Synthesis of Pilocarpine Analogs *via* Radical Cyclization

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Pilocarpine analogs were prepared by empoying a radical cyclization reaction as a key step for the five-membered ring formation.

Introduction

Pilocarpine (1), one of the most important imidazole alkaloid natural products, was first isolated from the leaves of *Pilocarpus jaborandi* in 1875.[1] Since its isolation, pilocarpine has received attentions because of its interesting pharmacological properties.[2] For example, because of its activity in reducing intraocular pressure, it has been successfully used for the long term treatment of wide-angle glaucoma.[3] Recently, pilocarpine receives attentions again in connection with Alzheimer's disease. Pilocarpine is the only cholinergic muscarinic agonist in clinical use, and muscarinic agonist could have a potential therapeutic use for senile dementia of the Alzheimer's type.[4] Because of these potential medicinal applications, pilocarpine has been a target for synthetic chemists[5] for some time and a number of analogs have been prepared for their biological evaluation.[6] In this paper, we would like to report a synthetic study on pilocarpine analogs **2** and **3** which employs a radical cyclization as a key step for the five-membered ring formation.

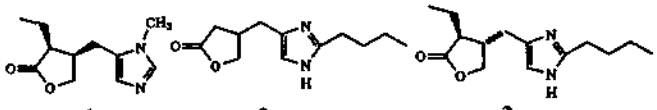
Experimental

2-Butyl-1-(1-ethoxyethyl)-1H-imidazole-4-carbaldehyde (5). To a stirred solution of **4** (14 g, 0.09 mol, unpurified) in $CHCl_3$-MeOH was added activated manganese dioxide (63 g, 0.72 mol). After 28 hr of the strring at room temp., manganese dioxide was filtered off. The filtrate was concentrated and purified by column chromatography on silica gel to afford 4 g of the aldehyde as white solid.

^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.92 (3H, t), 1.36 (2H, m), 1.69 (2H, m), 2.81 (2H, t), 6.28 (NH, br. s), 7.78 (1H, s), 9.63 (1H, s).

To a stirred solution of the product obtained above (4 g, 26.3 mmol) in CH_2Cl_2 were added ethyl vinyl ether (10 m*l*, 104.6 mmol) and few drops of trifluoroacetic acid. After 4 hrs of stirring, the reaction mixture was concentrated and purified by column chromatography on silica gel to afford 5.6 g (95%) of **5** as oil.

^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.97 (3H, t), 1.19 (3H, t), 1.42 (2H, sextet), 1.62 (3H, d), 1.79 (2H, quin), 2.76 (2H, t), 3.33 (2H, m), 5.39 (1H, q), 7.71 (1H, s), 9.82 (1H, s).



1 2 3

Figure 1.

3-[2-Butyl-1-(1-ethoxyethyl)-1H-imidazol-4-yl]-acrylic acid ethyl ester (6). To a stirred solution of **5** (3 g, 13.4 mmol) in benzene was added (carbethoxymethylene)-triphenylphosphorane (7 g, 20.1 mmol). After 20 hrs of stirring at room temperature, the reaction mixture was concentrated and purified by column chromatography on silica gel to afford 3.9 g (99%) of **6** as oil.

^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.95 (3H, t), 1.17 (3H, t), 1.29 (3H, t), 1.40 (2H, sextet), 1.57 (3H, d), 1.70 (2H, quin), 2.70 (2H, t), 3.29 (2H, m), 4.19 (2H, q) 5.30 (1H, m), 6.49 (1H, d), 7.14 (1H, s), 7.51 (1H, d).

3-[2-Butyl-1-(1-ethoxyethyl)-1H-imidazol-4-yl]-prop-2-en-1-ol (7). To a stirred solution of **6** (2.23 g, 7.6 mmol) in THF was added lithium triethylborohydride (17 mL, 17.0 mmol, 1 M in THF) dropwise *via* syringe at 0℃. After 30 min., the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated and purified by column chromatography on silica gel to afford 1.75 g (92%) of **7** as oil.

^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.95 (3H, t), 1.18 (3H, t), 1.40 (2H, sextet), 1.58 (3H, d), 1.69 (2H, m), 2.69 (2H, m), 3.30 (2H, m), 4.27 (2H, d), 5.29 (1H, q), 6.48 (2H, m), 6.92 (1H, s), 7.28 (1H, s).

4-[3-(2-Bromo-1-ethoxyethoxy)-propenyl]-2-butyl-1-(1-ethoxyethyl)-1H-imidazole (8). To a stirred solution of **7** (630 mg, 2.5 mmol) in CH_2Cl_2 were added ethyl vinyl ether (1.2 mL, 12.5 mmol) and NBS (533 mg, 3.0 mmol) at −40℃. After 2 hrs of stirring, the reaction mixture was concentrated and purified by column chromatography on silica gel to afford 496 mg (49%) of **8** as oil and 185 mg (29%) of unreacted **7**.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.96 (3H, t), 1.18 (3H, t), 1.26 (3H, t), 1.42 (2H, sextet), 1.59 (3H, d), 1.71 (2H, m), 2.70 (2H, m), 3.30 (2H, m), 3.41 (2H, m), 3.50 (1H, m), 3.71 (1H, m), 4.25 (2H, m), 4.80 (1H, t), 5.30 (1H, q), 6.38 (1H, m), 6.55 (1H, m), 6.92 (1H, s).

2-Butyl-1-(1-ethoxyethyl)-4-(5-ethoxy-tetrahydrofuran-3-ylmethyl)-1H-imidazole (9). To a stirred solution of **8** (231 mg, 0.57 mmol) and AIBN (15.6 mg, 0.11 mmol) in toluene was added triphenyltin hydride (302 mg, 0.86 mmol). After degassing with nitrogen, the reaction mixture was brought to reflux. After 2 hr, toluene was evaporated and the residue was dissolved in Et_2O and treated with DBU.[14] Resulting white precipitate was filtered off and the filtrate

was concentrated and purified by column chromatography on silica gel to afford 130 mg (70%) of **9** as oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.96 (3H, t), 1.19 (3H, t), 1.24 (3H, t), 1.40 (2H, sextet), 1.58 (3H, d), 1.69 (3H, m), 2.21 (2H, m), 2.65 (4H, m), 3.28 (2H, m), 3.41 (1H, m), 3.59 (1H, m), 3.77 (1H, m), 3.98 (1H, m), 5.12 (1H, m), 5.28 (1H, q), 6.68 (1H, s).

4-[2-Butyl-1-(ethoxyethyl)-1H-imidazol-4-ylmethyl]-dihydrofuran-2-one (10). To a stirred solution of **9** (19 mg, 0.06 mmol) in acetone was added aqueous sulfuric acid (180 μl, 0.72 mmol, 2 M in H_2O). The resulting solution was brought to reflux. After 30 min the reaction mixture was basified with excess sodium bicarbonate in solid and filtered. The filtrate was concentrated and dried *in vacuuo* to afford 14 mg (80%) of lactol as oil.

^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.95 (3H, t), 1.16 (3H, t), 1.38 (2H, m), 1.59 (3H, d), 1.69 (2H, m), 2.64 (4H, m), 3.28 (2H, m), 3.68 (1H, m), 4.05 (1H, m), 5.28 (1H, q), 5.51 (1H, m), 6.69 (1H, s).

To a stirred solution of lactol (14 mg, 0.047 mmol) in CH_2Cl_2 were added NIS (106 mg, 0.47 mmol) and tetrabutylammonium iodide (35 mg, 0.095 mmol). After 3.5 hr, the saturated aq. solution of $Na_2S_2O_3$ (1 ml) was added to the reaction mixture. After disappearance of yellow color, the reaction mixture was poured into EtOAc. The combined organic layer was washed with H_2O and brine, dried over magnesium sulfate, filtered, concentrated and purified by column chromatography on silica gel to afford 11 mg (79%) of **10** as oil.

^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.95 (3H, t), 1.16 (3H, t), 1.39 (2H, sextet), 1.57 (3H, d), 1.66 (2H, m), 2.30 (1H, m), 2.60 (5H, m), 2.92 (1H, m), 3.29 (2H, m), 4.07 (1H, m), 4.37 (1H, m), 5.27 (1H, q), 6.70 (1H, s).

4-(2-Butyl-1H-imidazol-4-ylmethyl)-dihydrofuran-2-one (2). To a stirred solution of **10** (11 mg, 0.037 mmol) in EtOH-H_2O (1 : 1) was added PPTS (47 mg, 0.187 mmol). The reaction mixture was heated to 90-100℃ (bath temperature). After 2 hr, the reaction mixture was concentrated and purified by column chromatography on silica gel to afford 3 mg (36%) of **2** as oil and 4 mg (36%) of unreacted **10**.

^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.92 (3H, t), 1.38 (2H, sextet), 1.69 (2H, quin), 2.30 (1H, dd), 2.61 (1H, dd), 2.72 (4H, m), 2.97 (1H, m), 4.08 (1H, dd), 4.38 (1H, dd), 6.69 (1H, s).

2-Butyl-1-(1-ethoxyethyl)4-(3-vinyloxy-propenyl)-1H-imidazole (13). To a stirred solution of **7** (610 mg, 2.42 mmol) in excess ethyl vinyl ether was added mercuric acetate (77 mg, 0.24 mmol). After refluxing for 4 hr, the reaction mixture was concentrated and purified by column chromatography on silica gel to afford 165 mg (25%) of **13** as oil and 398 mg (65%) of unreacted **7**.

^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.95 (3H, t), 1.16 (3H, t), 1.40 (2H, m), 1.57 (3H, d), 1.69 (2H, m), 2.69 (2H, m), 3.22 (2H, m), 4.03 (1H, m), 4.25 (1H, m), 4.37 (2H, d), 5.30 (1H, q), 6.42 (3H, m), 6.95 (1H, s).

4-[3-(2-Bromo-1-phenoxyethoxy)-propenyl]-2-butyl-1-(1-ethoxyethyl)-1H-imidazole (14). To a stirred solution of **13** (137 mg, 0.49 mmol) and phenol (231 mg, 2.46 mmol) in CH_2Cl_2 was added NBS (88 mg, 0.49 mmol) at −40℃. After 1.5 hr, the reaction mixture was poured into EtOAc. The combined organic layer was washed with 1N NaOH and brine, dried over $MgSO_4$, filtered, concentrated and purified by column chromatography on silica gel to afford 94 mg (42%) of **14** as oil.

^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.92 (3H, m), 1.18 (3H, m), 1.39 (2H, m), 1.68 (3H, d), 1.63 (2H, m), 2.69 (2H, m), 3.30 (2H, m), 3.54 (2H, m), 4.20 (1H, m), 4.39 (1H, m), 5.28 (1H, q), 5.45 (1H, t), 6.33 (2H, m), 6.81 (1H, m), 6.38 (1H, s), 7.02 (2H, m), 7.24 (2H, m).

2-Butyl-1-(1-ethoxyethyl)-4-(5-phenoxy-tetrahydrofuran-3-yl)-1H-imidazole (15). To a stirred solution of **14** (83 mg, 0.18 mmol) and AIBN (10 mg, 0.07 mmol) in toluene was added triphenyltin hydride (129 mg, 0.36 mmol). After degassing with nitrogen, the reaction mixture was brought to reflux. After 2 hr, toluene was evaporated and the residue was dissolved in Et_2O and treated with DBU. Resulting white precipitate was filtered off and the filtrate was concentrated and purified by column chromatography on silica gel to afford 56 mg (82%) of **15** as oil.

^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.95 (3H, t), 1.16 (3H, t), 1.39 (2H, m), 1.56 (3H, d), 1.68 (2H, m), 1.95 (1H, m), 2.37 (1H, m), 2.71 (5H, m), 3.29 (2H, m), 3.70 (1H, m), 4.11 (1H, m), 5.28 (1H, q), 5.80 (1H, m), 6.71 (1H, s), 6.99 (3H, m), 7.25 (2H, m).

1-[3-[2-Butyl-1-(1-ethoxyethyl)-1H-imidazol-4-yl]allyloxy]-butan-2-ol (17). To a stirred solution of **7** (708 mg, 2.81 mmol) in THF was added sodium hydride (404 mg, 8.42 mmol, 50% in oil) at 0℃. After 30 min., 15-crown-5 (167 μl, 0.84 mmol) and 1,2-epoxybutane (2.4 mL, 27.86 mmol) were added to the reaction mixture. After refluxing for 4 hr, the reaction mixture was poured into EtOAc. The combined organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, concentrated and purified by column chromatography on silica gel to afford 520 mg (57%) of **17** as oil and 105 mg (15%) of unreacted **7**.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.92 (6H, m), 1.17 (3H, t), 1.40 (4H, m), 1.57 (3H, d), 1.68 (2H, m), 2.69 (2H, m), 3.28 (3H, m), 3.50 (1H, m), 3.69 (1H, m), 4.13 (2H, d), 5.29 (1H, q), 6.34 (1H, m), 6.47 (1H, m), 6.92 (1H, s).

4-[3-(But-1-enyloxy)-propenyl]-2-butyl-1-(1-ethoxyethyl)-1H-imidazole (18). To a stirred solution of **17** (485 mg, 1.50 mmol) in CH_2Cl_2 were added triethylamine (1.1 ml, 7.89 mmol) and methanesulfonyl chloride (580 μl, 7.49 mmol) at 0℃. After 10 min., ice bath was removed. After 3.5 hr, the reaction mixture was poured into EtOAc. The combined organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, concentrated and purified by column chromatography on silica gel to afford 350 mg (58%) of the methanesulfonyl compound as oil and 97 mg (20%) of unreacted **17**.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.97 (3H, t), 1.03 (3H, t), 1.21 (3H, t), 1.44 (2H, m), 1.57 (5H, m), 1.60 (3H, d), 1.72 (4H, m), 3.10 (3H, s), 3.35 (2H, m), 3.61 (2H, d), 4.17 (2H, m), 4.75 (1H, m), 5.36 (1H, m), 6.48 (2H, m), 6.96 (1H, s).

To a stirred solution of the methanesulfonyl compound (200 mg, 0.50 mmol) in THF was added potassium t-butoxide (279 mg, 2.49 mmol). After refluxing for 1 hr, the reaction mixture was poured into EtOAc. The combined organic layer was washed with H_2O and brine, dried over $MgSO_4$, filter, concentrated and purified by column chromatography on silica gel to afford 48 mg (32%) of **18**.

H-NMR (300 MHz, $CDCl_3$) δ 0.97 (3H, t), 0.99 (3H, t), 1.18 (3H, t), 1.42 (2H, sextet), 1.58 (3H, d), 1.59 (2H, m), 1.93 (1H, s), 2.10 (1H, s), 2.70 (2H, m), 3.31 (2H, m), 4.32 (2H,

m), 4.88 (1H, m), 5.29 (1H, q), 6.25 (1H, m), 6.38 (1H, m), 6.50 (1H, m), 6.92 (1H, s).

4-[3-(2-Bromo-1-phenoxybutoxy)-propenyl]-2-butyl-1-(1-ethoxyethyl)-1H-imidazole (19). To a stirred solution of **18** (75 mg, 0.25 mmol) and phenol (46 mg, 0.49 mmol) in CH_2Cl_2 was added NBS (48 mg, 0.27 mmol) at −40℃. After 30 min, the reaction mixture was concentrated and purified by column chromatography on silica gel to afford 50 mg (43%) of **19** as oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.95 (3H, t), 1.10 (3H, t), 1.18 (3H, m), 1.42 (2H, sextet), 1.58 (3H, d), 1.70 (2H, m), 1.89 (1H, m), 2.16 (1H, m), 2.69 (2H, m), 3.30 (2H, m), 4.10 (1H, m), 4.21 (1H, m), 4.38 (1H, m), 5.29 (1H, q), 5.40 (1H, m), 6.33 (2H, m), 6.89 (1H, s), 7.07 (3H, m), 7.29 (2H, m).

2-Butyl-1-(1-ethoxyethyl)-4-(4-ethyl-5-phenoxytetrahydrofuran-3-ylmethyl)-1H-imidazole (20). To a stirred solution of **19** (50 mg, 0.10 mmol) and AIBN (3 mg, 0.02 mmol) in toluene was added triphenyltin hydride (73 mg, 0.21 mmol). After degassing with nitrogen, the reaction mixture was brought to reflux. After 2 hr, toluene was evaporated and the residue was dissolved in Et_2O and treated with DBU. Resulting white precipitatewas filtered off and the filtrate was concentrated and purified by column chromatography on silica gel to afford 38 mg (91%) of **20** as oil.

4-[2-Butyl-1-(1-ethoxyethyl)-1H-imidazol-4-ylmethyl]-3-ethyldihydrofuran-2-one (21). To a stirred solution of **20** (35 mg, 0.087 mmol) in acetone was added several drops of 6N HCl. The reaction mixture was heated to ~70℃ (bath temperature). After 20 min, the reaction mixture was basified with solid $NaHCO_3$. White solid was filtered. The filtrate was concentrated and separated by column chromatography on silica gel to afford 23 mg (81%) of the lactol as oil.

To a stirred solution of lactol (27 mg, 0.083 mmol) in CH_2Cl_2 were added NIS (187 mg, 0.83 mmol) and tetrabutylammonium iodide (61 mg, 0.165 mmol). After 1 hr, the saturated aq. solution of $Na_2S_2O_3$ was added. After disappearance of yellow color, the reaction mixture was poured into EtOAc. The combined organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, concentrated and purified by column chromatography to afford 25 mg (93%) of **21** as oil.

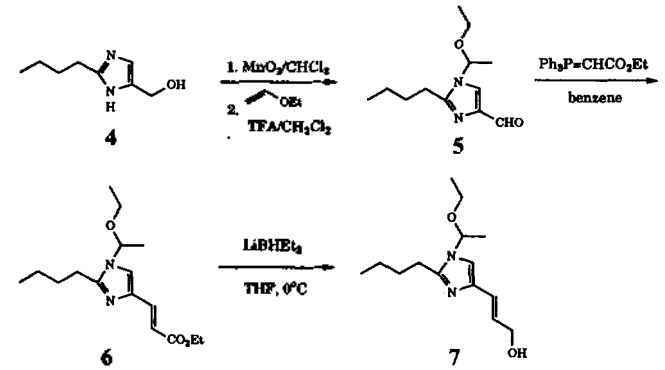
^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.95 (3H, t), 0.99 (3H, t), 1.19 (3H, m), 1.39 (2H, m), 1.59 (3H, d), 1.67 (4H, m), 2.25 (1H, m), 2.69 (4H, m), 2.78 (1H, m), 3.25 (1H, m), 3.35 (1H, m), 3.98 (1H, m), 4.34 (1H, m), 5.30 (1H, q), 6.76 (1H, s).

4-[2-Butyl-1H-imidazol-4-yl)-3-ethyldihydrofuran-2-one (3). To a stirred solution of **21** (11 mg, 0.034 mmol) in EtOH-H_2O (1 : 1) was added pyridinium *p*-toluenesulfonate (43 mg, 0.17 mmol). The reaction mixture was heated to 90-100℃ (bath temperature). After 7 hr, the reaction mixture was concentrated and purified by column chromatography on silica gel to afford 4 mg (47%) of **3** as oil and 4 mg (36%) of the unreacted **21**.

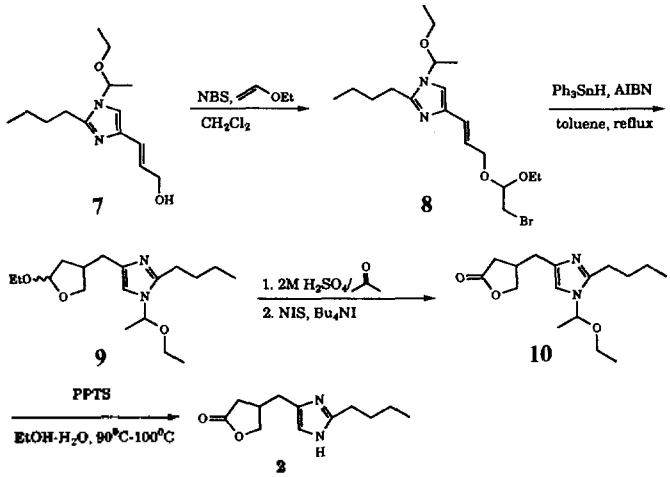
^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.93 (3H, t), 0.99 (3H, t), 1.36 (2H, m), 1.66 (4H, m), 2.29 (1H, m), 2.69 (4H, m), 2.78 (1H, m), 3.97 (1H, m), 4.34 (1H, m), 6.67 (1H, s).

Results and Discussion

A synthesis started with 2-butyl-4-hydroxymethylimidazole



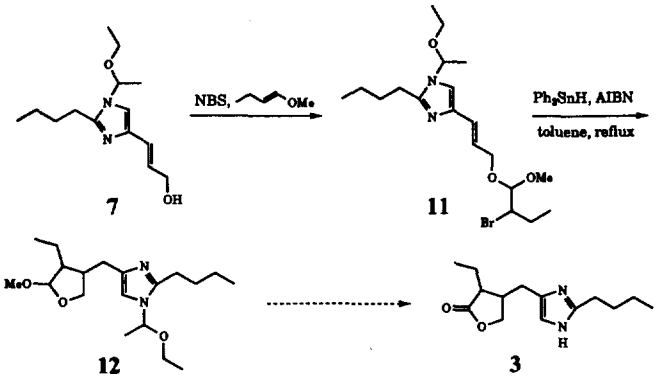
Scheme 1.



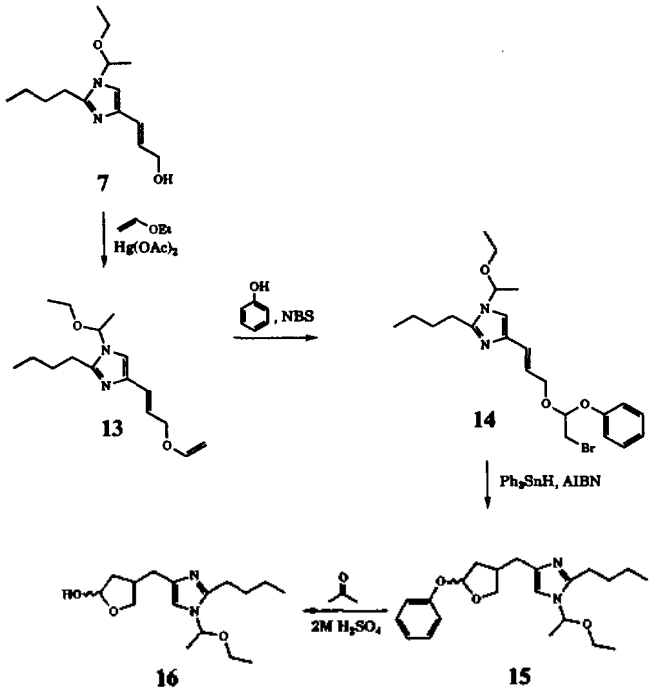
Scheme 2.

readily available in our laboratory.[7] As shown in Scheme 1, the oxidation of the imidazole alcohol **4** and a subsequent protection of the imidazole nitrogen produced **5** in good yield. A number of protecting groups for the imidazole nitrogen have been tested and 1-ethoxyethyl group turned out to be a good protecting group for the subsequent chemical transformation. The Wittig reaction on the aldehyde **5** furnished the ester **6** in excellent yield. Next, we attempted the reduction of the α,β-unsaturated ester **6** to the unsaturated alcohol **7** by DIBAL to get the desired unsaturated alcohol **7** in low yield. After testing several reducing agents, we found that the reduction with super-hydride was effective. Thus, the α,β-unsaturated ester **6** was treated with super-hydride in THF at 0℃ to afford **7** in 92% yield.

With the compound **7** in hand, we then focused our attention to the synthesis of the simpler pilocarpine analog **2**. We envisioned that the five-membered ring of pilocarpine could be obtainable by the cyclization of a suitably generated radical. To this end, the allylic alcohol **7** was converted to the bromo acetal **8** by the alkoxybromination reaction with ethyl vinyl ether and N-bromosuccinimide (NBS).[8] Then the radical cyclization of the bromo acetal **8** was carried out with triphenyltin hydride in the presence of a catalytic amount of AIBN. The reaction proceeded smoothly to give the five-membered 2-ethoxytetrahydrofuran **9** in good yield and no six-membered cyclic product was observed. This result is in good agreement with a generally observed exocyclic mode



Scheme 3.

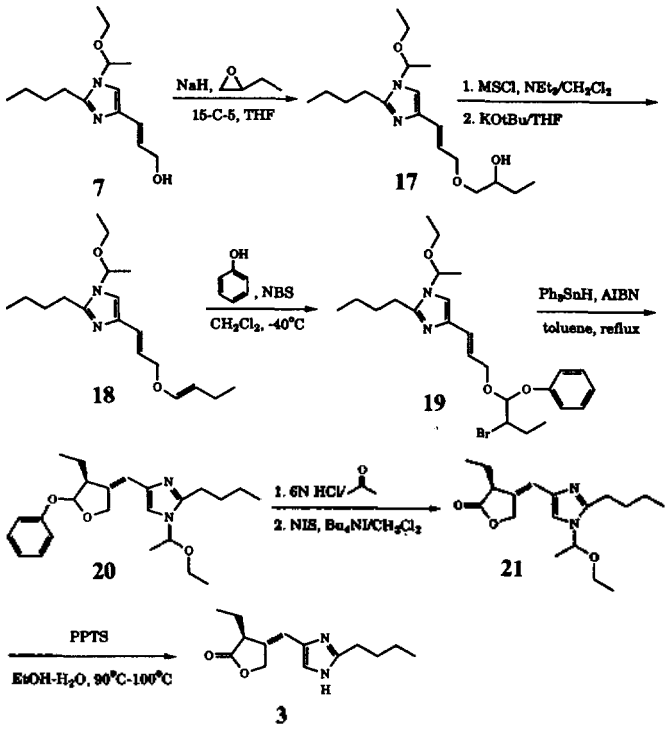


Scheme 4.

of the radical cyclization.

Initial attempts to convert **9** to the lactone **10** directly turned out to be unsatisfactory. For instance, the oxidation of **9** with mCPBA[9] in the presence of BF_3OEt_2 provided the lactone **10** in only 12% yield. The Jone's oxidation[9] was also not satisfactory only to give **10** in 21% yield. Therefore we decided to convert **9** to **10** stepwise. First, acid hydrolysis of the acetal furnished the corresponding lactol which was then converted to the lactone **10** by the oxidation method developed by Hanessian *et al.*[11] In this process, the purification of the resulting lactol was not necessary and unoptimized yield for two steps was 63%. Final deprotection of **10** was carried out in weakly acidic condition with pyridinium p-toluenesulfonate (PPTS) to give the pilocarpine analog **2**.

With a successful synthesis of pilocarpine analog **2** by a radical cyclization, we then turned our attention to the synthesis of a more elaborated analog **3**. The substrate for the radical cyclization, **11**, was prepared by treating the allylic alcohol **7** with 1-butenyl methyl ether and N-bromosuccinimide as described previously. We then subjected **11** to the



Scheme 5.

radical cyclization reaction condition. However, with this substrate, the radical reaction afforded a mixture of the desired product, **12**, and an unidentified product in 3 : 2 ratio.

Various reaction conditions did not improve the formation of the desired product. Therefore, we decided to examine the effect of various alkoxy groups on the acetal moiety. The idea was that by attaching a larger group on the acetal moiety, it would be possible to bring the olefin moiety and the radical site in proximity to facilitate the cyclization. A computer modeling study suggested that a phenyl group would be one of suitable groups for this purpose. To test this hypothesis, the compound **14** was synthesized. A phenoxy-bromination reaction of the vinyl ether **13**, which was prepared by the alkoxy-exchange reaction[12] with ethyl vinyl ether in the presence of a catalytic amount of mercuric acetate, was successful to give the bromo phenyl acetal **14**. The compound **14** underwent the radical cyclization smoothly to give the cyclized product **15** in good yield demonstrating that the phenyl group seemed to facilitate the radical cyclization. Furthermore, the phenoxy group could be removable under a mild condition to give the lactol **16**.

With these successful preliminary results, we prepared the bromo acetal **19** according to the Scheme 5. The alcohol **7** was treated with 1,2-epoxybutane in the presence of sodium hydride and 15-crown-5 to give the β-hydroxy ether **17**. Two step dehydration reaction of **17**[13] provided the allyl vinyl ether **18** which was then transformed into the bromo acetal **19** by the alkoxy-bromination reaction described previously. The radical cyclization of **19** proceeded smoothly to give the cyclized product **20** in excellent yield. Finally, the pilocarpine analog **3** was obtained by employing the same methodology described in the synthesis of the analog **2**. Hydrolysis, oxidation and subsequent deprotection of **20** affor-

ded the desired product **3**. The relative stereochemistry of two side chains in the compound **3** was determined to be *trans* by comparing with a sample prepared by the alkylation of **10**.

In conclusion, we have successfully used the radical cyclization reaction for the construction of the five-membered ring for the pilocarpine family and found that this method was useful for the synthesis of the pilocarpine analogs. The diastereofacial control during the cyclization reaction and the scope of this reaction will be discussed in due course.

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