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Tandem Pericyclic Reactions. The first X-Ray Structure of an Initial Pyrone-Olefin Adduct and an Easy, Stereocontrolled, Entry into Polyoxygenated Cyclohexanes ¶

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¶ Dedicated fondly to Dr Yun Gao for his continuous encouragements

Abstract: *Under high-pressure conditions, 2-pyrone undergoes Diels-Alder reaction with a variety of dienophiles, leading to isolable, bridged, bicyclic lactones. The first X-Ray structure of one of these lactones and its conversion into polyoxygenated cyclohexane derivatives is reported.*

Tandem reactions are amongst the most useful synthetic methods available, generating several bonds or rings in a single step.[1] We have recently reported a unique cascade sequence, starting with 2-pyrone and involving three consecutive pericyclic reactions (Figure 1).[2]

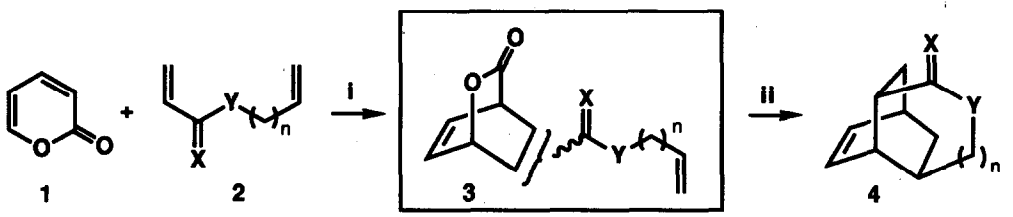


Figure 1

This tandem process begins with the intermolecular Diels-Alder cycloaddition between 2-pyrone and α,ω-dienes **2**, giving the adducts **3**. These bicyclic lactones have long been proposed as intermediates in the reaction of pyrones with dienophiles but have rarely been isolated[3] and their structures were usually deduced from further chemical modifications.[4]

In this Letter, we report the first X-ray crystallographic analysis of one of these cycloadducts. By a combination of X-ray crystallography and spectroscopic analysis, a firm basis for the structural elucidation of bicyclic lactones of this type has also been established.

When 2-pyrone is reacted with methyl acrylate, under high pressure, a mixture of 4 diastereoisomeric adducts **5b, 6b, 7b** and **8b** is obtained, in the ratio 85:35:15:7. These isomers were separated by HPLC and fully characterised. Crystallisation of the crude reaction mixture from ether gave the major diastereoisomer **5b** as beautiful needles. X-ray diffraction analysis revealed it to possess the β-*endo* structure shown in Figure 2.[5] Correlation of the spectroscopic properties

of this adduct with the other, minor isomers, allowed their unambiguous structural determination. Selected ^1H NMR data are collected in Table 1 and deserve a few comments.

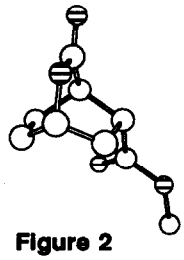
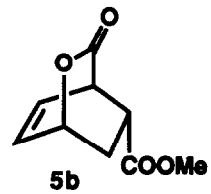
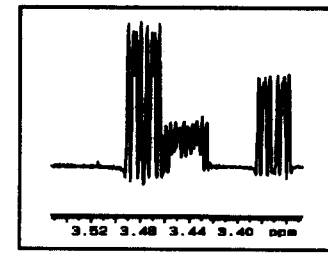


Figure 2

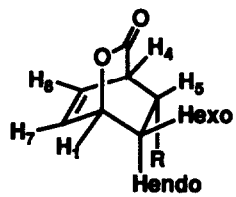


5b

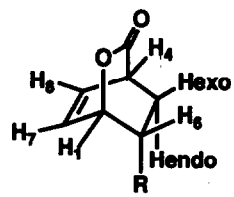


The distinction between *endo*- and *exo*-isomers can be readily deduced from the pattern of the signal belonging to the vinylic protons H7 and H8 located at δ = 6.5 - 6.6 ppm.[6] In an *exo*-product, both hydrogens give rise to a unique multiplet centered around δ = 6.55 ppm.

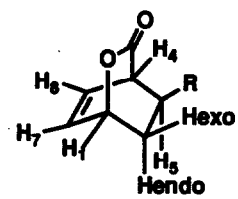
Table 1. Selected proton NMR Data of Bicyclic Lactones



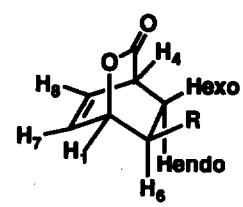
β-*endo* 5



γ-*endo* 6



β-*exo* 7



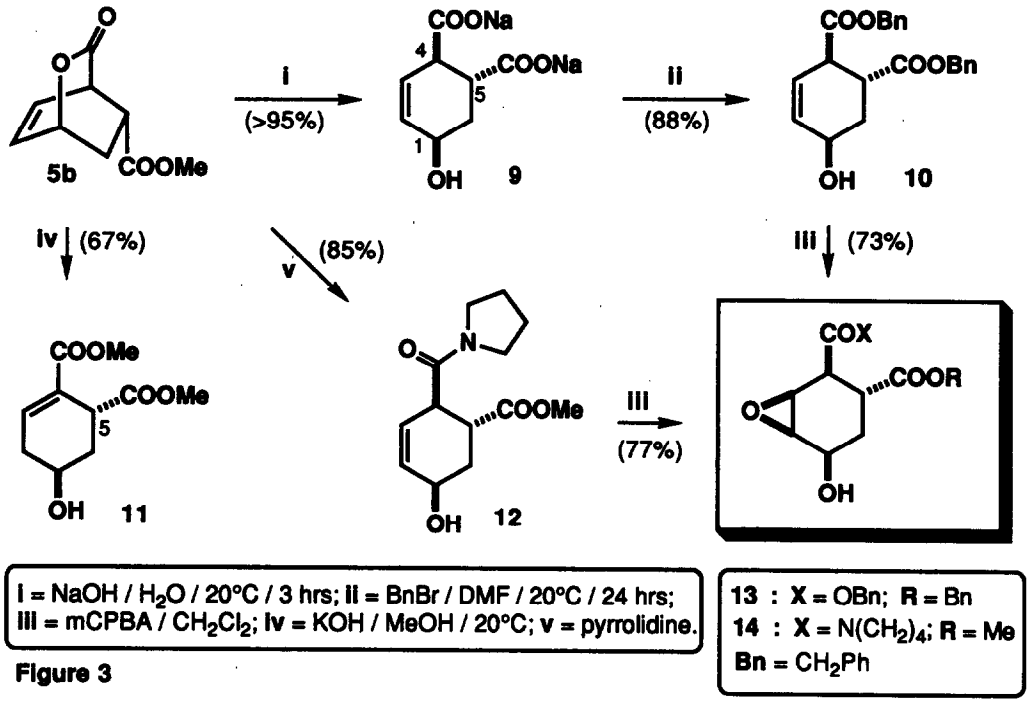
γ-*exo* 8

	H_1	H_4	H_5	H_6	H_7	H_8	H_{endo}	H_{exo}
5a	5.32	3.75	3.08		6.63	6.51	1.89	2.33
6a	5.43	3.47		3.35	6.63	6.51	1.71	2.09
5b	5.28	3.92	3.05		6.55	6.45	2.10	2.48
6b	5.48	3.55		3.36	6.57	6.45	1.94	2.22
7b	5.23	3.67	2.66		6.53	6.53	1.93	2.43
8b	5.50	3.52		2.77	6.53	6.53	1.76	2.45
5c	5.33	3.95	3.09		6.57	6.47	2.10	2.48
6c	5.50	3.55		3.39	6.60	6.45	1.95	2.22
7c	5.27	3.75	2.71		6.55	6.55	1.95	2.50
8c	5.55	3.55		2.80	6.55	6.55	1.80	2.48
5d	5.27	3.70	3.10		6.55	6.50	1.85	2.55
6d	5.45	3.52		3.40	6.65	6.53	1.65	2.29

a : R = COOH ; **b** : R = COOMe ; **c** : R = $COOCH_2$-CH = CH_2; **d** : R = $COOCH_2CHCH = CH_2$

In contrast, a pair of multiplets ($\Delta\delta$ ~ 0.1 ppm), resulting from the splitting of the vinylic hydrogens by the *endo*-substituent, is observed in *endo*-adducts.[7] Noteworthy is the observed difference in chemical shift for protons H_5 or H_6 in *endo*- and *exo*-isomers. In all cases, H_5 *endo* appears at higher field than H_5 *exo* and so does H_6 *endo* as compared to H_6 *exo*. The $\Delta\delta$ is greater for the γ-isomers (e.g. **6b** and **8b** $\Delta\delta$ ~0.6 ppm) than for the β-isomers (e.g. **5b** and **7b** $\Delta\delta$ ~0.4 ppm).

Further distinctions between β and γ-adducts can be made when examining H_1 and H_4. In the *endo*-series, H_1 resonates at lower field in the β-isomer than in the γ-isomer. The reverse behaviour holds true for H_4. The coupling constants of this latter hydrogen are particularly indicative. For example, in the case of both β-isomers of adduct **3** (X = H,H; Y = CH_2; n = 1), H_4 appears as a ddd (*endo:* J^1 = 1,5 Hz; J^2 = 2.5 Hz; J^3 = 6.0 Hz; *exo:* J^1 = 1.5 Hz; J^2 = 2.0 Hz; J^3 = 6.0 Hz) whereas a more complex pattern (theoretically 16 peaks) is observed for the γ-isomer. The inset in Figure 2 shows the relevant portion of the 400 MHz NMR spectrum of this crude mixture of adducts; the major isomer clearly being the β-*endo* one. In all cases examined so far, the *endo*-adducts predominate over their *exo*-counterparts (4:1 to 8:1) and the β-isomers over the γ-ones.



I = NaOH / H_2O / 20°C / 3 hrs; II = BnBr / DMF / 20°C / 24 hrs;
III = mCPBA / CH_2Cl_2; Iv = KOH / MeOH / 20°C; v = pyrrolidine.

13 : X = OBn; R = Bn
14 : X = $N(CH_2)_4$; R = Me
Bn = CH_2Ph

Figure 3

These bicyclic lactones are interesting synthetic intermediates which can be employed for the stereocontrolled preparation of highly oxygenated cyclohexane ring systems. This is illustrated by some modifications of adduct **5b** which are described in Figure 3. Ring opening of isomerically pure bicyclic lactone **5b** with excess aqueous NaOH gives quantitatively the

disodium salt **9**. Esterification using benzyl bromide in DMF affords the bis-ester **10** as a single stereoisomer. Under these conditions, no double bond migration or epimerisation at C_4 or C_5 is observed. On the other hand, ring opening of adduct **5b** using KOH in methanol leads rapidly to the conjugated ester **11** without epimerisation at C_5.[8] To discriminate between the two carbonyl groups present in **10**, advantage was taken of the increased reactivity of the bridged lactone function of **5b**. Upon treatment with pyrrolidine, adduct **5b** smoothly produces amido-ester **12** as a single diastereoisomer, allowing chemoselective reactions to be performed on **12**. Finally, hydroxyl-directed epoxidation[9] of **10** and **12** gives products **13** and **14** with full stereocontrol at the 5 chiral centres. Further exploration of the rich chemistry of these bicyclic lactones is being actively pursued in this laboratory and will be reported in due course.

Acknowledgements

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(5) Monoclinic, a = 10.684(10), b = 6.198(5), c = 13.132(12)A, beta = 99.61(7)°, U = 857.3(13)A^3, D_c = 1.411g cm^{-3}, Z = 4. Space group $P2_1/a$, Mo-Kα X-radiation (λ = 0.71069A) with graphite monochromator, μ (Mo-Kα) = 1.05 cm^{-1}, F(000) = 383.96. Dimensions 0.40x0.20x0.10 mms.

(6) Harano, K.; Aoki, T.; Masashi, E.; Hisano, T. *Chem. Pharm. Bull.* **1990**, *38*, 1182.

(7) One exception to this general rule is provided by the β-*endo* adduct obtained from 2-pyrone and allyl methacrylate. Both H_7 and H_8 appear at δ = 6.49 ppm as a unique multiplet.

(8) In contrast to examples described in Ref. **3a** and **3b**, in which neither isomerisation nor epimerisation is possible, our bicyclic lactones are exceedingly prone to isomerisation, epimerisation and rearrangement. The exact experimental conditions, which are crucial to the success of these transformations, will be reported in detail in the full paper.

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