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# Intramolecular [2+2] Photocycloaddition for the Direct Stereoselective Synthesis of Cyclobutane Fused γ-Lactols

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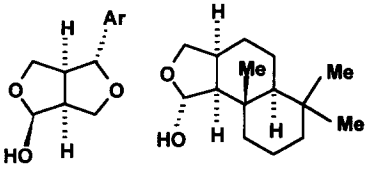
**Abstract :** A direct stereoselective route for the synthesis of γ-lactols fused to cyclobutanes *via* intramolecular [2+2] photocycloaddition of 1,6-dienes is described.



γ-Lactols fused to other rings are frequently encountered in a wide range of natural products. Representative examples include the lignan samin **1**[1] and the sesquiterpene drimane **2**.[2] In addition, γ-lactols serve as valuable reactive intermediates in organic synthesis.[3] The usual way of annulating lactols involves either intramolecular hemiacetalisation[4] of appropriately disposed aldehyde and alcohol functionalities in a prebuilt ring, or reduction of lactones[5] and proceeds nonstereoselectively in many occasions. We here report a topologically different strategy that results in the direct stereoselective synthesis of cyclobutane fused γ-lactols which, by virtue of the properties of two reactive rings, will be of great synthetic potential.



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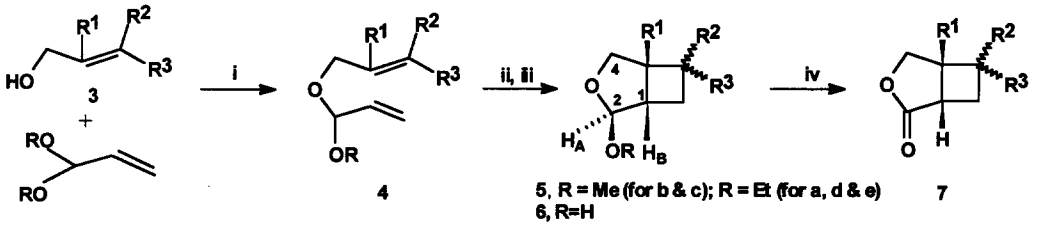
The key step in the present strategy is the cycloaddition of two π units linked together through an acetal oxygen. The overall synthetic plan is illustrated with the synthesis of the lactol **6a (Scheme 1).** Acid catalysed trans-acetalisation of acrolein diethyl acetal with the allyl alcohol **3a** in refluxing benzene with azeotropic removal of ethanol afforded the mixed acetal **4a**[6] in 68% yield. Cycloaddition[7] of the diene **4a** could be achieved through irradiation of its ether solution in the presence of cuprous trifluoromethane sulfonate ( CuOTf ) as the catalyst to afford the protected lactol **5a** in 50% yield thus demonstrating the compatibility of the acetal functionality to CuOTf catalysis in the photocycloaddition. The exo-stereochemical assignment to the photoadduct **5a** was based on comparison of the coupling constant of $H_A$ ($J$ =0) to those reported[8] for analogous *exo* ($J_{A,B\text{-trans}}$ = 1.5 Hz)-and *endo* ($J_{A,B\text{-syn}}$ = 5.5 Hz)-2-substituted-3-oxa-bicyclo[3.2.0]heptanes. Brief exposure of the adduct **5a** to hot 80% aqueous acetic acid led to smooth deprotection to afford the lactol **6a** in 71% yield. Retention of configuration during deprotection was indicated by the appearance of a singlet at δ 5.19 and is attributed to be the result of addition of $H_2O$ to the intermediate oxonium ion **8a** from the least hindered *exo* face. The generality of this three step protocol was established by the synthesis of a series of lactols **6b-e** in very good yields **(Table 1).** It is to be noted that deprotection



**a, R1=H, R2=R3=Me; b, R1=R2=R3=H; c, R1=Me, R2=R3=H; d, R1=H, R2,R3=H, Me; e, R1=H, R2,R3=H, CH=CHMe**

**Scheme 1.** Reagents and conditions : i) PPTS, $C_6H_6$, Δ . ii) hv , CuOTf, $Et_2O$, iii) HOAc-$H_2O$, Δ, iv) Jones reagent.

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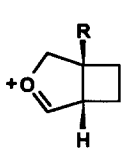
of the lactol **5c** (entry3) resulted in inversion of configuration at $C_2$ to lead to the thermodynamically more stable lactol **9** ($J_{A,B}$ = 9.9 Hz), arising through addition of $H_2O$ to the oxonium ion **8c** from the *endo* face as addition from the *exo* face is blocked by the Me group. The lactols **5** or **6**, on Jones oxidation, could be transformed to the cyclobutane fused lactones **7**[9] which are also useful synthetic intermediates.

To demonstrate the synthetic potential of the cyclobutane fused lactols, the lactone **7c**, obtained as above, was transformed to the diol **10** (71%) on reaction with excess MeLi in ether. Swern oxidation of the diol **10** afforded a diastereoisomeric mixture of the lactols **11** (63%) which has already been transformed[3] to grandisol **12**,[10] a component of the aggregation pheromone of the Boll weevil.

In conclusion, trans-acetalisation of an acrolein acetal with allyl alcohols in conjunction with photocycloaddition offers an excellent stereoselective route to cyclobutane fused lactols.

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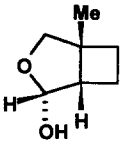


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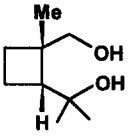


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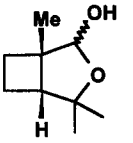


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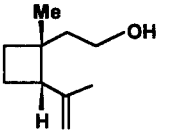


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**Table 1. Synthesis of cyclobutane fused lactols and lactones**

| Entry | Dienes | Lactols | Lactones |
|---|---|---|---|
| 1 | **4a** (68)[a] | **5a** (50), **6a** (71) | **7a** (68) |
| 2 | **4b** (72) | **6b** (59)[b] | **7b** (60) |
| 3 | **4c** (68) | **9** (56)[b] | **7c** (70) |
| 4 | **4d** (74) | **5d** (69)[c] , **6d** (77)[c] | **7d** (72) |
| 5 | **4e** (77) | **5e** (70)[d] ,**6e** (70)[d] | **7e** (71) |

[a] Figures in the parenthesis represents yields of products isolated by chromatography. [b] The photoadducts were directly hydrolysed without characterisation. [c] Obtained as a mixture of two diastereoisomers in 2.5:1 ratio with *exo*-Me isomer as the major one. [d] Obtained as a mixture of four components in 5:2.5:1.5:1 ratio arising from two diastereoisomers of each of the two geometrical isomers.

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**References and Notes**

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6. All new compounds were characterised through $^1H$ (300 MHz) and/or $^{13}C$ NMR (75 MHz ) and IR (in appropriate cases) spectroscopy. NMR data for selected compounds : **5a**, $^1H$ δ 0.93 (s, 3H), 1.13 (s,3H), 1.16 (t, *J*=7.2 Hz, 3H), 1.73 (m, 2H), 2.45 (m, 1H), 2.77 (m, 1H), 3.41 (q, *J*=6.9 Hz, 2H), 3.74 (dd, *J*=6.3 and 9.6 Hz, 1H), 3.96 (d, *J*=9.6Hz, 1H), 4.82 (s, 1H); $^{13}C$ 15.3, 23.9, 31.3, 32.6, 35.5, 38.5, 46.6, 62.1, 67.1, 107.4. **6a**, $^1H$ δ 0.87 (s, 3H), 1.09 (s,3H), 1.67-1.74 (m, 2H), 2.45 (t, *J*=6.6 Hz, $C_5$-H), 2.71-2.79 (m, 1H), 3.87 (dd, *J*=6.6 and 9.6 Hz, $C_4$-H), 3.96 (d, *J*=9.6Hz, $C_4$-H), 5.19 (s, 1H).
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