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A one-step synthesis of tetrahydropyranopyranones from carbonyl compounds

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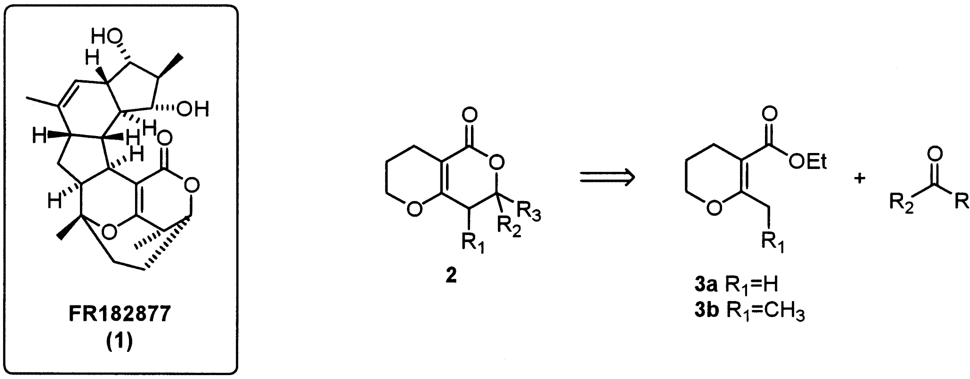
Abstract—A one-step synthesis of tetrahydropyranopyranones, a ring system present in the natural product FR182877, from carbonyl compounds is described. © 2001 Elsevier Science Ltd. All rights reserved.

The natural product FR182877 was isolated by workers at Fujisawa in Japan from the fermentation broth of *Streptomyces* sp. No. 9885.[1] It is of significant biological interest since it exhibits microtubule stabilisation properties reminiscent of taxol.[2] Its structure and relative stereochemistry were determined[1c] by X-ray crystallography on a derivative which revealed an intriguing polycyclic structure **1** (Scheme 1) including a strained bridgehead olefin. This combination of biological activity and fascinating structure will undoubtedly attract the interest of synthetic chemists.[3,4] Indeed, Sorensen has already described progress towards an ingenious proposed biomimetic synthesis.[3] One of the most interesting subunits of **1** is the tetrahydropyranopyranone **2**. We envisaged that a rapid synthesis of this ring system might be possible by reaction between a carbonyl compound and the anion derived from γ-deprotonation of ester **3**. Here we report the realisation of this goal, providing a simple synthesis of the tetrahydropyranopyranone unit and allowing the rapid preparation of a range of analogues.

Initial studies centred on the unsubstituted system **3a**. Compound **3a** is commercially available but may be prepared in a single step from ethyl acetoacetate and 1,3-dibromopropane.[5] With **3a** in hand, we investigated anion generation. Treatment with 1 equiv. LDA in THF at −78°C followed by addition of benzaldehyde and subsequent standing in the freezer overnight at −22°C pleasingly led after standard aqueous work up to the desired tetrahydropyranopyranone **2** in 81% yield (Scheme 2 and Table 1, entry 1). As well as spectroscopic characterisation, the product structure was confirmed by X-ray crystallography.[6] We were pleased to find that the method could be extended to an aliphatic aldehyde, propionaldehyde (entry 2), and ketones



FR182877
(1)

2

3a R_1=H
3b R_1=CH$_3$

Scheme 1.

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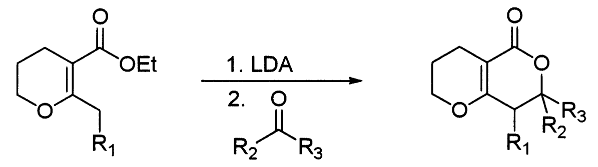

3a R_1=H
3b R_1=CH_3

2

Scheme 2.

Table 1. Synthesis of tetrahydropyranopyranones from carbonyl compounds[7]

Entry	R_1	R_2	R_3	*cis*:*trans*[e]	Yield[f]
1	H	Ph	H	–	81[g]
2	H	^{n}Pr	H	–	83
3	H	-$(CH_2)_5$-		–	82[g]
4[a]	H	CO_2Et	CO_2Et	–	42
5	H	CH=CH_2	H	–	42
6	CH_3	Ph	H	55:45	82
7[b]	CH_3	Ph	H	43:57	n.d.[h]
8[c]	CH_3	Ph	H	30:70	n.d.[h]
9[d]	CH_3	Ph	H	22:78	n.d.[h]
10	CH_3	^{n}Pr	H	50:50	77
11	CH_3	-$(CH_2)_5$-		–	39

[a] The initial adduct was treated with CSA (1 equiv.) in toluene at reflux for 14 h to effect cyclisation.

[b] 0.5 equiv. of DMPU added before the aldehyde.

[c] 2 equiv. of DMPU added.

[d] 8 equiv. of DMPU added.

[e] Ratio measured by GC. Stereochemistry assigned by ^{1}H NMR coupling constant analysis.

[f] Isolated yield of *cis*:*trans* mixture.

[g] Product structure confirmed by X-ray crystallography.[6]

[h] n.d., not determined.

(cyclohexanone, entry 3; diethyl ketomalonate, entry 4). In the ketomalonate case, treatment of the initial adduct with CSA was necessary after the anion-addition step in order to induce lactonisation. Particularly noteworthy is the fact that acrolein gave a reasonable yield (entry 5), since the exocyclic olefin in the product could provide a handle for eventual closure of the seven-membered ring in the natural product by, for example, olefin metathesis. We next investigated the incorporation of the methyl substituent present in the natural product. The required ester **3b** was again prepared in a single step from 1,3-dibromopropane and commercially available ethyl propionylacetate.[5] Anion formation and reaction with benzaldehyde again led to tetrahydropyranopyranone formation in good yield, with the product being formed as a 55:45 mixture of *cis*:*trans* diastereomers (entry 6). We investigated the effect of the presence of DMPU on this diastereomeric ratio (entries 7–9); while the products from these reactions were not purified, GC analysis of the crude reaction mixture indicated that this additive promoted formation of the *trans*-isomer.

In conclusion, we have demonstrated an extremely short synthesis of the tetrahydropyranopyranone ring system, which is present in the natural product FR182877. Efforts to extend this and related cyclisation reactions to more functionalised substrates are underway.

Acknowledgements

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References

1. (a) Sato, B.; Muramatsu, H.; Miyauchi, M.; Hori, Y.; Takase, S.; Hino, M.; Hashimoto, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 123–130; (b) Sato, B.; Nakajima, H.; Hori, Y.; Hino, M.; Hashimoto, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 204–206; (c) Yoshimura, S.; Sato, B.; Kinoshita, T.; Takase, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 615–622.
2. Review: Nicolaou, K. C.; Hepworth, D.; King, N. P.; Finlay, M. R. V. *Pure Appl. Chem.* **1999**, *71*, 989–997.
3. Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *Org. Lett.* **1999**, *1*, 645–648.
4. Banwell, M.; Hockless, D.; Jarrott, B.; Kelly, B.; Knill, A.; Longmore, R.; Simpson, G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3555–3558.
5. Ester **3a** was prepared (40% yield) by reaction of 1,3-dibromopropane and ethyl acetoacetate with 1 equiv. NaOEt in EtOH at reflux for 5 h according to a literature procedure: (a) Cacciapaglia, R.; Mandolini, L. *Tetrahedron* **1990**, *46*, 1353–1356. Spectroscopic data in agreement with: (b) Chan, Y. Y.; Li, X.; Zhu, C.; Liu, X.; Zhang, Y.; Leung, H. K. *J. Org. Chem.* **1990**, *55*, 5497–5504. Compound **3b** was prepared in a similar way from ethyl propionylacetate (38–40% yield).
6. The authors thank Dr. A. J. P. White of the Department of Chemistry, Imperial College of Science, for the X-ray structure determinations. Details will be reported in a full account of this work.
7. Typical procedure (entry 1 in Table 1, preparation of 7-phenyl-3,4,7,8-tetrahydro-2*H*-pyrano[4,3-*b*]pyran-5-one): A solution of ^{n}BuLi in hexanes (0.293 ml, 2.51 N, 0.735 mmol) was added to ^{i}Pr$_2$NH (0.109 ml, 0.772 mmol) in THF (1.5 ml) under nitrogen at 0°C. The reaction mixture was stirred for 30 min, then cooled to −78°C before dropwise addition of a solution of ester **3a** (100 mg, 0.588 mmol) in THF (0.5 ml). The reaction mixture was stirred at −78°C for 35 min. Benzaldehyde (0.090 ml, 0.882 mmol) was then added dropwise and the reaction mixture stirred for 90 min at −78°C, then the reaction flask was sealed up and placed in the freezer (at −22°C) overnight. The reaction mixture was taken up in diethyl ether and water, and the aqueous layer extracted twice with diethyl

ether. The combined organic layers were washed with sat. brine solution and dried over magnesium sulphate, filtered, then concentrated in vacuo. The resulting crude was purified by flash column chromatography, eluting with 3:10 ethyl acetate:petrol spirit (40–60°C), to obtain the desired product (109 mg, 81%) as a white solid, mp 116–118°C; ν_{max} 1689, 1648 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.45–7.30 (5H, m, ArH), 5.41 (1H, dd, *J* 12.4, 4.0, CHPh), 4.28–4.06 (2H, m, CH_2O), 2.87–2.28 (4H, m), 1.98 (2H, m); δ_C (300 MHz, $CDCl_3$): 167.3 (C), 165.2 (C), 138.9 (C), 128.6 (CH), 128.5 (CH), 126.0 (CH), 100.6 (C), 76.6 (CH), 67.7 (CH_2), 34.6 (CH_2), 21.6 (CH_2), 18.6 (CH_2); MS found: $[M+H]^+$, 231.1010; $C_{14}H_{14}O_3+H^+$ requires: $[M+H^+]$, 231.1021.