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Tetrahydropyran Derivatives from γ- and δ-Hexonolactones

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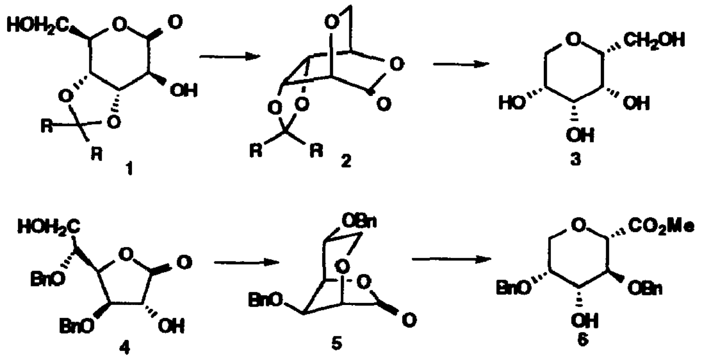
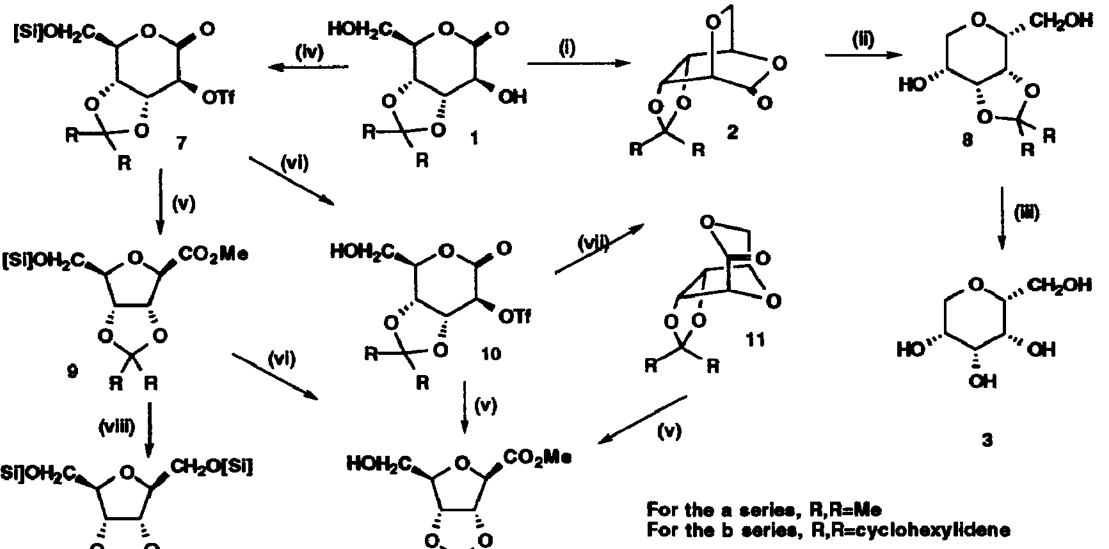
Abstract: Both δ- and γ-hexonolactones provide templates for the construction of bicyclic lactones in which a new tetrahydropyran ring has been formed from overall elimination of water from the C-2 and C-6 hydroxyl groups. Such studies may provide a strategy for the synthesis of C-glycosides from elimination of water between C-2 and C-6 of heptonolactones.

Carbohydrate lactones have provided relatively short and efficient routes to a wide range of complex targets,[1] including carbocycles[2] and nitrogen heterocycles.[3] Reactions of protected α-triflates of γ-lactones with potassium carbonate in methanol give oxetanes in good yields,[4] whereas under the same conditions α-triflates of δ-lactones afford excellent yields of tetrahydrofurans.[5] Treatment of both α-triflates of γ- and δ-lactones with methanol under acidic conditions induces the formation of tetrahydrofurans, usually in very high yields.[6] The formation of oxetanes and tetrahydrofurans involves overall loss of water between the hydroxyl groups at C-2 and either C-4 or C-5 of the lactones; the loss of water between C-2 and C-6 of a lactone would give rise to a new tetrahydropyran synthesis and in the case of seven carbon lactones would provide a method for the formation of C-glycoside derivatives.

This paper reports studies in which loss of water from δ-lactones such as **1** and γ-lactones such as **4** gives bicyclic lactones **2** and **5**, which by subsequent ring opening reactions may be converted to the tetrahydropyran derivatives **3** and **6**, respectively.



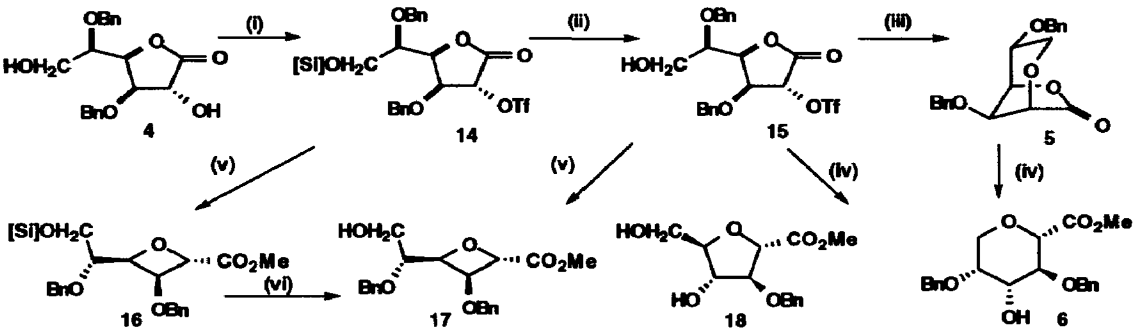
The isopropylidene **1a**[7] and cyclohexylidene **1b**[8] δ-lactones [Scheme 1] can be directly dehydrated to the bicyclic lactones **2a** m.p. 190-192 °C, $[\alpha]_D^{20}$ -46.0 (*c*, 0.88 in $CHCl_3$)[9,10] and **2b**[11] m.p. 204-205 °C, $[\alpha]_D^{20}$ -43.8 (*c*, 1.1 in $CHCl_3$) under Mitsunobu conditions [triphenylphosphine and diethyl azodicarboxylate in tetrahydrofuran] in yields of 60% and 69% respectively. The structure of the bicyclic lactones **2** were confirmed by the reduction of **2b** by lithium borohydride in tetrahydrofuran to give the ketal **8b** oil, $[\alpha]_D^{20}$ +21.9 (*c*, 1.13 in $CHCl_3$), [93% yield]; removal of the cyclohexylidene protecting group in **8b** by hydrolysis with 40% aqueous trifluoroacetic acid afforded the known 2,6-anhydro-D-altritol **3** as a gum, $[\alpha]_D^{20}$ -7.5 (*c*, 0.72 in H_2O)[lit[12] -11.5 (*c*, 4.85 in H_2O)] in 89% yield. The formation of the tetrahydropyran ring under these conditions involves nucleophilic displacement of an activated C-6 hydroxyl group by the C-2 hydroxyl group, resulting in retention of configuration at C-2; conversion of the C-2 hydroxyl group to a leaving group followed by intramolecular nucleophilic displacement by the C-6 hydroxyl group should present an alternative strategy in which the tetrahydropyran is formed by inversion of configuration at C-2. Accordingly, the isopropylidene ketal **1a** was first protected as the primary silyl ether and then esterified with triflic anhydride in the presence of pyridine in dichloromethane at -20°C to give the fully protected triflate **7a** in an overall yield of 83%; similar treatment of **1b** afforded the cyclohexylidene analogue **7b** m.p. 157-159 °C, $[\alpha]_D^{20}$ -32.3 (*c*, 0.9 in $CHCl_3$), in 92% yield. Reaction of either **7a** or **7b** with potassium carbonate in methanol gave the corresponding ring contracted *cis*-2,5-tetrahydrofurans **9a** m.p. 33-34 °C, $[\alpha]_D^{20}$ -32.8 (*c*, 1.0 in $CHCl_3$), and **9b** oil, $[\alpha]_D^{20}$ -36.7 (*c*, 1.2 in $CHCl_3$), in yields of 58% and 68%, together with very small amounts of the carboxylates epimeric at C-2 of the tetrahydrofuran ring. The *cis* relationship of the carbon substituents on the tetrahydrofuran ring was demonstrated by reduction of the ester function in the cyclohexylidene derivative **9b** by lithium aluminum hydride in tetrahydrofuran, followed by conversion to the symmetrical *bis*-silyl ether **12b**[13] oil, $[\alpha]_D^{20}$ +0.0 (*c*, 1.98 in $CHCl_3$), in an overall yield of 84%. The fully protected lactone **7b** on treatment with aqueous acetic acid at room temperature for 13h gave **10b** m.p. 109-111 °C, $[\alpha]_D^{20}$ +29.0 (*c*, 0.9 in $CHCl_3$), [70% yield], in which the primary hydroxyl group is free. Reaction of **10b** with potassium carbonate in methanol afforded the tetrahydrofuran **13b** oil, $[\alpha]_D^{20}$ -58.3 (*c*, 0.47 in $CHCl_3$), in 94% yield; **13b** was also formed in 60% yield by removal of the silyl group from **9b** on treatment with aqueous acetic acid.



Scheme 1. (i) Ph_3P, EtOOC.N=N.COOEt, THF (ii) $LiBH_4$, THF (iii) 40% aq. CF_3COOH (iv) Me_2Bu^tSiCl, imidazole, DMF or Me_2Bu^tSiOTf, pyridine, THF; then Tf_2O, pyridine, CH_2Cl_2 (v) K_2CO_3, MeOH (vi) 80% aq. CH_3COOH (vii) CH_3COONa, DMF (viii) $LiAlH_4$, THF; then Me_2Bu^tSiCl, imidazole, DMF

It is clear that the open chain intermediate formed by methoxide opening of **10b** closes exclusively to form a tetrahydrofuran, rather than a tetrahydropyran, ring; thus for the alternative formation of a tetrahydropyran, the new 6 membered ring must be formed before the opening the lactone ring. Reaction of the triflate **10b** with sodium acetate in dimethylformamide led to a mixture of the two bicyclic lactones **2b** [26% yield] and **11b**[14] m.p. 76-80 °C (ethyl acetate / hexane); $[\alpha]_D^{20}$ +40.9 (*c*, 0.64 in $CHCl_3$), [46% yield]. The formation of **2b** requires initial base-catalysed epimerisation of the C-2 triflate before closure whereas **11b** arises from attack of the C-6 primary hydroxyl group at the lactone carbonyl group, followed by subsequent displacement of triflate by the C-5 oxygen of the sugar. The structure of **11b** was confirmed by reaction with potassium carbonate in methanol to give **13b** in 63% yield.

In order to investigate the formation of pyrans from γ-lactones, the lactone **4**, oil, $[\alpha]_D^{20}$ +10.9 (*c*, 1.0 in $CHCl_3$) in which the C-3 and C-5 hydroxyl groups are protected as benzyl ethers, was prepared from diacetone glucose.[15] However, neither **4** - nor the lactone epimeric at C-2 - underwent dehydration under the Mitsonobu conditions that were successful for the dehydrative cyclisation of the δ-lactone **1**. Accordingly, the primary alcohol function in **4** was protected as a silyl ether [Scheme 2] and the remaining free hydroxyl group esterified with triflic anhydride in dichloromethane in the presence of pyridine to give **14** [88% yield] as an unstable oil. Reaction of **14** with potassium carbonate in methanol gave the ring contracted oxetane **16** oil, $[\alpha]_D^{20}$ -29.0 (*c*, 0.8 in $CHCl_3$) with inversion of configuration at C-2 in 75% yield; as long as the benzyl and silyl ether protecting groups remain in place there is no alternative ring closure process possible for **14**. The silyl protecting group could be removed from **16** to give **17**[16] oil, $[\alpha]_D^{20}$ -44.5 (*c*, 0.4 in $CHCl_3$).



$[Si] = Me_2Bu^tSi$; $Tf = CF_3SO_2$; $Bn = PhCH_2$

Scheme 2. (i) Me_2Bu^tSiCl, imidazole, DMF; then Tf_2O, pyridine, CH_2Cl_2 (ii) CF_3COOH in aq. dioxan (iii) DMF, room temperature (iv) HCl, MeOH (v) K_2CO_3, MeOH (vi) Bu_4NF, THF

The silyl ether protecting group was removed from **14** by careful treatment with trifluoroacetic acid in aqueous dioxan to give the triflate **15**, isolated in 86% yield, again as an unstable gum. When **15** was left in dimethylformamide at room temperature, a spontaneous cyclisation occurred to give the bicyclic lactone **5**[17] oil, $[\alpha]_D^{20}$; -31.2 (c, 1 in $CHCl_3$) in 85% yield; the bicyclic lactone **5** reacted with methanolic hydrogen chloride to give the tetrahydropyran **6**[18] oil, $[\alpha]_D^{20}$ -17.5 (c, 1 in $CHCl_3$) in 90% yield. Although this clearly demonstrates that the tetrahydropyran ring system may be formed from closure of the ring prior to opening of the lactone ring, it is possible that basic or acidic conditions which generate open chain hydroxy triflates would also allow the formation of **6**.

Accordingly a methanolic solution of the triflate **15** was treated with potassium carbonate; the *major* product from the reaction was the oxetane **17** [60% yield] with only a small amount of the tetrahydropyran **6** being formed [about 20%]. When **15** was treated with acidic methanol, a mixture of the tetrahydrofuran **18**[19] oil, $[\alpha]_D^{20}$ +45.0 (c, 0.4 in $CHCl_3$) (52% yield) and the tetrahydropyran **6** (30% yield) was formed. The different formation of 4 and 6 membered rings in base but of 5 and 6 membered rings in acid may have implications for the controlled cyclisations of lactone triflates to oxetane, tetrahydrofuran or tetrahydropyran rings.

In summary, δ- and γ-lactones can undergo an overall dehydrative cyclisation to bicyclic lactones containing a new tetrahydropyran ring with either retention or inversion of configuration at C-2. While the generality of these cyclisations has yet to be demonstrated, analogous reactions in which dehydration occurs between the C-2 and C-6 hydroxyl functions of heptonolactones would provide an approach to the synthesis of *C*-glycopyranosides.[20]

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[9] All new compounds in this paper have spectroscopic data consistent with the structures proposed; correct microanalyses have been obtained for **2a, 2b, 3, 4, 5, 6, 7b, 8b, 9a, 9b, 10b, 12b, 13b, 16, 17** and **18.**

[10] Selected data for bicyclic lactone **2a**: δ_C (CD_3CN) 23.4, 23.6 (2 x q), 62.5 (t), 70.3, 72.5, 73.7, 73.8 (4 x d), 110.5 (s), 168.6 (s).

[11] Selected data for bicyclic lactone **2b**: δ_C ($CDCl_3$) 23.5, 23.7, 24.8, 33.9, 35.2 (5 x t), 62.8 (t), 70.6, 72.4, 73.5, 73.6 (4 x d), 112.1 (s), 168.0 (s).

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[13] Selected data for symmetrical tetrahydrofuran **12b**: δ_C ($CDCl_3$) -5.6 (q, Me_2Si), 18.2 (s, $Me_3\underline{C}Si$), 23.5, 23.9, 24.9 (3 x t), 25.8 (q, $\underline{Me}_3C$), 35.0, 37.2 (2 x t, cyclohexylidene), 64.1 (t, C-1, C-6), 81.7, 85.3 (2 x d, C-2, C-3, C-4, C-5), 114.0 (s).

[14] Selected data for bicyclic lactone **11b**: δ_C ($CDCl_3$) 23.5, 23.8, 24.6, 34.3, 35.5 (5 x t), 69.7 (t, C-6), 77.6, 81.0, 81.9, 82.9 (4 x d), 115.0 (s), 165.8 (s).

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[16] Selected data for oxetane **17**: δ_C ($CDCl_3$); 52.3 (q, OCH_3), 60.9 (t), 71.8, 72.3 (2 x t), 75.6, 76.6, 83.8, 84.1 (4 x d), 127.7, 127.8, 128.1, 128.4, 128.5 (5 x d), 136.9, 138.4 (2 x s), 170.6 (s).

[17] Selected data for lactone **5**: δ_C ($CDCl_3$): 64.9, 71.8, 72.1 (3 x t), 69.8, 71.1, 75.5, 77.4 (4 x d), 128.0, 128.3, 128.5, 128.8, 129.0 (5 x d), 136.7, 137.6 (2 x s), 170.8 (s).

[18] Selected data for tetrahydropyran **6**: δ_C ($CDCl_3$); 52.2 (q, OCH_3), 63.7, 71.4, 73.8 (3 x t), 70 8, 73.8, 75.5, 77.7 (4 x d), 128.1, 128.3, 128.7, 128.8 (4 x d), 137.8, 138.1 (2 x s), 170.2 (s).

[19] Selected data for tetrahydrofuran **18**: δ_C ($CDCl_3$,): 52.5 (q, -OCH_3), 62.0, 72.1 (2 x t), 76.3, 81.0, 86.5, 87.9 (4 x d), 128.1, 128.3, 128.6 (3 x d), 137.2 (s), 172.5 (s).

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