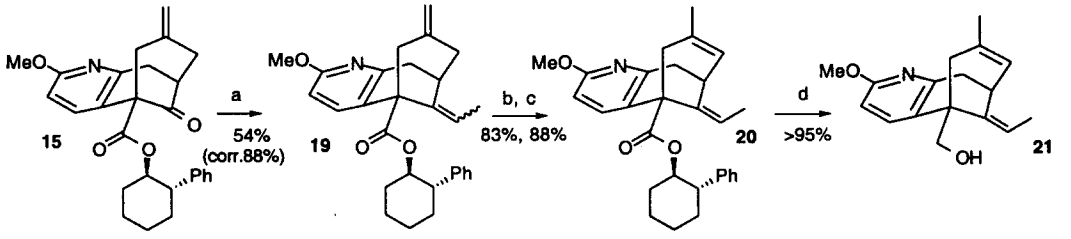
After these encouraging results in the benzenic series, use of the same chiral auxiliary was extended to the synthesis of huperzine A **1** itself. Thus, β-keto ester **13**, prepared in 43% overall yield from 2-methoxy-6-methylpyridine[11] was transesterified as previously described and the resulting ester **14** was submitted to the palladium annulation conditions. As in the previous experiment, the reaction was performed at room temperature for 18 h. The expected tricyclic compound **15** was isolated as a single isomer in 75% yield. The measure of the diastereoselectivity of this reaction was secured after the same set of reactions as in the benzenic series. Wittig olefination affording the olefinic ester **16** was followed by reduction of the ester group. The resulting primary alcohol **17** was then esterified giving rise as above nearly quantitatively to the Mosher ester **18** (Scheme 3).[16] ^{19}F NMR and GC of ester **18** allowed to measure a diastereomeric excess of 92%. At this stage, these results are quite competitive from both a yield and diastereoselectivity point of view with those obtained in the previous asymmetric syntheses of huperzine A **1** and prompted us to correlate **15** with an advanced intermediate in the synthesis of this alkaloid.



Scheme 3. (a) (1*R*,2*S*)-2-Phenylcyclohexanol, 1.5 equiv., APTS, 0.1 equiv., C_6H_6, Dean–Stark, 48 h, rfx; (b) $Pd(PPh_3)_4$, 0.05 equiv., 2-methylene-1,3-propanediol diacetate, 1.1 equiv., TMG, 1.1 equiv., 1,4-dioxane, 18 h, 20°C; (c) (1) $MePPh_3^+Br^-$, *n*-BuLi, THF, 30 min, 20°C; (2) **15**, THF, 90 min, 0°C; (d) $LiAlH_4$, 1 equiv., 1 h, 20°C; (e) (1) (*R*)-(+)-Mosher acid, 1.9 equiv., C_7H_{16}, $(COCl)_2$, 3.8 equiv., DMF, cat., 1 h, 20°C; (2) (*R*)-(+)-Mosher acid chloride, 1.9 equiv., DMAP, 3.8 equiv., CH_2Cl_2, 15 min, 20°C

Accordingly, β-ketoester **15** was treated with ethylenetriphenylphosphorane affording the ethylidene derivative **19** as a 39:61 mixture of *Z* and *E* isomers in 54% yield along with 34% of recovered starting

material. Radical mediated isomerisation of the ethylidene double bond increased this selectivity up to 15:85 after treatment with thiophenol–AIBN for 7 days.[7a] Isomerisation of the vinylic double bond was then achieved in high yield with triflic acid in 1,4-dioxane at 80°C in a sealed tube and gave rise to ester **20**. The chiral auxiliary was cleaved at this stage with lithium aluminium hydride reduction which afforded nearly quantitatively the known primary alcohol **21**, a direct synthetic precursor of huperzine A **1** (Scheme 4).[7a] The measure of the optical rotation of alcohol **21** showed the same absolute value as the product described by Kozikowski[7a] but the reverse positive sign ($[\alpha]_D$=+37 (*c* 1, $CHCl_3$)) indicating that **21** is antipodal to the natural series.[18,19]



Scheme 4. (a) $Ph_3P^+Et\ Br^-$, 9 equiv., *tert*-BuOK, 8.5 equiv., THF, 20 h, 20°C. (b) PhSH, 1.7 equiv., PhMe, AIBN, 7 days, 85°C. (c) TfOH, 1.4 equiv., 1,4-dioxane, 18 h, 85°C, sealed tube. (d) $LiAlH_4$, 1 equiv., THF, 5 h, 20°C

In conclusion, alcohol **21**, a four-step synthetic precursor of (+)-huperzine A **1**, has been prepared in high enantiomeric purity, in 11 steps and in 23.8% overall yield from 2-methoxy-6-methylpyridine. As both 2-phenylcyclohexanol enantiomers are available,[12] this synthesis also constitutes a competitive access to the acetylcholinesterase inhibitor alkaloid (±)-huperzine A **1**. The asymmetric synthesis of huperzine B[20] using a similar procedure is in progress in our laboratory.

Acknowledgements

We thank ADIR, CNRS and Université de Paris-sud for financial support and Dr. Claude Riche (ICSN, CNRS, Gif-sur-Yvette) for X-ray analysis of compound **15**.

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13. Campiani, G.; Sun, L.-Q.; Kozikowski, A. P.; Aagaard, P.; McKinney, M. *J. Org. Chem.* **1993**, *58*, 7660.
14. β-Ketoesters such as **9** and **15** (vide infra) gave rise easily to a retro Dieckman reaction.
15. Methylenetriphenyl phosphorane was chosen in this model study to avoid the formation of a mixture of *Z* and *E* isomers observed when ethylenetriphenyl phosphorane was used in this Wittig reaction, see Ref. 4.
16. Racemic alcohols **11a** and **17** were also prepared and esterified with (*R*)-(+)-Mosher acid for comparison. GC: SE 52, 30 m.
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18. The absolute configuration was determined in the huperzine A **1** series by a correlation with a known intermediate (vide infra). This correlation showed that the products resulting from the palladium annulation were antipodal to the natural (−)-huperzine. From a practical point of view, both 1*R*,2*S*- and 1*S*,2*R*-2-phenylcyclohexanols are available (see Ref. 12), so (±)-huperzine A **1** can be prepared by the same scheme using the antipodal chiral auxiliary.
19. X-Ray analysis confirmed the absolute configuration of compound **15** and following products, Riche, C. to be published.
20. For the first synthesis of (±)-huperzine B, see: Wu, B.; Bai, D. *J. Org. Chem.* **1997**, *62*, 5978.