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An asymmetric dihydroxylation route to (*S*)-oxybutynin☆

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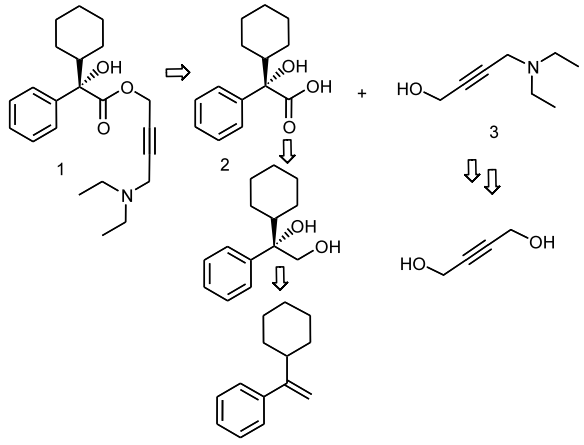
Abstract—An asymmetric synthesis of (*S*)-oxybutynin **1** is described using the Sharpless asymmetric dihydroxylation of α-cyclohexylstyrene as the key step.

Racemic oxybutynin (Ditropan) is a widely prescribed muscarinic receptor antagonist for the treatment of urinary frequency, urgency and urge incontinence.[1] It has been revealed that it exhibits classical antimuscarinic side effects, such as dry mouth. However, preliminary biological results suggest that (*S*)-oxybutynin **1** displays an improved therapeutic profile compared to its racemic counterpart, and it is currently in phase III clinical trials. Like the majority of muscarinic receptor antagonists, oxybutynin is composed of a tertiary α-hydroxy acid as a key component.[2] The abundant occurrence and biological significance of compounds containing a tertiary α-hydroxy acid[2,3] prompted us to investigate the synthesis of (*S*)-oxybutynin.

A few reports have appeared on the asymmetric synthesis of (*S*)-acid **2**[4] and (*S*)-oxybutynin.[5] These involve the use of carbohydrate systems which contain an asymmetric benzylic center,[6] the application of *cis*-aminoindanol or related constrained amino alcohols as highly defined chiral handle,[4a] a chiral mandelic acid template[4b] or catalytic chiral cyanosilylation of a ketone[4c] for the preparation of an enantiopure tertiary α-hydroxy acid. As part of our research programme aimed at developing enantioselective syntheses of naturally occurring lactones[7a–c] and amino alcohols,[7d–i] the Sharpless asymmetric dihydroxylation[8] was envisaged as a powerful tool to chiral dihydroxy compounds offering considerable opportunities for synthetic manipulations. While several aryl substituted and α-methyl styrenes[8,9] have been employed in the Sharpless asymmetric dihydroxylation, there has been no report on the asymmetric dihydroxylation of α-cyclohexylstyrene. We have now developed a new and enantioselective synthesis of the tertiary α-hydroxy acid **2** employing the Sharpless asymmetric dihydroxylation of α-cyclohexylstyrene as the key step.

Our synthetic strategy for the synthesis of (*S*)-oxybutynin **1** was envisioned through the retrosynthetic route shown in Scheme 1. The chiral *tert*-α-hydroxy acid **2**, one of the components of the target molecule, could be obtained by the Sharpless asymmetric dihydroxylation of α-cyclohexylstyrene and subsequent oxidation of the primary hydroxyl group. The other component **3** required for the oxybutynin synthesis could be easily derived from 2-butyne-1,4-diol, a readily available starting material.

The synthesis of *tert*-α-hydroxy acid **2** started from cyclohexyl phenyl ketone **4** as illustrated in Scheme 2. Compound **4** was treated with methylene triphenylphosphorane to give the Wittig product **5** in 92% yield. The asymmetric dihydroxylation of olefin **5**



Scheme 1. Retrosynthetic route to (*S*)-oxybutynin.

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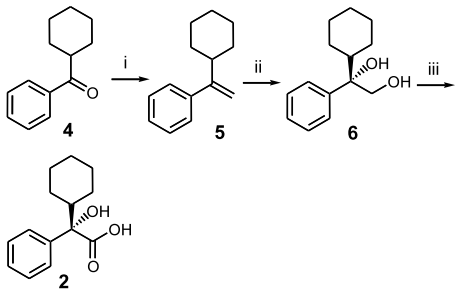
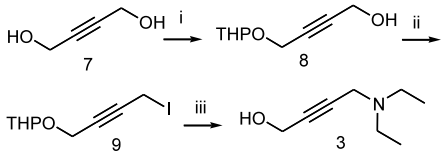


Scheme 2. *Reagents and conditions*: (i) $Ph_3P^+CH_3I^-$, *n*-BuLi, THF, 0°C–rt, 8 h, 92%; (ii) $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O (1:1), OsO_4, 0°C, 18 h, 70%; (iii) (a) $(COCl)_2$, DMSO, −78°C, Et_3N, CH_2Cl_2 (b) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, 2-methyl-2-butene, *t*-BuOH, rt, 4 h, 70%.



Scheme 3. *Reagents and conditions*: (i) DHP, *p*-TsOH (cat.), CH_2Cl_2, rt, 60%; (ii) PPh_3, I_2, imidazole, CH_2Cl_2, 0°C–rt, 90%; (iii) (a) Et_2NH, EtOH, $NaHCO_3$ (b) 6N HCl, Et_2O (c) 2N KOH, CH_2Cl_2, 70%.

with osmium tetroxide and potassium ferricyanide as cooxidant in the presence of $(DHQ)_2$-PHAL as the chiral ligand under Sharpless asymmetric dihydroxylation conditions[8,9] gave the crude product which on recrystallisation twice from EtOAc/pet. ether afforded the pure diol **6** in 70% yield with 92% ee.[10] The subsequent Jones' oxidation of the primary alcohol in **6** in order to obtain the acid **2** was unsuccessful resulting in cleavage of the diol affording the starting ketone **4** in a quantitative yield. Hence we attempted a two-step process in the following way. The alcohol **6** was first oxidized to the corresponding aldehyde under standard Swern oxidation conditions followed by further oxidation with $NaClO_2$ and $NaH_2PO_4{\cdot}2H_2O$ to furnish the acid **2** in 70% yield, $[\alpha]_D^{20}=+23.3$ (*c* 1, EtOH) [lit.[4a] $[\alpha]_D^{20}=+22.6$ (*c* 1.4, EtOH)].

Scheme 3 summarizes the synthesis of 4-*N*,*N*-diethyl aminobut-2-yn-1-ol **3** from the commercially available 2-butyne-1,4-diol **7**. The mono hydroxyl protection of **7** as the THP ether was followed by conversion of the free hydroxyl group into the iodide **9** in good yield. Displacement of iodide with diethylamine and subsequent acid treatment resulted in the formation of the hydrochloride salt of **3** with concomitant deprotection of the THP ether. Subsequent neutralization with base furnished the desired compound **3** in 70% yield.

The final step involved the coupling of acid **2** with amino alcohol **3** which could readily be performed by activating the acid as a mixed anhydride and condensation with **3** as previously described.[5]

In summary, a practical and short synthesis of (*S*)-oxybutynin has been realized employing the Sharpless asymmetric dihydroxylation of α-cyclohexylstyrene for the first time as the key step. The synthetic strategy can be further extended to the asymmetric synthesis of (*R*)-oxybutynin and other related analogs. Currently studies are in progress in this direction.

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References

1. Thompson, I. M.; Lauvetz, R. *Urology* **1976**, *8*, 452–454.
2. Atkinson, E. R.; McRitchi, D. D.; Schoer, L. F. *J. Med. Chem.* **1977**, *20*, 1612–1617.
3. (a) Caldwell, C. G.; Rupprecht, K. M.; Bondy, S. S.; Davia, A. A. *J. Org. Chem.* **1990**, *55*, 2355–2361; (b) Boeck, R. K., Jr.; Yoon, S. K.; Heckendorn, D. K. *J. Am. Chem. Soc.* **1991**, *113*, 9682–9684; (c) Yamada, K.; Niwa, H.; Ogawa, T.; Okamoto, O. *Tetrahedron* **1992**, *48*, 10531–10548; (d) Kanda, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **1993**, *115*, 8451–8452; (e) Schreiber, S. L.; Valentekovich, R. J. *J. Am. Chem. Soc.* **1995**, *117*, 9069–9070.
4. (a) Senanayake, C. H.; Fang, K.; Grover, P.; Bakale, R. P.; Vandenbossche, C. P.; Wald, S. A. *Tetrahedron Lett.* **1999**, *40*, 819–822; (b) Grover, P. T.; Bhongle, N. N.; Wald, S. A.; Senanayake, C. H. *J. Org. Chem.* **2000**, *65*, 6283–6287; (c) Masumoto, S.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 8647–8651.
5. Bakale, R. P.; Lopez, J. L.; McConville, F. X.; Vandenbossche, C. P.; Senanayake, C. H. US Pat. 6,140, 529.
6. Inch, T. D.; Ley, R. V.; Rich, P. *J. Chem. Soc. (C)* **1968**, 1693–1699.
7. (a) Pais, G. C. G.; Fernandes, R. A.; Kumar, P. *Tetrahedron* **1999**, *55*, 13445–13450; (b) Fernandes, R. A.; Kumar, P. *Tetrahedron: Asymmetry* **1999**, *10*, 4349–4356; (c) Fernandes, R. A.; Kumar, P. *Eur. J. Org. Chem.* **2002**, 2921–2923; (d) Fernandes, R. A.; Kumar, P. *Tetrahedron: Asymmetry* **1999**, *10*, 4797–4802; (e) Fernandes, R. A.; Kumar, P. *Eur. J. Org. Chem.* **2000**, 3447–3449; (f) Pandey, R. K.; Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2002**, *43*, 4425–4426; (g) Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2000**, *41*, 10309–10312; (h) Naidu, S. V.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 1035–1037; (i) Kandula, S. V.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 1957–1958.
8. (a) Becker, H.; Sharpless, K. B. *Angew Chem., Int. Ed. Engl.* **1996**, *35*, 448–451; (b) Kolb, H. C.; VanNiewenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.
9. (a) Weissman, S. A.; Rossen, K.; Reider, P. J. *Org. Lett.* **2001**, *3*, 2513–2515; (b) Lawrence, N. J.; Bushell, S. M. *Tetrahedron Lett.* **2001**, *42*, 7671–7674; (c) Ramacciotti, A.; Fiaschi, R.; Napolitano, E. *Tetrahedron: Asymmetry* **1996**, *7*, 1101–1104.
10. The enantiomeric excess was determined by converting the diol into the mono-Mosher ester and analyzing the ^{19}F spectrum.