The Furan Approach to the Synthesis of Natural Products having Highly Substituted Cyclic Ether Moieties

Abstract

We describe the synthesis of useful building blocks towards the synthesis of many natural products bearing substituted cyclic ether moieties, using our previously described method we called 'The Furan Approach" and which is based on singlet oxygen oxidation of a furan ring followed by an intramolecular oxa-Michael addition.

Keywords: Oxacyclic compounds; Furan; Singlet oxygen; Natural products; Stereoselective synthesis

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Introduction

Highly substituted cyclic ethers occur in many natural products exhibiting important biological activities [1-6]. These units can be found in monocyclic as well as in polycyclic structures some of them are depicted in Figure 1. Due to the biological importance of these compounds, they have been the targets of numerous synthetic studies [7-13]. In our research group we have developed a new methodology for the synthesis of oxacyclic compounds using furan as starting material [14-27]. The scope and limitations of this very powerful methodology are being determined.

Results and Discussion

We now report that using our method we can easily access the 2,6-disubstituted tetrahydropyran and 2,5-disubstituted tetrahydrofuran systems, which are advanced model intermediates towards the synthesis of the natural compounds depicted in Figure 1. It was anticipated that butanetriol (1) could be a common starting material for accessing the 2,6-disubstituted tetrahydropyran 13 (Figure 2) and 2,5-disubstituted tetrahydrofuran 22 (Figure 3).

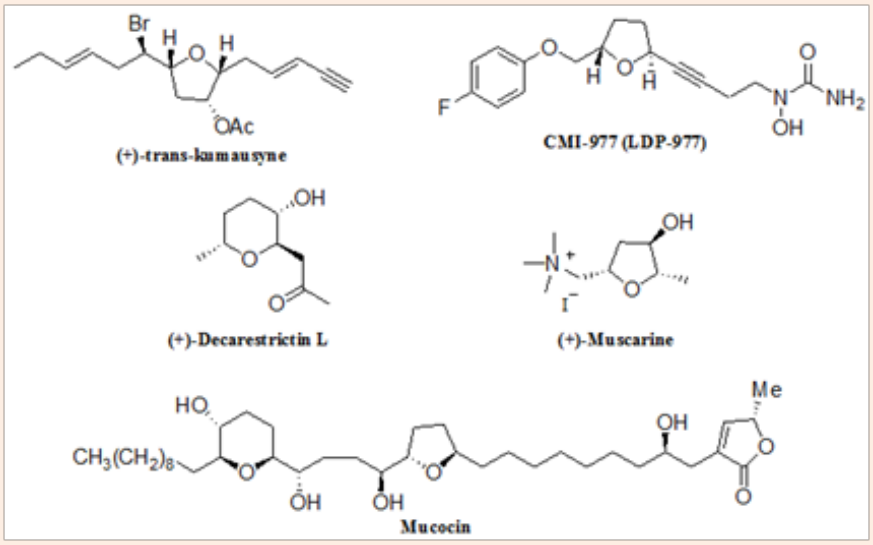

Figure 1: Examples of biologically active natural products bearing substituted cyclic ether moieties.

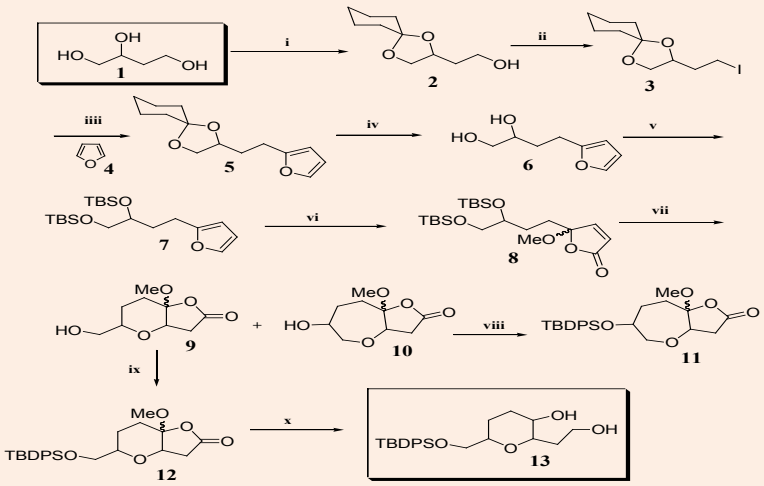

Figure 2: Reagents and conditions:
(i) Cyclohexanone, $BF_3.OEt_2$, Et2O, 0 °C to rt (97%)
(ii) PPh_3, Imid, I_2, THF (93%)
(iii) 4, bipy, nBuLi, THF, 0°C to rt (91%)
(iv) Dowex 50W-X8, MeOH, rt, 20h (89 %)
(v) TBSCl, Imid, DMAP, DMF, rt(97 %)
(vi) $^1O_2$, MeOH, rose Bengal, hν
(vii) Ac_2O, py, DMAP (97%%, 2 steps)
(viii) TBAF, THF, rt(35%, 9; 45%, 10)
(ix) TBDPSCl, Imid, DMAP, DMF, rt (92 %)
(x) TBDPSCl, Imid, DMAP, DMF, rt (87 %)
(xi) LAH, $BF_3.OEt_2$ (86%)

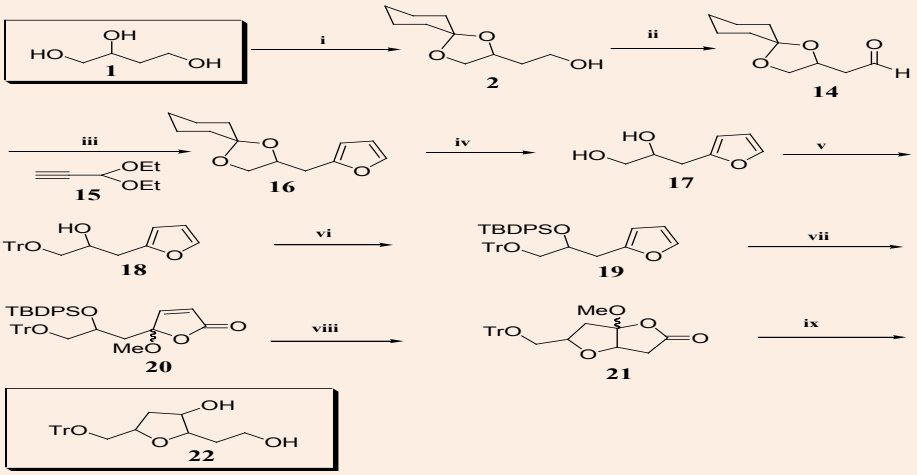

Figure 3: Reagents and conditions:
(i) Cyclohexanone, $BF_3.OEt_2$, Et_2O, 0 °C to rt (97%)
(ii) Swern (99 %)
(iii) 15, nBuLi, THF, 0 °C to -78 °C (91%)
(iv) H_2 / Pd Lindlar
(v) PPTs (66%)
(vi) Dowex 50W-X8, MeOH, rt, 20h (80 %)
(vii) TrCl, pyr, DMAP, DMF, rt (82 %)
(viii) TBDPSCl, Imid, DMAP, DMF, rt (85 %)
(ix) $^1O_2$, MeOH, rose Bengal, hν
(x) Ac_2O, py, DMAP (77%%, 2 steps)
(xi) TBAF, THF, rt (98%)
(xii) LAH, $BF_3.OEt_2$ (86 %)

Thus protection of the C1, C2-hydroxyl groups of 1 with cyclohexanone afforded alcohol 2 [28] (97%) easily converted into iodide 3 [28] in 93% yield. Lithiation of furan 4 and reaction with 3 afforded the alkylated furan 5 [28] (91%). Removal of the cyclohexylidene group of 5 using Dowex 50W-X8 in methanol, [29] gave diol 6 [28] in 89% yield. The hydroxyl groups of 6 were protected as silylethers affording furan 7. [28] Oxidation of 7 with singlet oxygen followed by treatment with acetic anhydride in pyridine, afforded butenolide 8 [28] in 97% yields (2 steps). Treatment of 8 with TBAF led to lactones 9 [28] and 10 [28] in 35 and 45% yield respectively.

Protection of the hydroxyl group of 9 followed by opening of the lactone ring afforded tetrahydropyran 13 [28] possible synthon towards the synthesis of decarestrictine L or mucocin (Figure 1). Having demonstrated the feasibility of highly substituted tetrahydropyrans from butanetriol (1), we now turned our attention to synthesizing tetrahydrofurans from the same starting material. In order to apply our method, we needed to prepare furan 19 (Figure 3) which has a side chain one carbon shorter than its homologue [30-31] (Figure 2). Swern oxidation of alcohol 2 afforded aldehyde 14 [28] in 99% yields.

Treatment of aldehyde 14 with the lithium derivative of alkyne 15 gave a mixture of epimeric propynyl alcohols which were hydrogenated over lindlar catalyst [30-31] to provide a mixture of diastereoisomeric (Z)-alkenes which upon treatment with catalytic pyridinium toluene -p- sulfonate (PPTS) gave the desired furan ring in 66% overall yield from the aldehyde 14. Removal of the cyclohexylidene group of 16 [28] using Dowex 50W-X8 in methanol [29] gave diol 17 [28] in 80% yield. The primary hydroxyl group of 17 was selectively protected as trityl ether and the secondary hydroxyl group as silylether affording furan 19 [28]. The stage was now set for the oxidation of 19 with singlet oxygen followed by treatment with acetic anhydride in pyridine which afforded butenolide 20 [28] in 77% overall yield. Treatment of 20 with TBAF led to lactone 21 [28] in 98% yields. Finally, opening of lactone 21 with LAH afforded tetrahydrofuran 22 [28]. Compound 22 can be considered as building block towards the synthesis of the natural products bearing a THF moiety depicted in Figure 1.

Conclusion

In conclusion, we have demonstrated that using racemic butanetriol we can apply the "Furan approach "to the synthesis of useful building blocks towards the synthesis of many natural products. As both enantiomers of butanetriol are commercially available, work is now in progress towards the enantioselective synthesis of the natural products described in Figure 1.

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Conflict of Interest

There is no conflict of interest.

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