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DMAP Promoted Tandem Addition Reactions Forming Substituted Tetrahydroxanthones

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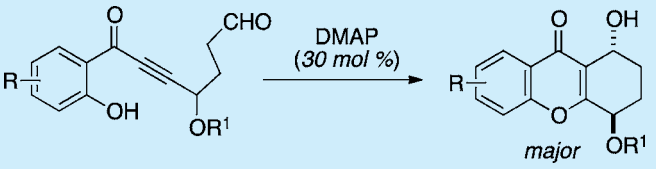
Supporting Information

ABSTRACT: Substituted tetrahydroxanthones are constructed using a DMAP-promoted tandem nucleophilic addition process. The reaction yields range from 39% to 73%. Disubstituted tetrahydroxanthones are generated as a ~2.3:1 mixture of diastereomers favoring the formation of the *trans*-isomer.



The set of secondary metabolites formed through the type 2 polyketide biosynthetic pathway that produce xanthones (9*H*-xanthene-9-one) is remarkable for their structural complexity and biological potency.[1] The synthesis of natural products within this biosynthetic class has largely been limited to those having substituted, yet fully aromatized, xanthone units. Consequently, much synthetic effort has been expended in the investigation of the synthesis of the aromatic xanthone subunit.[2] A fascinating subset of these xanthone polyketide natural products feature substituted tetrahydroxanthone (THX) subunits (Figure 1).[3] Synthetic methods that generate

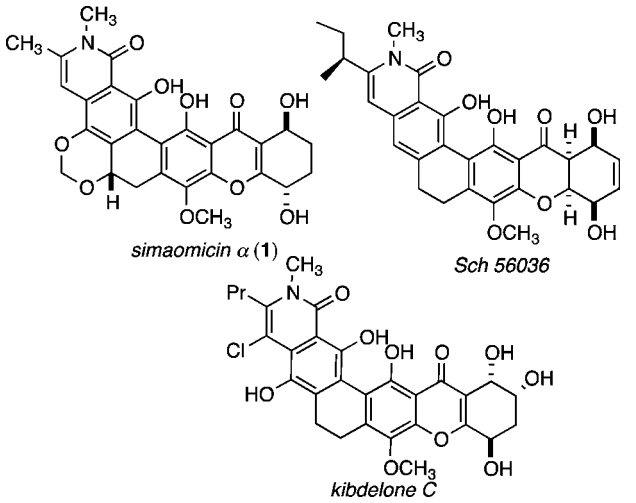
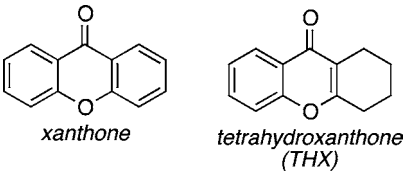


Figure 1. Polyketide containing THX fragments.

substituted THX fragments are rare compared to the methods developed to produce substituted xanthones.[4] As a result, the synthetic efforts required for the construction of THX containing natural products such as kibdelone C or Sch 56036 become even more noteworthy and elegant.[5,6]

The synthetic work in this manuscript was inspired by the structure and activities of simaomicin α (**1**) (Figure 1). This secondary metabolite, isolated from the fungus *Actinomadura*



madurae in 1989−90,[7] has been demonstrated to possess significantly greater biological activity against two malaria strains (IC_{50} 0.045 ng/mL vs K1 strain; 0.0097 ng/mL vs FCR3 strain) compared to standard treatments such as artemisinin and chloroquine. In addition, **1** has been recently shown to arrest the cell cycle at the G1 phase with suppression of retinoblastoma protein phosphorylation.[8] It has a biological profile suggesting that **1** may be an effective compound against a variety of solid tumors that exhibit multidrug resistance.

In initiating a new program of scientific inquiry guided by the medicinal potential of these tetrahydroxanthone natural products, we were compelled to examine synthetic routes that would enable the synthesis of the THX core of **1** and its structural relatives. It should be noted that Ready and his collaborators have completed an elegant total synthesis of *ent*-**1**.[9] Our synthetic work not only should assist in an approach to the construction of **1** but also, and more importantly, should enable access to structurally simplified analogs that might maintain biological potency.

We were inspired by recent disclosures describing a chromenone synthesis that incorporated a metal-catalyzed oxymetalation of an alkynone.[10] Thus, we postulated that a suitably functionalized substrate in the presence of an appropriate transition metal catalyst would undergo the mechanistic equivalent of an oxametalation across a C−C triple bond of an alkynone (Scheme 1). It was then conceived that the organometallic intermediate thus generated would add to an appropriate electrophile to produce the functionalized THX fragment. An advantage to this route is that, in the event the metal-catalyzed route failed, the desired transformation

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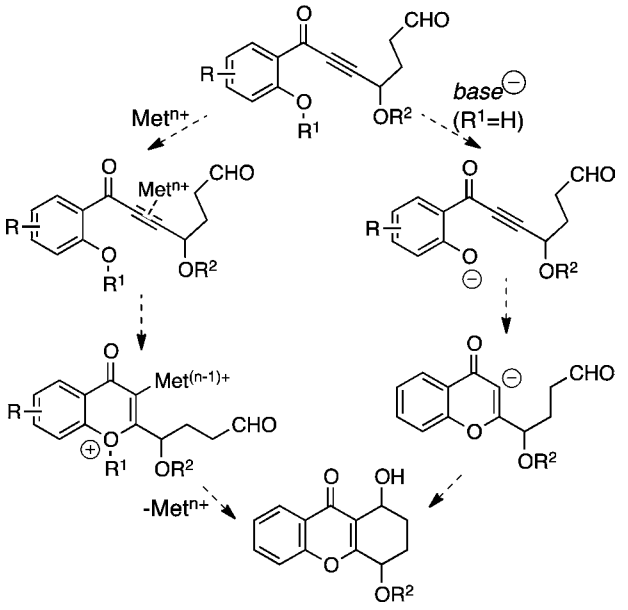
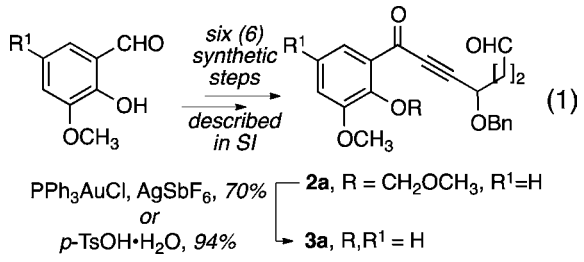
Scheme 1. Approach to 1



could in principle be coerced to occur through other mechanistic manifolds including a base-promoted anionic transformation or a nucleophile-promoted Baylis–Hilman-type process followed by condensation.

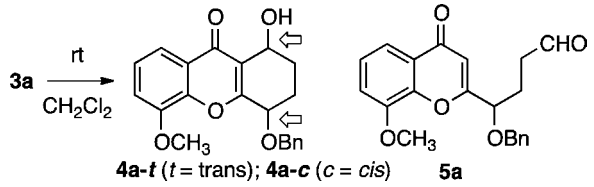
Ynone substrates such as **2a** were synthesized using standard synthetic methods that are described in detail in the Supporting Information; the most interesting transformation within the sequence is a duo of Moffatt–Swern oxidations on two hydroxyl functions in one step that generates both an alkynone and an aldehyde function in 70% yield (eq 1).[11]



Subjecting **2a** to Ph_3PAuCl (10 mol %) and $AgSbF_6$ (23 mol %) in acetonitrile at 23 °C produced only the phenol **3a** in 70% yield, a process that is more effectively carried out using *p*-TsOH·H_2O in CH_2Cl_2 (94%) (eq 1). Unfortunately, the treatment of **2a** to a variety of catalysis systems involving Au(I)/Ag(I), Ag(I), Au(III)/Ag(I), Pd(II), Ni(0), Ni(II), or Cu(I) species resulted in either no reaction or the generation of **3a** followed by decomposition.

Attention was turned to the use of inorganic bases with **3a** in order to promote a conjugate addition–aldol reaction process (Table 1).[12] Inorganic Bronsted bases were disastrous, providing either no reaction or a rapid decomposition (entries 1–5). Reactions of **3a** with organic bases and nucleophilic catalysts were surveyed by ^1H NMR analysis of the conversion of **3a** to **4a** (THX, mixture of diastereomers) and **5a** (chromenone). A reaction promoter that could maximize, at room temperature for 30 min, both the conversion of **3a** and the formation of THX's **4a** was sought. Thankfully, the reaction of **3a** with DBU gave a first indication of a tandem reaction, as

Table 1. Experimental Attempts To Convert 3a to THXs 4a



entry	base/promoter[a]		% conv[c]	ratio **4a**:**5a**[d]
1	K_2CO_3 (1.2 equiv)	144	NR	NR
2	Cs_2CO_3 (1.1 equiv)	24	trace	–
3	NaH (1.2 equiv)	0.5	dec	–
4	KH (2.5 equiv)	0.3	dec	–
5	LDA (1.05 equiv)[b]	0.5	dec	–
6	DBU (40 mol %)	2	47	1.4:1
7	DBU (100 mol %)	2	48	2.4:1
8	C_5H_5N (30 mol %)	0.5	55	1:1
9	2,6-lutidine (30 mol %)	0.5	15	2.4:1
10	NEt_3 (30 mol %)	0.5	14	1.9:1
11	**DMAP (30 mol %)**	**0.5**	**95**	**7.9:1**
12	PPh_3 (30 mol %)	0.5	49	1:1
13	PCy_3 (30 mol %)	0.5	70	1:1
14	P(*i*-C_3H_7)$_3$ (30 mol %)	0.5	47	1.8:1
15	P(4-$C_6H_4OCH_3$)$_3$ (30 mol %)	0.5	50	2.9:1
16	$P(NEt_2)_3$ (30 mol %)	0.5	35	4.6:1
17	DABCO (30 mol %)	0.5	76	3.6:1
18	quinuclidine (30 mol %)	0.5	98	3.3:1

[a]Reaction T = 22 °C. Entries 6–18: NMR experiments using 1,4-dimethoxybenzene as an internal standard. [b]Reaction solvent: THF. [c]Conversion established by integration of signal of **3a** and internal standard in NMR spectrum of crude reaction extract. [d]Ratio established by integration of signals of **4a** and **5a** in crude reaction extract.

4a was believed to be observed to be present as an equimolar component in a relatively low conversion process (entries 6 and 7). The use of amine bases such as pyridine, 2.6-lutidine, and triethylamine gave unsatisfactory results for either the conversion or product ratio (entries 8–10). The breakthrough came with the use of catalytic DMAP (30 mol %) as the promoter (entry 11). This reaction featured excellent conversion of starting material (95%) and generated a remarkable product ratio favoring tricycles **4a** to bicycle **5a** in an ~8:1 ratio. Other prospects were scouted, including phosphines (entries 12–16) and potential nucleophilic catalysts such as DABCO (entry 17) and quinuclidine (entry 18). The results of phosphine catalysis were largely unremarkable, featuring roughly ~50% conversions and poor ratios. Triethylphosphine and tributylphosphine gave similar results to tri(isopropyl)phosphine. Both DABCO and especially quinuclidine catalysis featured rapid conversion of **3a**, but the product ratios were poor compared to the DMAP result in entry 11.

As the reaction shown in Table 1 indicates, THXs **4a** are formed as a diastereomeric mixture of *trans*- and *cis*-isomers. The NMR chemical shift and coupling data suggested that the major diastereomer was *trans*-configured, but the spectroscopic data could not be unequivocally interpreted. Indeed, early on in our studies, due to the well-documented cyclizations of substituted phenols to aurones and benzofurans,[13] even the

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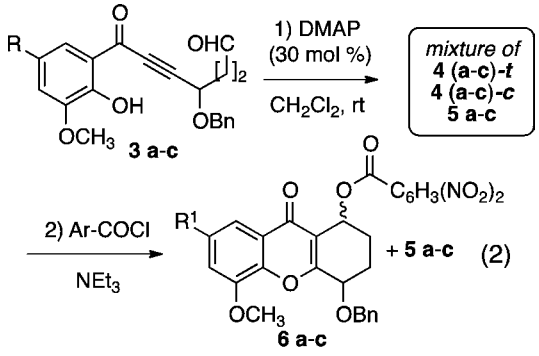
gross constitution of the diastereomeric set **4a** was not incontestably determined.

The NMR studies in Table 1 established the use of 30 mol % of DMAP at rt as an empirically superior promotion system. Milligram quantities of phenols **3a**–**c** were subjected to this process (eq 2). The NMR conversions of **3a**–**c** to products



a) R = H, *65%* of **6a**-*t*, **6a**-*c* (2.4:1); *10% of* **5a**
b) R = Br, *39% of* **6b**-*t*, **6b**-*c* (2.3:1); *14% of* **5b**
c) R = CCH, *59%* of **6c**-*t*, **6c**-*c* (2.4:1); *14%* of **5c**

4a–**c** and **5a**–**c** appeared to be excellent for **3a** and **3c** (94%, 99%) and adequate for **3b** (63%). Lowering the amounts of DMAP to 10 mol % or the reaction temperature simply lengthened the reaction time with no further advantage. Unfortunately, isolation, diastereomer separation, and characterization of these product mixtures were complicated by solubility and chromatography problems. Therefore, the product mixtures of **4a**–**c** and **5a**–**c** were treated with 3,5-dinitrobenzoyl chloride and triethylamine to form aryl esters of **4a**–**c**. Diastereomer separation was possible at this stage, but clear product losses occurred during this sequence. Fortunately, the 3,5-dinitrobenzoate derivatives of the major THX diastereomers, **6b**-*t* and **6c**-*t*, were amenable to characterization using X-ray crystallography. The solid state molecular structure of **6b**-*t* is provided in Figure 2. These solid state molecular structures of **6b**-*t* and **6c**-*t* confirm the *trans*-configuration in the major diastereomers **6a**–**c**-*t*.[14]

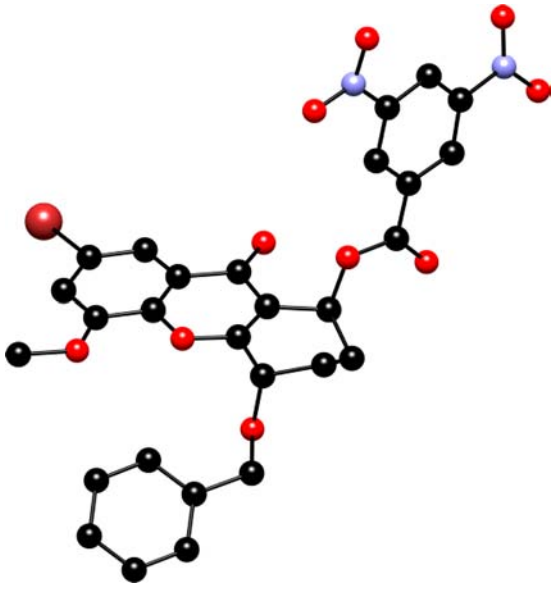
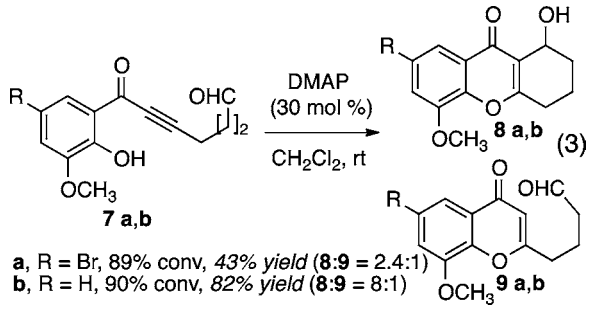


Figure 2. Solid state molecular structure of THX **6b**-*t*.

Similar comparative results to the reactions of **3a** and **3b** were observed using substrates **7a** and **7b** that lack a benzyloxy substituent (eq 3). The substituted *p*-bromophenol **7a** cyclized



a, R = Br, 89% conv, *43% yield* (**8**:**9** = 2.4:1)
b, R = H, 90% conv, *82% yield* (**8**:**9** = 8:1)

to form tricycle **8a** as the major product in mediocre isolated yield. The reaction of the (presumably) more electron-rich phenol **7b** was more effective in forming **8b**. Isolation and purification of the reaction products is clearly compromised by the presence of the halogen substituent.

Although we have not found a direct literature precedent for the conjugate addition activation of Michael acceptors with DMAP, the results suggest that a conjugate addition process between DMAP and the ynone function may be the activating step in the mechanism of the reaction. Whether this conjugate addition process initiates a Baylis–Hilman-type aldol reaction or a phenoloxy-6-*endo* cyclization process is not clear. Our attempts to catalyze Baylis–Hilman reactions on ynones that were unable to undergo oxy-Michael additions using DMAP lead to uncharacterizable decomposition products.

A tandem addition C–O, C–C bond-forming process yielding diastereomeric substituted tetrahydroxanthones using catalytic amounts of DMAP has been presented. Both *cis*- and *trans*-configured THX patterns are observed in reduced xanthone natural products. This procedure allows for the formation of stereoisomeric analog structures. Future work will focus on the development of structurally truncated THX analogs having the appropriate three-dimensional structural space for biological studies. This work will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for previously unreported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) Steps in the sequence include nucleophilic ethynylation, protection (silyl ether), addition to 4-silyloxybutanal, protection (benzyl ether), desilylation, and oxidation.

(12) Porco has used a halide ion initiated addition to an alkyne to form a THX ring F synthetic equivalent: see ref 5e.

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(14) Spectral (^{1}H NMR) data for the C-1 methine C−H in the *trans*-isomers **6a**−**c**-*t*: δ ∼6.50−6.53 (t, J = 3 Hz). The *cis*-isomers **6a**−**c**-*c* displayed: δ ∼6.46 (t, J = 4.1 Hz).

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