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An efficient asymmetric synthesis of (*S*)-2-cyclohexyl-2-phenylglycolic acid, the acid segment of oxybutynin

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Abstract—An innovative and facile synthesis of the title compound has been developed starting from (*R*)-cyclohexylidene glyceraldehyde. The key step in the synthesis is a chiral template-driven Grignard addition with absolute diastereocontrol. The other attractive features are the operational simplicity and the use of inexpensive compounds/reagents.

Tertiary hydroxy acids and their derivatives are important intermediates in the asymmetric synthesis of a variety of medicinal agents[1] and natural products.[2] One such compound, oxybutynin (Ditropan) (**1**), is widely prescribed in racemic form for the treatment of urinary frequency, urgency and urge incontinence,[3] although its (*S*)-enantiomer displays a better therapeutic profile devoid of antimuscarinic side effects.[4] In view of the medicinal importance, oxybutynin and its congeners have become important targets for organic chemists leading to several asymmetric syntheses of (*S*)-**1**[5a–e] and its constituent acid segment **2**.[6a] Further, various congeners of **1** with improved receptor subtype selectivity and less side effects have also been synthesized.[1b,6b–d]

Earlier, the key acid subunit (*S*)-**2** was synthesized using a chiral Gd-complex-mediated asymmetric cyanosilylation of a suitable ketone,[5a,c] Sharpless asymmetric dihydroxylation,[5b] organometallic addition to a chiral mandelic acid template[5d] and via a proline-catalyzed asymmetric aldol reaction.[5e] In addition, its asymmetric synthesis by addition of a cyclohexyl Grignard reagent in the presence of various additives to a chiral ketoamide or a ketoester possessing a rigid benzocycloalkl-ene-derived vicinal amino alcohol platform was also reported.[6a] For our part, we have developed a practical synthesis of **2** with excellent enantioselectivity and high yield.

Earlier, we found[7a–c] that addition of Grignard reagents to easily accessible glyceraldehyde derivative **3** proceeded efficiently to furnish the diastereomeric alkanetriol derivatives. It was envisaged that extension of a similar strategy with a suitable glyceraldehyde-derived ketone might be an efficient alternative for the synthesis of **2**. It was anticipated that the bulky cyclohexyl group in the chiral ketone might provide good diastereomeric bias for the Grignard addition, while the acetal functionality of the resultant compound would ensure its easy conversion to the required acid moiety.

Thus, we reacted **3** with phenylmagnesium bromide to furnish **4** in excellent yield as a mixture of two chromatographically separable diastereomers. Since the stereochemical course of the reaction was of no consequence to the present synthesis, we did not assess the diastereoselectivity of the reaction. Oxidation of **4** with buffered pyridinium chlorochromate (PCC)[8] afforded ketone **5**. Reaction of **5** with cyclohexylmagnesium bromide proceeded uneventfully to afford tertiary alcohol **6a** in excellent yield, and as a single diastereomer

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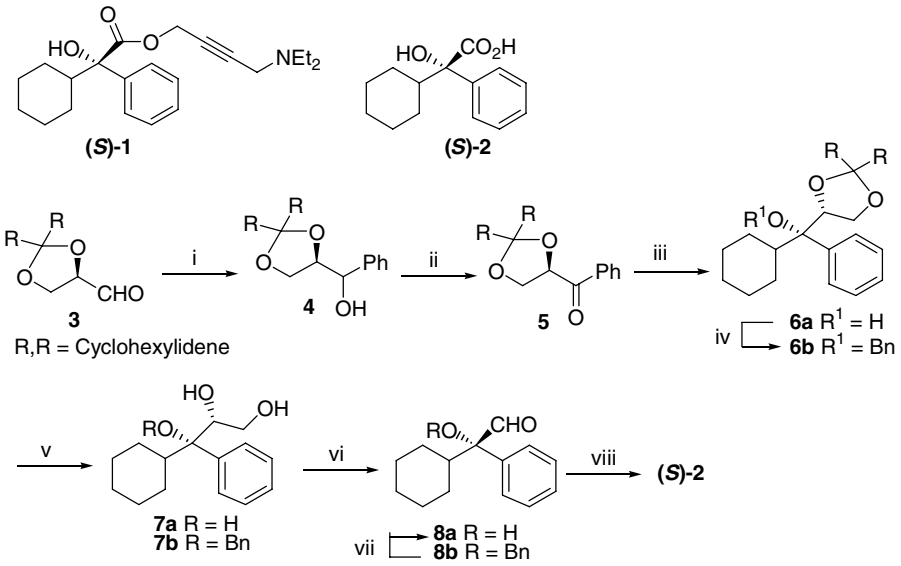

Scheme 1. Reagents and conditions: (i) PhMgBr/THF (88%), (ii) PCC/NaOAc/CH_2Cl_2 (84%), (iii) cyclohexylmagnesium bromide/THF (87%), (iv) BnBr/NaH/THF/Δ (88%), (v) 1% HCl–MeOH (77% and 92% from **6a** and **6b**, respectively), (vi) $NaIO_4$/MeCN/H_2O (45% and 81% from **7a** and **7b**, respectively), (vii) DDQ/CH_2Cl_2/45 °C (88%), (viii) $NaClO_2$ (68%).

as revealed from its ^1H and ^{13}C NMR spectra.[9] Attempted hydrolysis of the acetal function of **6a** with 25–70% aqueous trifluoroacetic acid or 5–30 mol % $CuCl_2{\cdot}H_2O$/MeOH[10] resulted in either decomposition of **6a**, or very low yields of the required product **7a**. Surprisingly, the desired transformation could be achieved in the presence of 1% HCl in methanol to give **7a** in an acceptable (77%) yield. This on treatment with $NaIO_4$ in aqueous CH_3CN provided aldehyde **8a** along with benzoylcyclohexane[5b] formed by further cleavage of the α-hydroxyaldehyde function of **8a**. Carrying out the reaction at 0 °C, and adding $NaIO_4$ in batches did not suppress this side reaction, and **8a** was obtained in ~45% yield. Oxidation of **8a** with $NaClO_2$ gave the target acid (*S*)-**2** (70%), which was characterized from its spectral data which matching those reported.[6a] The $[\alpha]_D$ value of our synthetic sample compared very well with the reported value confirming the absolute stereochemistry as (*S*). The enantiomeric excess (98%) of (*S*)-**2** was determined by HPLC (Chiracel OD-H column, mobile phase 95% hexane/5% IPA) analysis.

In view of the low yield of **8a**, an alternative strategy for the synthesis of (*S*)-**2** was developed. Thus, alcohol **6a** was benzylated to give **6b**, which was converted to diol **7b** in excellent yield (92%) as above. Reaction of **7b** with $NaIO_4$ proceeded uneventfully to give **8b** (81%), which on debenzylation with DDQ afforded **8a**. This was then oxidized with $NaClO_2$ to furnish (*S*)-**2** in 68% yield. Although the alternative scheme requires two additional steps, the overall yield of the target compound was higher (Scheme 1).

Overall, a highly enantiocontrolled synthesis of the core acid unit (*S*)-**2** of oxybutynin has been developed. One of the notable features of the synthesis is the absolute stereocontrol in the Grignard addition to the ketone, providing the required tertiary carbinol as a single diastereomer. Further, the method can also be used for the synthesis of (*R*)-**2** by altering the sequence of the Grignard addition or using the easily accessible[11] (*S*)-**3** as the chiral template.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.07.101.

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9. *Data for* **6a**: $[\alpha]_D^{22}$ +20.97 (*c* 1.03, $CHCl_3$); IR: 3349, 3060, 1588, 1480 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.08–1.25 (m, 8H), 1.40–1.68 (m, 12H), 2.08–2.14 (m, 1H), 2.59 (s, D_2O exchangeable, 1H), 3.35–3.52 (m, 2H), 4.64 (t, $J = 8.6$ Hz, 1H), 7.18–7.31 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.4, 25.6, 25.9, 26.1, 26.3, 26.8, 29.4, 34.6, 35.2, 47.6, 65.1, 75.5, 78.0, 109.5, 124.7, 125.9, 126.9, 141.0. Anal. calcd for $C_{21}H_{30}O_3$: C 76.32, H 9.15; found: C 76.10; H 9.05.
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