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Short communication

An efficient approach to the asymmetric total synthesis of (–)-anisodine

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Abstract

–Anisodine (L-6,7-epoxy-3-tropyl-α-hydroxytropate), which was isolated from the medicinal plant *Scopolia tanguticus Maxim*, was the first efficiently prepared using 6-β-acetyltropine as the starting material via a key step of the Sharpless asymmetric dihydroxylation (AD). The intermediate compounds **10** and **11** showed promising cholinergic activity.
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1. Introduction

The medicinal plant *Scopolia tanguticus Maxim* is locally known as "Zhangliushen" in the Qinghai–Xizang Plateau [1]. It has often been used as a folklore medicine for the treatment of toothache, stomachache and other pains [1]. The close resemblance of *S. tanguticus Maxim* in appearance to *Phytolacca esculenta* has caused trouble in the past, since the latter is a regular article of commerce in traditional medical practice for the treatment of oedema [1]. When *Anisoclus tanguticus* was mistakenly used as *P. esculenta*, it caused mydriate, hallucination, and other severe mental disturbances [1]. These led people to study their chemical principles of those plants in details. As a results, (-)anisodine **1** and anisodamine **2**, (–)-6(s)-hydroxytropane have been isolated (Fig. 1) [2]. The related pharmacological studies have showed that (–) anisodine alkaloid possesses stronger central nervous system action and is a better antidote against organophosphorous toxicities [3]. Its LD_{50} is less than atropine **3**, scopolamine **4**, and anisodamine **2**. It is a good ganglion-blocking agent, used clinically for the treatment of motion sickness, migraine and vascular spasm of fundus oculi [1].

Subsequent research indicates that the quaternary ammonium salts of anisodine had weaker amnestic effect than sco-

polamine and its quaternary ammonium salts. In our earlier work, racemic anisodine was prepared from scopolamine [4]. In order to study the structure-activity relationship of anisodine, it would be desirable to have optical isomers of anisodine. It would also be useful to prepare the related optically active compounds for the potential studies of chiral drugs, which are becoming the subject of many research interests [5, 6]. Chemically, transition metal-catalyzed oxidation of carbon–carbon double bonds has become one of the most commonly used transformations in organic synthesis [7–11]. Among these reactions, the osmium-catalyzed dihydroxylation in its asymmetric version represents a benchmark when it comes to generality and selectivity [12–20].

2. Results and discussion

We considered that the stereogenic center of the diol unit in (–)-anisodine could be installed by the catalytic asymmetric dihydroxylation of compound **11** (Scheme 1). It is well known that the chiral ligand [21] plays the most important role in the Sharpless asymmetric dihydroxylation, since it directs the stereochemistry of the reaction. Three ligands are commercially available: hydroquinidine 1,4-phthalazinediyl diether [(DHQD)$_2$PHAL], hydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether [(CDHQD)$_2$PYR], and hydroquinidine anthraquinone-1,4-diyl diether [(CDHQD)$_2$AQN] [22]. Each of these has a dihydroquinine analog: (DHQ)$_2$PHAL, (DHQ)$_2$PYR and (DHQ)$_2$AQN. According to Sharpless [21], the phthalazine

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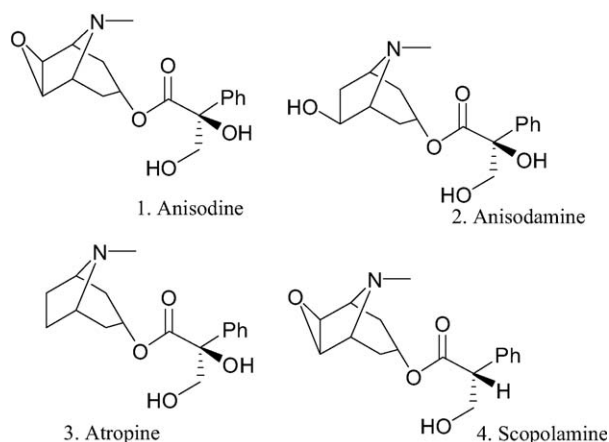J. Chang et al. / European Journal of Medicinal Chemistry 41 (2006) 397–400
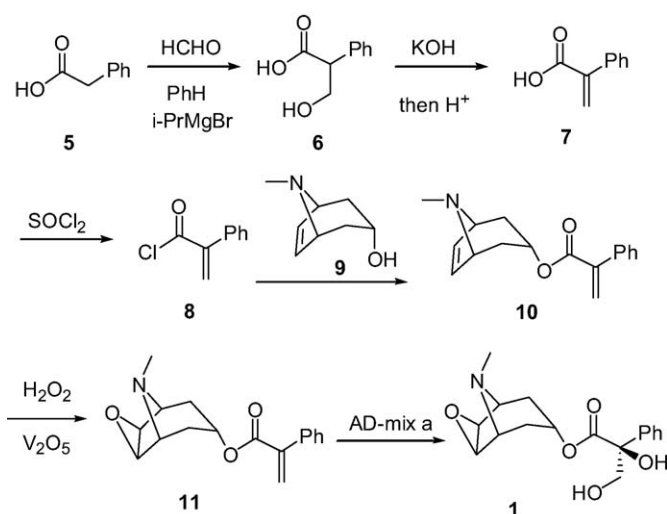

Fig. 1. Structures of anisodamine, anisodine, atropine, and scopolamine.

Scheme 1.

(PHAL) derivative is most general and leads to high enantios-electivities for most alkenes; whereas the pyrimidine (PYR) ligand is best for sterically congested alkenes (especially 1,1′-disubstituted alkenes) and the anthraquinone (AQN) derivatives is most suitable for almost all alkenes having only aliphatic substituents. Armed with this information, we employed the commercially available AD-mix α with (DHQ)$_2$-PHAL as a ligand for the Sharpless asymmetric dihydroxylation reaction.

As shown in Scheme 1, the key intermediate 11 can be easily obtained by straightforward reactions. Phenylacetic acid 5 was converted to chloride 8 through aldol condensation, dehydration and chloride formation. Atropic chloride 8 reacted with trop-Δ-3α-ol 9 to give 10, which was selectively oxidized to 11 by H$_2$O$_2$/V$_2$O$_5$ oxidation. It is well known that osmium-catalyzed dihydroxylation of olefins is one of most efficient methods for the preparation of vicinal diols [23]. In 1982, we reported the total synthesis of Anisodine by using N-methyl morpholine N-oxide (NMO) and osmium tetroxide with low yield [24]. In this paper, we report efficiently preparing of Anisodine by using Sharpless asymmetric dihydroxylation(AD) method in high yield and high ee%. Oxidation of 11 by a standard procedure with commercially available AD-mix α, a mix-

ture of potassium osmate, K$_3$[Fe(CN)$_6$], K$_2$CO$_3$ and (DHQ)$_2$-PHAL, provided the (−)-anisodine in 85% yield and 80% ee. The enantio selectivity is moderate, but it demonstrates that low-molecular weight materials can be used as catalyst to reach the similar enantioselectivities to those obtained in enzymatic reactions. This is the first example of the total synthesis of the (−)-enantiomer of anisodine, which is achieved via simple six steps in overall 21.6% yield.

3. Conclusion

Based on literature results and our own investigations, we prepared (−)-anisodine using the Sharpless asymmetric dihydroxylation (AD) method. Herein, we wish to report our preliminary results on the asymmetric dihydroxylation of dehydroxy scopolamine. In particular, the asymmetric dihydroxylation of 6,7-epoxy-3-(α-methyl-phenylacetoxy)-8-methyl-bicyclo[3,2,1] azaoctane afforded the diols in high yield and 80% ee.

4. Experimental

4.1. General

Melting points were taken on a Reichert microscope and uncorrected. Infrared spectra were recorded on a PE-580B spectrophotometer. ^{1}H-NMR spectra data were obtained on a Bruker-300 spectraspin spectrometer in CDCl$_3$. Mass spectra were recorded on a Shimadzu ZAB-2B spectrometer. Sillica gel G and GF$_{254}$ were used for column chromatography and TLC.

4.1.1. Synthesis of tropic acid 6

Magnesium (25 g) and anhydrous ether (500 ml) were placed in flask, which was equipped with a stirrer, dropping funnel and reflux condenser. A mixture of ethyl bromide (1 ml) and isopropyl chloride (4 ml) was then added. After the initiation of the reaction by warming, isopropyl chloride (85 g, 1.41 mol) was then added at such a rate that the mixture was kept gently refluxed. After all of the chloride had been added, the mixture was further refluxed for additional one and half hours.

To above-mentioned solution was added a mixture of phenylacetic acid (60 g, 0.44 mol) and dry benzene (500 ml) slowly to just maintain the mixture refluxed. After the addition was completed, the reaction mixture was refluxed until no gas was evolved. The mixture was then cooled using an ice-bath, and the dropping funnel was replaced by the side arm of a distillation flask. Paraformaldehyde (40 g), which had been dried far two days in a desiccator over P$_2$O$_5$, was placed in a distillation flask, and heated to 180–200 °C in an oil-bath. The formaldehyde was carried into the vigorously stirred mixture by a slow stream of dry nitrogen in the period of 4 hours. After the reaction mixture was poured into a mixture of concentrated. H$_2$SO$_4$ (75 ml) and crushed ice (700 g), the mixture was stirred for 2 hours. The solid material was removed by filtration, the

organic layer separated. The aqueous layer and the filtered solid, which were placed in the original reaction flask, were warmed on a steam bath for 2 hours until most of the solid disappeared. After thoroughly cooled, solid materials were filtered and aqueous layer was extracted with ether (2 × 100 ml). The ether extracts and the organic layer were combined, and the solvents were removed under reduced pressure until the volume was reduced to about 100 ml. The mixture was then cooled for overnight to precipitate tropic acid, which was collected by filtration. The filtrate was concentrated and cooled to give the second crop of tropic acid after filtration. The crude tropic acid was heated with benzene (120 ml), cooled, filtered, and washed with a small amount of cold benzene. The collected materials were air-dried to give tropic acid **6** (51 g, 69.6%), m.p. 116–117 °C ([25]; m.p. 116–117 °C). ^{1}H-NMR (CDCl$_3$) δ ppm: 3.70–4.30 (m, 4H, CHCH$_2$OH), 7.30 (m, 5H, Ph). IR (KBr, cm^{-1}): 3399(–OH), 3087(=C–H), 1710(–O–C=O). MS: *m/z*(%), M-30(100), 118(55), 104(39), 91(58), 77 (19).

4.1.2. Synthesis of atropic acid 7

To a solution of KOH (19.0 g) in H$_2$O (40 ml) was added tropic acid **6** (15.2 g, 91.6 mmol). The reaction mixture was refluxed for 1 hour, and then cooled to 0 °C. The 35% HCl (60 ml) was added to give white solid, which was filtered and washed with a small amount of cold water. Removal of residue solvents in vacuo afforded 12.2 g of the compound **7** (90.0%), m.p. 101–103 °C. ^{1}H-NMR (CDCl$_3$) δ ppm: 5.2 (d, *J* = 1.10 Hz, 1H, =CH), 5.55 (d, *J* = 1.10 Hz, 1H, =CH), 7.40 (m, 5H, Ph), 11.0 (br, s, 1H, COOH). IR (KBr, cm^{-1}): 3423 (OH), 3063(=C–H), 1699(C=O), 1600(C=C).

4.1.3. Synthesis of 3α-atropoyltropene-6 10

To a solution of compound **7** (3.7 g, 25 mmol) in dry benzene (20 ml) was added SOCl$_2$ (40 ml). The reaction mixture was heated at 60 °C for 4 h. After removal of the solvent, the TsOH salt of trop-Δ6-3α-ol (6 g, 20 mmol) in dry chloroform (200 ml) was added, and kept at 60 °C for 8 h under N$_2$. After the completion of the reaction by TLC, solvent was removed and the resulting crude product was purified by flash column chromatography on neutral Al$_2$O$_3$ using 3:1:0.01 CHCl$_3$/EtOAc/25% NH$_3$·H$_2$O as an eluent to give 3.5 g (51.4%) of **10**. This compound was acidified with 16% aqueous hydrochloric acid; m.p. 190–191 °C (3α-atropoyltropene hydrochloride). ^{1}H-NMR (CDCl$_3$) δ ppm: 2.20 (m, 2H), 2.92 (s, 3H, NCH$_3$), 2.90–3.41 (m, 2H), 4.28 (br, s, 2H, 2 × NCH), 5.25 (d, *J* = 5.12 Hz, 1H, CH–O–), 5.85 (d, *J* = 1.10 Hz, 1H, =CH), 6.10 (brs, 2H, CH=CH), 6.35 (d, *J* = 1.10 Hz, 1H, =CH), 7.35(m, 5H, Ar–H). IR (KBr, cm^{-1}): 3078(=C–H), 1700(O–C=O), 1600(C=C). MS: *m/z*(%), 269(M+, 60), 138 (50), 103(30), 122(80), 94(100).

4.1.4. 3α-acetoxytrop-6β,7β-epoxy-tropane 11

To a solution of compound **10** (538 mg, 2 mmol) in anhydrous CH$_3$CN (30 ml) was added V$_2$O$_5$ (100 mg) and 30% H$_2$O$_2$ (3.5 ml). The reaction mixture was heated at 45 °C for

8 h. After removal of the solvent, aqueous K$_2$CO$_3$ was added slowly to pH ~ 8.0 and the solution was extracted with chloroform (4 × 15 ml). The organic layer was dried over anhydrous Na$_2$SO$_4$ and evaporated. The resulting crude product was purified by flash column chromatography on Al$_2$O$_3$ using 3:1:0.01 CHCl$_3$/EtOAc/25% NH$_3$·H$_2$O as an eluent to give **11** (450 mg, 78.9%), which was converted to its hydrochloride salt; m.p. 128–130 °C. ^{1}H-NMR (CDCl$_3$) δ ppm: 1.90–1.95 (m, 2H), 2.87 (s, 3H, –NCH$_3$), 3.23–3.56 (m, 2H), 3.55 (s, 2H), 3.82 (br, s, 2H, 2 × NCH), 5.43 (t, *J* = 5.12 Hz, 1H, CH–O–), 5.60 (d, *J* = 1.10 Hz, 1H, =CH), 6.45 (d, *J* = 1.10 Hz, 1H, =CH), 7.38 (m, 5H, Ar–H). IR (KBr, cm^{-1}): 3080 (=C–H), 1700 (–O–C=O), 1600 (C=C). *m/z* (%): 285 (M$^+$, 65), 154 (45), 138 (80), 103 (55), 94 (100).

4.1.5. Synthesis of (–)-anisodine 1

To a mixture of 25 ml of *t*-butyl alcohol and 25 ml of water, 8 g of AD-mix α was added. The solution was stirred at room temperature to produce two clear phases. The mixture was cooled to 0 °C, compound **11** (2.85 g, 10 mmol) was then added at once to give a heterogeneous slurry, which was stirred at 0 °C for 24 h. After the completion of the reaction (progress was monitored by TLC), solid sodium sulfite (8 g) was added to the stirred mixture, which was allowed to warm to room temperature and to be further stirred for 30 min. Methylene chloride was added to the reaction mixture and, after separation of the organic layer, the aqueous phase was further extracted with methylene chloride. The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated. The crude product was purified by column chromatography using 90:8:2 CH$_3$OH/CH$_2$Cl$_2$/25% NH$_3$·H$_2$O as an eluent to give (–)-anisodine **1** (2.71 g, 85.1%). Anisodine HBr: $[\alpha]_D$ [25] = 22.64 (*c* = 0.27 CH$_3$OH), ([2] $[\alpha]_D$ [15] = 29.46 (c1.0 H$_2$O); $[\alpha]_D$ [15] = 12.26 (c0.93 CH$_3$CH$_2$OH)). m.p. > 192 °C (decompose). ^{1}H-NMR (CDCl$_3$) δ ppm: 1.53 (1H, d, 2-eq-H), 1.66 (1H, d, 4-eq-H), 2.16 (2H, m, 2,4-ax-H), 2.50 (3H, s, –NCH$_3$), 3.18–3.25 (4H, m, 2 × NCH, 2-OH), 3.30, 3.57 (2H, d, *J* = 3 Hz, 6,7-H), 3.75 (1H, d, *J* = 10 Hz, CH$_2$–OH), 4.30 (1H, d, *J* = 10 Hz, –CH$_2$OH), 4.98 (1H, t, *J* = 5.4 Hz, 3-H), 7.31–7.57 (5H, m, Ar–H). IR (KBr, cm^{-1}): 3450 (–OH), 3051 (=C–H), 1730 (–O–CO–), 1600 (C=C). *m/z* (%): 319 (M$^+$, 25), 154 (20), 138 (100), 108 (40), 94 (60).

5. Cholinergic activity

5.1. Method

Anticholinergic activity was characterized in isolated guinea-pig whole ideal segments. The experiment was divided into three groups: compound **10** group, compound **11** group, solvent comparison group (Table 1).

5.2. Results

The frequency and height of contractions were used to calculate the percent inhibitory actions. The results showed that

Table 1
The percent inhibitory effect on acetylcholine-induced contractions in isolated guinea-pig whole ileal segments

Group	Inhibition (%)				
	10^{-7} mol l^{-1}	10^{-6} mol l^{-1}	10^{-5} mol l^{-1}	10^{-4} mol l^{-1}	10^{-3} mol l^{-1}
Solvent control group	2.83 ± 0.86	-1.25 ± 0.32	-2.53 ± 0.95	1.58 ± 0.49	0.07 ± 0.03
Compound **10**	5.77 ± 1.92**	$0.91 \pm .83$**	11.12 ± 3.46**	76.38 ± 15.30**	100**
Compound **11**	4.75 ± 1.75	2.63 ± 1.10**	58.96 ± 13.45**	95.13 ± 31.35**	100**

Note: $*P < 0.05$, $**P < 0.01$ vs. that solvent control group. Concentration of acetylcholine $= 2.75 \times 10^{-6}$ mol l^{-1}.

compounds **10** and **11** had inhibitory function on acetylcholine-induced contractions in isolated guinea-pig whole ileal segments.

5.3. Conclusion

Compound **10** and compound **11** had dose-dependent inhibitory effect on acetylcholine-induced contractions of guinea-pig whole ileum segments in vitro [25].

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