Chinese Chemical Letters Vol. 15, No. 3, pp 265-268, 2004
http://www.imm.ac.cn/journal/ccl.html

Toward Total Synthesis of Yohimbine and Reserpine Alkaloids; Part 1. An Improved Synthesis of *cis*-5, 8-Dihydroxy-1, 4, 5, 8, 9,10-hexahydronaphthalene-1, 8-lactone *via* Selective Reduction of the Conjugated Ketone with Zn $(BH_4)_2$

Yong Ye LI, Mei XU, Fen Er CHEN*

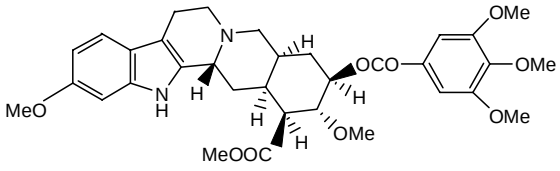
Department of Chemistry, Fudan University, Shanghai 200433

Abstract: An improved and high-yielding synthesis of *cis*-5, 8-dihydroxy-1, 4, 5, 8, 9, 10- hexahydronaphthalene-1,8-lactone **7**, an intermediate for (-)-reserpine **1** is presented. The conjugated ketone **5** was regioselectively reduced to afford lactone **7** with zinc borohydride formed *in situ* from KBH_4 and $ZnCl_2$ in THF.

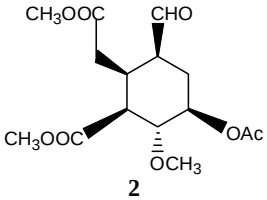
Keywords: (-)-Reserpine, lactone, zinc borohydride, reduction, synthesis.

cis-5, 8-Dihydroxy-1, 4, 5, 8, 9, 10-hexahydronaphthalene-1, 8-lactone **7** is the key intermediate to build E ring **2** possessing five chiral centers in total synthesis of (-)-reserpine **1**[1, 2]. In 1958, Woodward firstly reported an artful route to the synthesis of (-)-reserpine from the acid **4**. One major drawback of this promising approach is the low yield obtained in the synthesis of the required lactone **7**. Herein, we described an efficient and improved method for the synthesis of **7** as shown in **Scheme 1**.

Figure 1



1



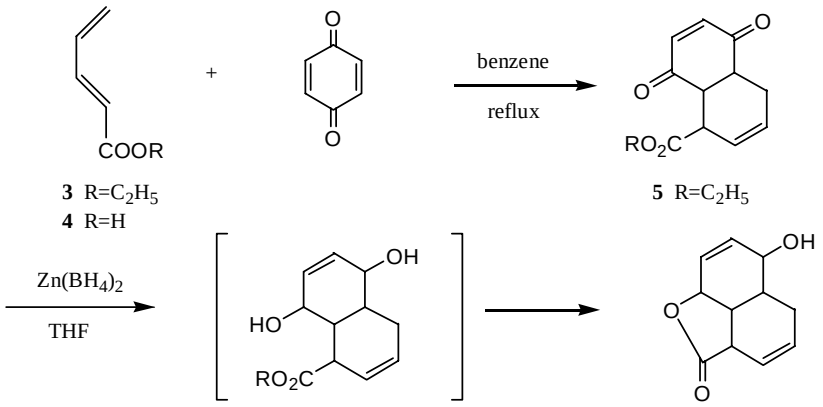
2

The conjugated ketone **5** was obtained from benzoquinone and the ester **3** prepared through the condensation of monoethyl malonate with acrolein according to the modified Rodriguez procedure[3]. Treatment of monoethyl malonate with acrolein in dry pyridine at room temperature for 24 h afforded crude **3** in 82% yield (including 92% pure product detected by GC-MS). **3** was used without any purification for the next step, avoiding

* E-mail: rfchen@fudan.edu.cn

the use of an expensive catalyst dimethylaminopyridine (DMAP)[3]. Diels-Alder reaction of benzoquinone with the ester **3** was carried out at N_2 atmosphere for 24 h to give the ketone **5** in 45% yield. It is interesting that if the reaction proceeded without N_2, the yield decreased to 15%.

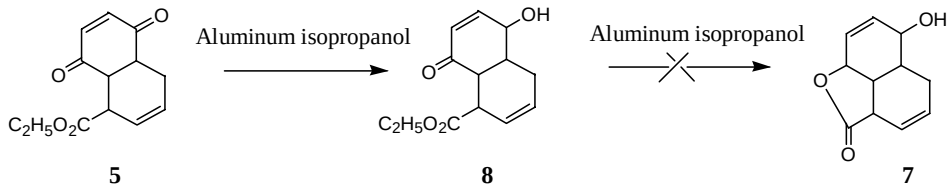
Scheme 1



3 R=C_2H_5
4 R=H
5 R=C_2H_5
6 R=C_2H_5
7

Selective reduction of the conjugated ketone **5** afforded the corresponding unsaturated diol **6**, which is the key intermediate to prepare lactone **7**. Considerable progress has been made in the development of various reducing agents for regioselective 1,2-reduction of the conjugated ketones[4]. We tried the various reducing agents and different reaction conditions (**Table 1)** for enhancing the chemoselectivity of this reaction.

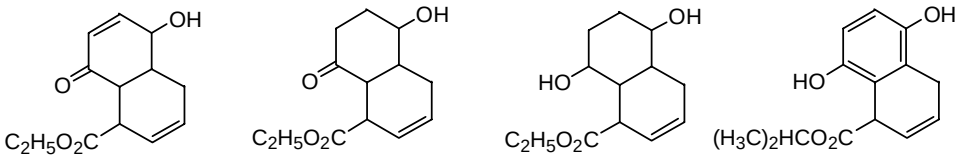
Scheme 2



5 **8** **7**

When we followed the Woodward procedure[2] to prepare **7**, the Meerwein-Porndorf-Verley (MPV) reduction of the ketone **5** resulted in the formation of the aromatic isomer **11** as the main product (Entry 1). When the reaction was carried out at 50°C[6], the ketone **5** was reduced to give 1,2-reduction product **8** and aromatic isomer **11** in ratio of 9:1(Entry 2). When the ketone **8**, isolated by crystallization, was further reduced in the same conditions, no required **7** was obtained and the ketone **8** was recovered unchanged (**Scheme 2**). Several reducing agents, such as $NaBH_4$, KBH_4, 9-BBN, BH_3-SMe_2, were tested[7-9]. However, all these approaches were failed to obtain **7**(Entry 3-6).

Figure 2



8 **9** **10** **11**

Table 1 The Reduction of Ketone **5** with various Reducing agents

Entry	Reducing agent (Equiv.)	Solvent	Temp. (℃)	Time (h)	Content of Products (%)[a]				
					7	**8**	**9**	**10**	**11**
1	$Al[OCH(CH_3)]_3$ (3)	Iso-PrOH	80/N_2	2	–	10	–	–	90
2	$Al[OCH(CH_3)]_3$ (3)	Iso-PrOH	50/N_2	3	–	88	–	–	10
3	$NaBH_4$ (0.33)	NEt_3/MeOH	-5/N_2	1	–	57	10	10	–
4	KBH_4 (2)	MeOH	r.t.	6	–	–	10	50	–
5	9-BBN/THF[b] (1)	THF	r.t.	5	Complicated products				
6	BH_3-SMe_2/THF[c] (1)	THF	0	2	Complicated products				
7	Zn $(BH_4)_2$/ether[d] (1)	C_6H_6	r.t.	5	–	77	–	–	–
8	Zn $(BH_4)_2$/ether[d] (2)	C_2H_5OH	r.t.	5	–	90	–	–	–
9	Zn $(BH_4)_2$/THF[e] (1)	THF	r.t.	2	40	50	–	–	–
10	Zn $(BH_4)_2$/THF[e] (1)	THF	r.t.	5	90	–	–	–	–
11	Zn $(BH_4)_2$/THF[e] (1)	THF	r.t.	10	75	–	–	–	–

[a] The content of the products was detected by GC-MS.
[b] 0.5 mol/L solution; [c] 2.0 mol/L solution; [d] 0.15 mol/L solution; [e] 0.5 mol/L solution

Table 1 showed that the best result was obtained by using Zn $(BH_4)_2$ as the reducing agent in THF at r.t. for 5 h (Entry 10). The yield of the crude product **7** was 83%, no appreciable 1,4-reduction products or aromatic isomer were observed. The reaction mixture was added water to quench the reaction. After extraction with ethyl acetate, the solvent was removed to afford crude product **7** in 83% yield, purity was 90% detected by GC-MS. When the reaction carried out for longer time (Entry 11), the yield was decreased due to increase the by-products. It is worthy of mention that the reaction was affected significantly by the solvents used. The ketone **5** was converted solely to **8** if the reaction was carried out in ether[5] with Zn $(BH_4)_2$ (Entry 7,8), only in THF the required product **7** can be obtained in high yield.

In summary, an improved synthesis of lactone **7** in 25% overall yield is developed. And the reduction of the conjugated ketone **5** with Zn $(BH_4)_2$ in THF showed high chemoselectivity.

References and Notes

1. R. B. Woodward, *Tetrahedron*, **1958**, *2*, 1.
2. R. B. Woodward, Belmont, Mass., US Patent 2,883,384, **1956**.
3. J. Rodriguez, B. Waegell, *Synthsis*, **1988**, *7*, 534.
4. B. C. Ranu, *et al*., *J. Org. Chem.*, **1991**, *56*, 4796.
5. T. Li, Yu Lin Wu, *J. Am. Chem. Soc.*, **1981**, *103*, 7007.
6. E. Adlerova, L. Blaha, *et al*., *Collection Czechoslov. Chem. Commun.*, **1960**, *25*, 221.
7. B. C. Ranu, *Synlett*, **1993**, 885.
8. J. Warnant, Neuilly, and J. Prost-Marechal, US Patent 2,983,753, **1957**.
9. S. Krishnamurthy, H. C. Brown, *J. Org. Chem.*, **1977**, *42*, 1197.
10. Compound **5**: white solid, $C_{13}H_{14}O_4$, Mp 110-112°C, ^{1}H NMR (500MHz, $CDCl_3$, δ ppm): 1.25(t, 3H, J=7.1 Hz), 2.13(m, 1H), 2.32(m, 1H), 3.22(m, 1H), 3.27(m, 1H), 4.04(m, 1H), 4.22(q, 2H, J=7.1 Hz), 5.73(m, 1H), 6.23(m, 1H), 6.60(d, 1H, J=10.3 Hz), 6.70(d, 1H, J=10.3 Hz), EI MS (*m/z*) 234 (M^+).
11. Compound **7**: white foam, $C_{11}H_{12}O_3$, ^{1}H NMR (500MHz, DMSO-d_6, δ ppm): 1.78(m, 1H), 2.02(m, 1H), 2.05(m, 1H), 2.08(m, 1H), 2.10(m, 1H), 2.35(m, 1H), 3.40(m, 1H), 4.00(m, 1H), 4.90(m, 1H), 5.12(m, 1H), 5.55(m, 1H), 6.00(m, 1H), EI MS (*m/z*) 192 (M^+).
12. Compound **8**: white solid, $C_{13}H_{16}O_4$, ^{1}H NMR (500MHz, $CDCl_3$, δ ppm): 1.25(t, 3H, J=7.1 Hz), 2.07(m, 1H), 2.18(m, 1H), 2.87(m, 1H), 3.13(m, 1H), 3.46(m, 1H), 4.21(q, 2H, J=7.1 Hz), 4.98(m, 1H), 5.4(s, OH), 5.72(m, 1H), 5.94(m, 1H), 6.15(m, 1H), 6.68(m, 1H), EI MS (*m/z*) 236 (M^+).
13. Compound **9**: $C_{13}H_{18}O_4$, ^{1}H NMR (500MHz, $CDCl_3$, δ ppm): 1.15(t, 3H, J=7.1 Hz), 1.27(m, 1H), 1.40(m, 1H), 1.65(m 1H), 1.76(m, 1H), 2.00(m, 1H), 2.14(m, 1H), 2.79(m, 1H), 3.03(m, 1H), 3.58(s, OH), 4.00(q, 2H, J=7.1 Hz), 4.38(m, 1H), 4.42(m, 1H), 5.33(m, 1H), 5.80(m, 1H), EI MS (*m/z*) 238 (M^+).
14. Compound **10**: $C_{13}H_{20}O_4$, ^{1}H NMR (500MHz, $CDCl_3$, δ ppm): 1.16(t, 3H, J=7.1 Hz), 1.27(m, 1H), 1.40(m, 1H), 1.47(m, 1H), 1.65(m 1H), 1.67(m, 1H), 1.75(m, 1H), 2.00(m, 1H), 2.18(m, 1H), 2.79(m, 1H), 3.06(m, 1H), 3.55(s, OH), 3.98(q, 2H, J=7.1 Hz), 4.38(m, 1H), 4.42(m, 1H), 5.33(m, 1H), 5.80(m, 1H), EI MS (*m/z*) 240 (M^+).
15. Compound **11**: white solid, $C_{14}H_{16}O_4$, Mp 158-162°C, ^{1}H NMR (500MHz, DMSO-d_6, δ ppm): 1.15(dd, 6H, J=6.2 Hz), 3.10(m, 1H), 3.20(m, 1H), 4.22(m, 1H), 4.83(m, 1H), 5.80(m, 1H), 6.10(m, 1H), 6.44(d, 1H, J=8.5 Hz), 6.52(d, 1H, J=8.5 Hz), 8.63(s, OH), 8.75(s, OH), EI MS (*m/z*) 248 (M^+).

Received 24 February, 2003