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Naphthopyranone synthesis via the tandem Michael–Dieckmann reaction of *ortho*-toluates with 5,6-dihydropyran-2-ones

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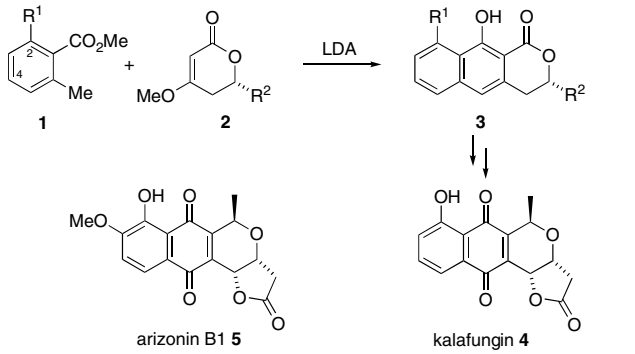
ABSTRACT

The tandem Michael–Dieckmann reaction between a series of *ortho*-toluates and the α,β-unsaturated lactone **25** is described. The tandem reaction delivers substituted naphthopyranones in moderate (20–49%) yields, whilst limitations in the tolerance of this reaction for different substituents on the *ortho*-toluate are identified.

The tandem Michael–Dieckmann reaction of *ortho*-toluates with cyclic and acyclic β-alkoxy-α,β-unsaturated ketones, the Staunton–Weinreb annulation, has been used regularly as an effective method for preparing polycyclic frameworks in the synthesis of natural products and related structures. Less commonly exploited is the tandem Michael–Dieckmann reaction of *ortho*-toluates **1** with α,β-unsaturated δ-lactones **2** (Scheme 1), a strategy first reported by Staunton and co-workers,[1] which provides a concise method for the rapid construction of naphthopyranones **3**.

Since the first reported application of this methodology to the synthesis of toralactone,[1] this approach has been exploited in the synthesis of a select group of naphthopyranone-based natural products including vioxanthin,[2] semivioxanthin[3,4] and cassiaside C_2.[5] Furthermore, naphthopyranones prepared using this methodology have served as useful synthetic intermediates in the preparation of other structure classes including naphthalenes,[6] naphthopyrans[7] and pyranonaphthoquinones.[8,9] We have applied the tandem Michael–Dieckmann reaction towards the synthesis of the extended quinone xylindein[10] and, more recently, prepared the naphthopyranone **3** (R^1 = OMe, R^2 = CH_2CH_2OTBS) as an intermediate in the preparation of the pyranonaphthoquinone antibiotic kalafungin **4** (Scheme 1).[9]

Although the minimum requirement of having an oxygen substituent at C-2 of the *ortho*-toluate (e.g., **1** R^1 = OMe) is recognized[1,11] and 2,4-dioxygenated *ortho*-toluates have found regular use,[1–8] the tolerance of this reaction for further oxygen substituents has not been reported. Having successfully applied this general methodology to the synthesis of kalafungin **4**, we sought to explore the potential scope of this strategy for the preparation of pyranonaphthoquinones related to kalafungin **4**, such as arizonin B1 **5**.



Scheme 1. Synthesis of naphthopyranones **3** via the tandem Michael–Dieckmann reaction.

The focus of our study was to prepare a series of naphthopyranones **3** (R^2 = CH_2CH_2OTBS, Scheme 1) that incorporate additional oxygen substituents in the peripheral aromatic ring. Thus, we firstly needed to prepare a series of oxygenated *ortho*-toluates (Table 1, **14**–**24**). Methyl 2-methylbenzoate **16** was prepared from *ortho*-toluic acid, whilst the 2-methoxytoluate **17** was prepared from 2,3-dimethylanisole[12] and the 2,4-dimethoxytoluate **21** from methyl acetoacetate.[13] Methyl opianate **12** (Scheme 2) serves as a suitable precursor for preparation of the 2,3-dimethoxytoluate **14**, and is available from opianic acid.[14] However, we chose to prepare **14** from the more readily available 3,4-dimethoxybenzaldehyde **6**. Thus, conversion of the aldehyde **6** to the cyclic acetal **8** proceeded smoothly using 1,3-propanediol/trimethyl orthoformate/TBATB.[15] Directed *ortho*-metalation of **8** followed by trapping with methyl chloroformate gave the benzoate **10** that could not be completely freed from unreacted **8**. Exposure of the mixture of **8** and **10** to acid delivered the benzaldehyde **12** in 57% yield over three steps from **6**. Finally, reduction of the aldehyde **12** gave the required

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0040-4039/$ - see front matter Crown Copyright © 2008 Published by Elsevier Ltd. All rights reserved.
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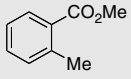
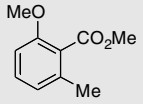
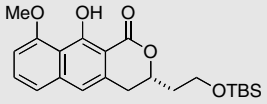
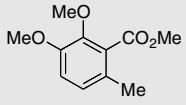
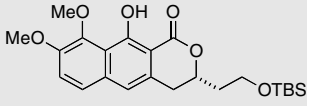
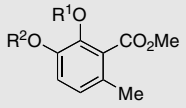
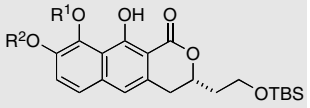
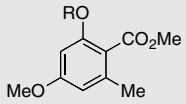
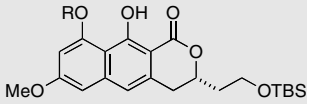
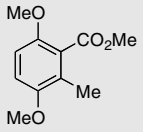
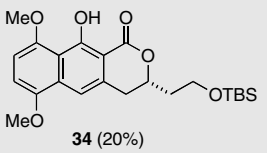
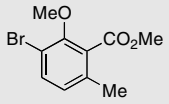
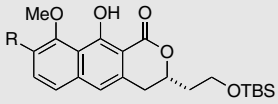
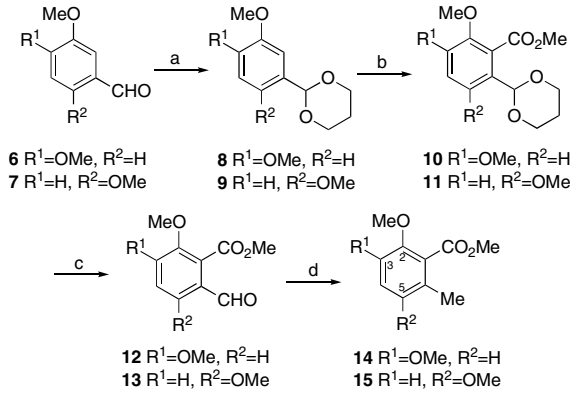
Table 1
Products and yields from reactions of *ortho*-toluates **14**–**24** with lactone **25**

Entry	*ortho*-Toluate	Product (yield)[a]
1	 **16**	–
2	 **17**	 **26** (46%)
3	 **14**	 **27** (~5%)[b]
4	 **18** R^1 = Me, R^2 = Piv	 **28** R^1 = Me, R^2 = Piv (0%)[c]
5	**19** R^1, R^2 = $-CH_2-$	**29** R^1, R^2 = $-CH_2-$ (0%)[c]
6	**20** R^1 = MEM, R^2 = Me	**30** R^1 = MEM, R^2 = Me (0%)[c]
7	 **21** R = Me	 **31** R = Me (41%)
8	**22** R = MEM	**32** R = MEM (49%)
9	**23** R = TBS	**33** R = TBS (0%)[d]
10	 **15**	 **34** (20%)
11	 **24**	 **35** (R=Br) + **26** (R=H) (10%)

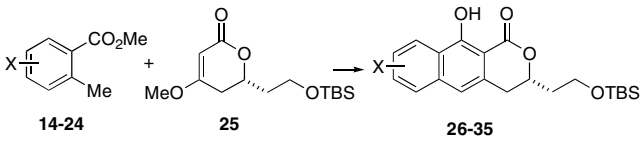
[a] Typically, unreacted toluate was also recovered from each reaction. However, all yields refer to isolated products *without* adjustment for recovered toluate.
[b] Yield estimated from the ^{1}H NMR spectrum of partially purified product still contaminated with toluate **14**.
[c] Recovery of toluate, lactone **25** and acid degradation product.
[d] Recovery of **23**, **25** and the product of Michael addition.

ortho-toluate **14** (95% yield). A similar sequence of reactions was used to prepare the 2,5-dimethoxytoluate **15** from 2,5-dimethoxybenzaldehyde **7**. In this case, the benzoate **13** was obtained in 77% yield over three steps from **7**. Reduction of the aldehyde **13** gave the required *ortho*-toluate **15** in somewhat lower yield (53%), due to concomitant formation of 4,7-dimethoxyphthalide (27% yield), resulting from lactonization of the intermediate benzyl alcohol.

With this initial series of *ortho*-toluates in hand, we began to explore their propensity to undergo a tandem Michael–Dieckmann reaction with lactone **25** (Scheme 3). The lactone **25** is itself available in 48% yield over six steps from aspartic acid.[9] Treatment of 2-methoxytoluate **17** with LDA (2 equiv) at −65 °C followed by addition of lactone **25** and warming to room temperature over



Scheme 2. Reagents and conditions: (a) 1,3-propanediol, $(MeO)_3CH$, $Bu_4N{\cdot}Br_3$, 16 h (92% for **8**, 97% for **9**); (b) ^{n}BuLi, $ClCO_2Me$, Et_2O, −78 °C to rt, 16 h; (c) 10% HCl, THF, 16 h (62% for **12**, 79% for **13**, two steps); (d) H_2, 50 psi, 5% Pd/C, MeOH, 6 h (95% for **14**, 53% for **15**).



Scheme 3. Tandem Michael–Dieckmann reaction of *ortho*-toluates **14**–**24** with lactone **25**. Reagents and conditions: LDA (2 equiv), THF, −65 °C to rt (30 min).

30 min gave the naphthopyranone **26** in 46% yield. At higher temperature (−40 °C), incomplete consumption of lactone **25** was observed, whilst at lower temperature (−78 °C) for longer periods the lactone **25** also underwent elimination to form the corresponding conjugated dienoic acid.

The optimized conditions were then applied to the series of *ortho*-toluates collected in Table 1. As expected, unsubstituted toluate **16** failed to give any naphthopyranone. This is consistent with previous reports that have shown that an oxygen substituent *ortho* to the carboxymethyl group is required for successful reaction.[1,11] Somewhat unexpectedly the 2,3-dimethoxytoluate **14** (entry 3) gave only trace amounts of the naphthopyranone **27**.

Believing that the electron-donating nature of the additional methoxy group was disfavouring deprotonation of the *para*-disposed methyl group in **14**, the pivaloyl protected derivative **18** (entry 4) was prepared. However, this toluate also failed to undergo the tandem reaction. Similarly unsuccessful were the reactions of the methylenedioxy derivative **19** and the MEM protected toluate **20**. Subsequently, successful reaction between the 2,5-dimethoxytoluate **15** (entry 10) and lactone **25** indicated that electronic factors are not the only consideration in this process. The 2,4-dimethoxytoluate **21** (entry 7) reacted efficiently (41%), whilst the MEM ether analogue **22** gave a further slight improvement in yield (49%). However, the bulkier TBS protecting group in **23** was not compatible with this process. The only identifiable product from the combination of the TBS-protected toluate **23** and lactone **25** appeared to be the product of Michael addition without subsequent cyclization.

The exploration of *ortho*-toluates **14** and **18**–**20** (entries 3–6) possessing oxygens at both C-2 and C-3 was driven by our interest in gaining direct access to a naphthopyranone framework that incorporates the necessary functionality for eventual elaboration to arizonin B1 **5**. With the failure of these substrates, we turned to the brominated toluate **24** (entry 11). The toluate **24** reacted with lactone **25** to deliver a mixture of products identified as the desired 8-bromonaphthopyranone **35** and the de-halogenated

material **26**. Unfortunately, the poor yield for this reaction precludes this as a viable method for accessing arizonin B1 **5**.

Some tentative conclusions may be drawn from the above results. Previously, it has been proposed that the oxygen substituent *ortho* to the carbonyl hinders nucleophilic attack at the carbonyl through both steric and electronic effects, and that after deprotonation, the toluate anion forms an extended enolate structure.[1,11] Such an anion may be stabilized by the *ortho* oxygen substituent through chelation. However, the necessary orientation for chelation of the lithium cation between the enolate oxygen and the lone-pair of electrons on the C-2 oxygen may not be achieved effectively when the C-2 oxygen possesses either (i) a bulky protecting group (entry 9), (ii) a conformationally restrictive protective group (entry 5) or (iii) if a second neighbouring group at C-3 (entries 3, 4 and 6) is present to exert a further steric influence. Electronic factors presumably have some role; however, the relative success of the 2,5-dimethoxytoluate **15** (entry 10) in comparison to the 2,3-dimethoxytoluate **14** (entry 3) shows that this is not the only consideration in the tandem Michael–Dieckmann process.

In conclusion, the tandem Michael–Dieckmann reaction between a series of *ortho*-toluates and the β-methoxy-α,β-unsaturated lactone **25** has been explored and limitations identified. Application of this methodology to the synthesis of biologically significant naphthopyranone natural products is under way; however, further work will be necessary to develop an efficient method for incorporation of additional oxygen substituents for the proposed synthesis of arizonin B1 **5**.

Acknowledgements

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