PROGRESSES FOR ACCESSING α'-METHOXY-γ-PYRONE HETEROCYCLE: APPLICATIONS TO THE SYNTHESIS OF VERTICIPYRONE AND AUREOTHIN

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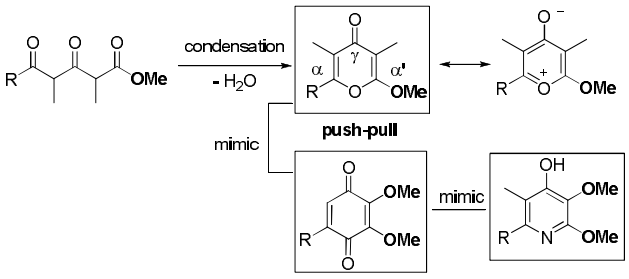
Abstract. *Focusing on the synthesis and reactivity of α'-methoxy-γ-pyrone scaffold, a heterocycle found in several natural products, this account presents the state of the art and the progresses made to access it. A recently developed abiotic strategy relied on the desymmetrization of α,α'-dimethoxy-γ-pyrone, a readily available building block, by conjugate addition with a nucleophile facilitating the construction of the side chain of the target. This transformation was studied with various nucleophiles and the strategy was successfully employed with tributylallylstannane/n-BuLi and 2-lithio-1,3-dithiane to concisely fashion verticipyrone and aureothin, two natural products with interesting biological activities.*

Contents

1. Introduction

The heterocyclic and aromatic α'-methoxy-γ-pyrone scaffold is a condensed and dehydrated form of diketone methyl ester that can be viewed as a cyclic vinylogous carbonate in which an electronic push-pull framework is effective (Scheme 1).



Scheme 1

Interestingly, this scaffold shares structural and electronic similarities with the 2,3-dimethoxybenzoquinone motif found in numerous natural products.[1] It has been suggested that α'-methoxy-γ-pyrone heterocycle could mimic the quinone scaffold as well as γ-hydroxypyridine.

Contained in several polyketides (a selection is shown in Figure 1) that have been isolated from mollusks or produced by bacteria,[2] the titled scaffold is connected to side chains that can be unsaturated such as cyercene A (**1**),[3] partially saturated as verticipyrone (**2**)[4] or completely saturated as nocapyrone B (**3**), a molecule inducing adiponectin production in murine ST-13 preadipocyte cells.[5] The recently isolated yoshinone A (**4**) and the kalkipyrone A (**5**) embed hydroxylated side chain connected to the α'-methoxy-γ-pyrone scaffold.

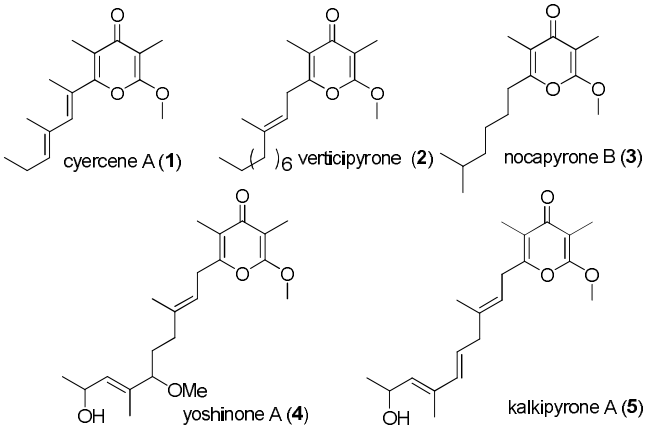


Figure 1

Noteworthy, the former molecule exhibited anti-obesity activity[6] while the latter displayed interesting cytotoxic activity against HC-460 cells (EC_{50} = 0.9 μM).[7]

Furthermore, natural products combining this motif with a complex side chain incorporating stereogenic quaternary carbon and (poly)cyclic framework were isolated (Figure 2). Biosynthetic origins of such structural complexity lay on a series of electrocyclizations of polyolefinic side chains.[8] Such biomimetic transformations were elegantly employed by Baldwin and Trauner to independently reach ocellanopyrone (**6**),[9,10] 9,10-deoxytridachione (**7**)[11] and (–)-crispatene (**8**).[12]

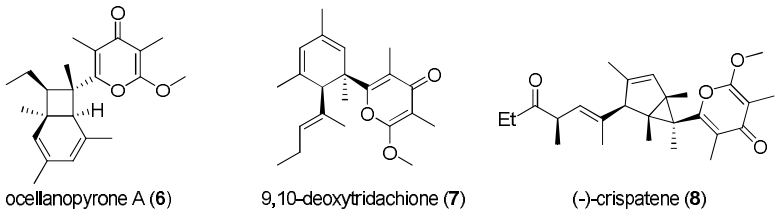


Figure 2

Another type of natural product harboring the α'-methoxy-γ-pyrone scaffold contains the cycloether heterocycle as part of the side chain. Aureothin (**9**) and spectinabilin (**10**) are two natural products structurally close that, in addition to the aforementioned heterocycles, feature respectively dienic and tetraenic framework connected to nitroaryl substituent (Figure 3). These natural products are prone to olefin isomerization as suggested by the isolation of alloaureothin (**11**)[13] and arabilin (**12**),[14] two congeners of the natural products. Actually, we demonstrated the photosensitivity of aureothin (**9**) and it is also probably the case of **10**. After olefin isomerizations promoted by light or transition metals, spectinabilin (**10**) can be converted through a series of 8π and 6π electrocyclizations into SNF 4435C (**13**) and SNF 4435D (**14**), two isomeric products featuring cyclobutane-fused cyclohexadiene motifs.[15]

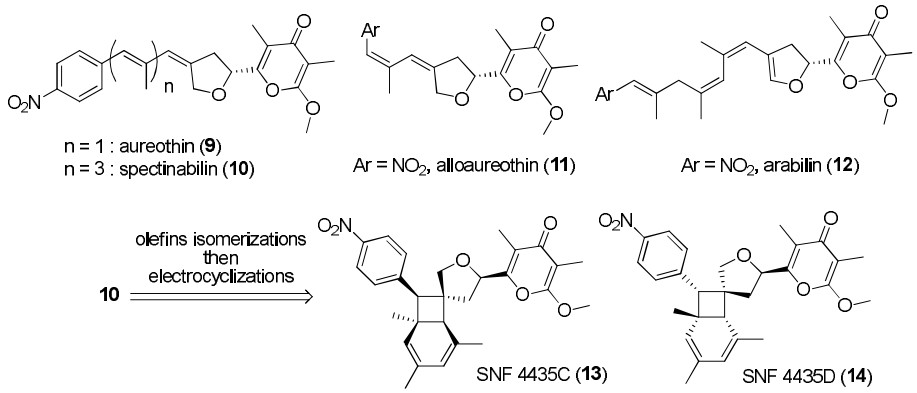


Figure 3

Beyond the synthetic efforts required to reach these targets, the preparation of the α'-methoxy-γ-pyrone scaffold is not trivial. Since the chosen route for its preparation strategically impacts the whole access to the desired natural product, enhancements of the process were sought.

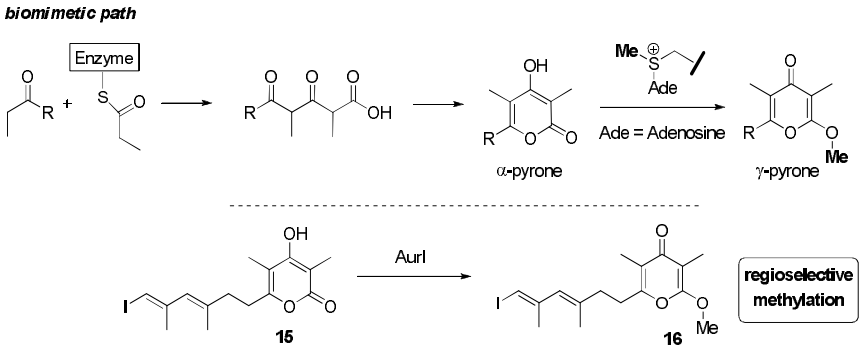
2. The α'-methoxy-γ-pyrone scaffold in detail

The syntheses of the heterocycle generally relies on biomimetic strategies in which polyketides are assembled, condensed into α-pyrones and methylated into γ-pyrones with methyltransferases (Scheme 2). Applying this strategy, Hertweck employed S-adenosyl methione dependent regiospecific pyrone methyltransferase AurI to convert **15** into **16** en route to aureothin (**9**).[16]

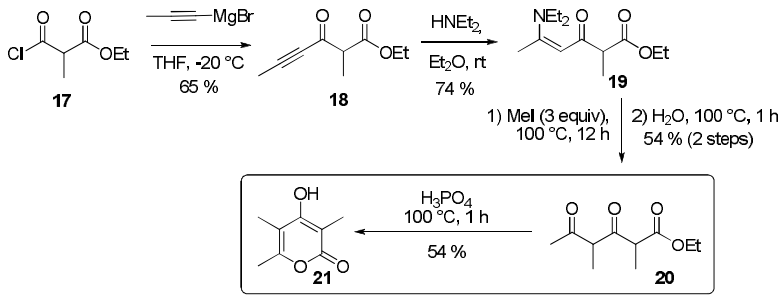
An access to α-pyrones resorted to the cyclization of diketoester **20** (Scheme 3).[17] Beginning with the condensation of propynyl magnesium bromide with acyl chloride **17**, the route to **20** included the treatment of the resulting ketoester **18** with Et_2NH to induce aza-Michael reaction. Hydrolysis of the generated enamine **19** afforded diketoester **20** that was cyclized upon treatment with H_3PO_4 (14 % yield, global).[18]

An alternative approach was employed by Takano et al.[19] and Baldwin et al.[20] for their program of total synthesis of polyketides. Construction of diketone **22** by condensation of 3-pentanone with propyl acetate was followed by carboxylation of the corresponding enolate to give diketocarboxylic acid **23**

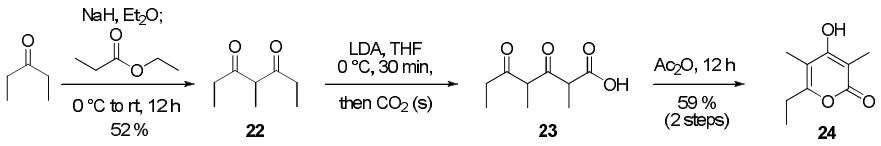
(Scheme 4). Upon activation with Ac_2O, compound **23** was converted into γ-hydroxy-α-pyrone **24** (31% global).



Scheme 2



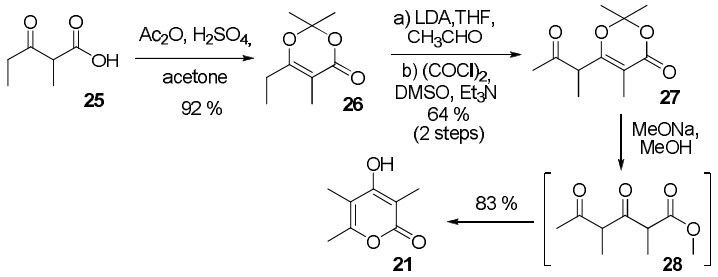
Scheme 3



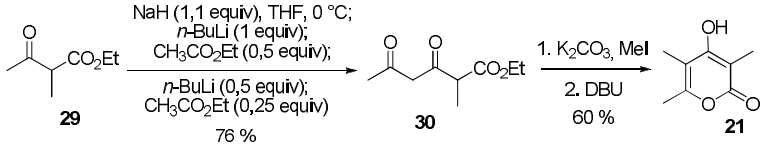
Scheme 4

Another route started with the conversion of α-ketoacid **25** into dioxinone **26** as reported by Omura et al. (Scheme 5).[4a] After treatment of **26** with lithium diisopropylamide (LDA), a reaction of aldolisation of the resulting enolate with acetaldehyde was followed by the oxidation of the generated alcohol (not shown) to produce **27**. Subsequent exposure of this compound to MeONa triggered a ring-opening process of the dioxinone. After release of acetone, the resulting diketoester **28** was converted into α-pyrone **21** (49 % global) upon the basic conditions employed.

Based on Solladié's methodology,[21] a short access to the same target was developed by Lipschutz et al.[4b] Hence, as starting materials, ketoester **29** was functionalized in one-pot procedure (Scheme 6). After double deprotonation of **29** with NaH and *n*-BuLi, the generated dianion was treated with ethyl acetate.



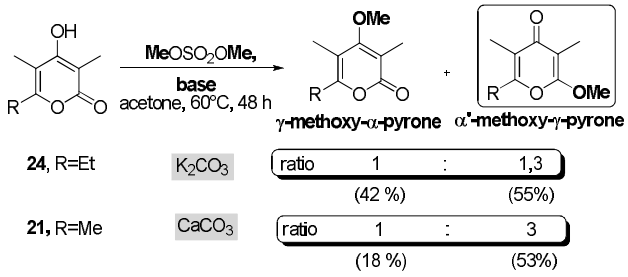
Scheme 5



Scheme 6

Because product **30** is more acidic than **29**, additional *n*-BuLi reagent was added followed by a second introduction of ethyl acetate. Proceeding this way, diketoester **30** was produced in 76% yield. Following a methylation step, the treatment of the resulting diketoester with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) led to α-pyrone **21** (46 % global).

Once constructed the α-pyrone scaffold, the setting of the methyl group remained to be accomplished in a regioselective manner. Despite an apparent simplicity, the methylation of a protomeric ambident nucleophile in a regioselective manner is not trivial and few solutions are actually available. To illustrate the case, methylation of **24** in the presence of Me_2SO_4 and K_2CO_3 was effected without regioselectivity (Scheme 7).



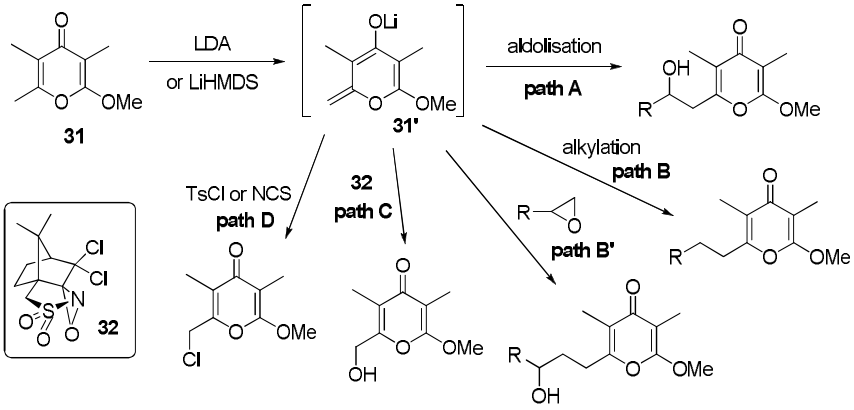
Scheme 7

An isomeric mixture of γ- and α'-methoxypyrones was obtained in almost equal amounts (1:1.3) while the desired α'-methoxy-γ-pyrone **47** was isolated in 55 % yield.

Progress in this regard was achieved with $CaCO_3$ as a base in combination with Me_2SO_4. Hence, Hosokawa and Tatsuta et al. reported that the selectivity of the reaction of methylation of **21** was enhanced

to 3:1 in favor of the α'-methoxy-γ-pyrone isomer reaching 53% yield.[22] Recycling the undesired isomer seems conceivable by a process encompassing its hydrolysis with H_3O^+ into **24**, thereby increasing the efficiency of a route that is especially suitable for large scale synthesis.

To complete the total synthesis, grafting of the side chain to **31** and synthetic elaboration were carried out (Scheme 8). After the deprotonation of the acidic position with lithium diisopropylamide (LDA) or lithium bis(trimethylsilyl)amide (LiHMDS), several strategies are available for this purpose. For example, aldolisation (path A)[4a] and alkylation (path B) reactions gave strategic tools for building the side chain from α'-methoxy-γ-pyrone heterocycle. Epoxides can also be employed successfully as electrophiles in combination with $BF_3.OEt_2$ to link the α'-methoxy-γ-pyrone ring with the hydroxylated side chain.[23] Moreover, upon treatment with an oxidant such as Davie's oxaziridine reagent **32**, the intermediate enolate was converted into alcohol (path C)[11] while the chloration (path D) of the scaffold was demonstrated upon exposure of the enolate to tosyl chloride (TsCl)[4b] or N-chlorosuccinimide (NCS).[24]

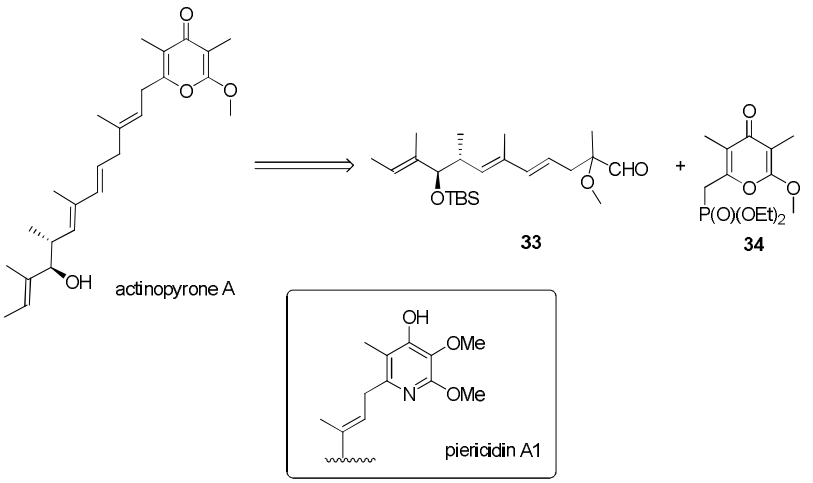


Scheme 8

From these functionalized and versatile scaffolds, side chains were further elaborated to eventually reach natural products and analogues. Hence, establishing a route to actinopyrone A (Scheme 9), Hosakawa and Tatsuta et al. reported the conversion of chlorinated α'-methoxy-γ-pyrone into the corresponding phosphonate **34** for the key Horner–Wadsworth–Emmons reaction of aldehyde **33**, the side chain of the natural product.[24]

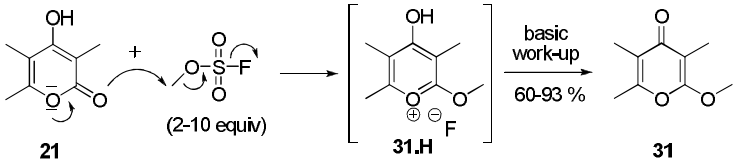
Of note is the structural similarity of actinopyrone A with piericidin A1, a potent inhibitor of the mitochondrial electron transport chain protein NADH-ubiquinone reductase, that share the same side chain connected to γ-hydroxypyridine.[25]

Regarding the initial problem of regioselective methylation of the α-pyrone scaffold, the generation of α'-methoxy-γ-pyrone from γ-hydroxy-α-pyrone is feasible with chemical reagents. Due to the protomeric and ambident nature of the nucleophile, basic conditions have to be avoided for the sake of selectivity of the alkylation step. As previously illustrated in Scheme 7, anionic species resulting from the deprotonation of **24** or **21** displayed scrambled nucleophilic reactivity toward Me_2SO_4. Without bases, stronger electrophiles were however required, γ-hydroxy-α-pyrone being a weak nucleophile.



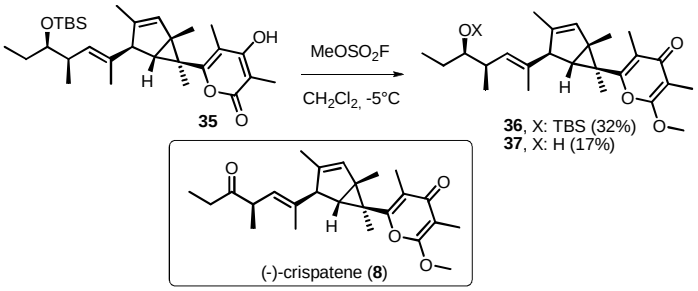
Scheme 9

As a solution, Beak reported the use of methyl fluorosulfonate ("magic methyl")[26] reagent to install, without basic conditions, the methyl group at the oxygen remote to the mobile proton, a basic work-up subsequently converting the oxonium intermediate **31.H** into the desired α'-methoxy-γ-pyrone product (Scheme 10). Yet, the chemistry remained hampered by the large excess of methyl fluorosulfonate (10 equiv) and the acute toxicity of this volatile reagent. As an enhancement, Lipshutz et al. reported the preparation of α'-methoxy-γ-pyrone **31** from **21** with a procedure in which the amount of methyl fluorosulfonate was reduced to 2 equiv by carrying out the methylation step in a sealed tube (40 °C, CH_2Cl_2, 3 h), a procedure that has not been tested with more elaborated substrates bearing nucleophilic heteroatoms.[4b]



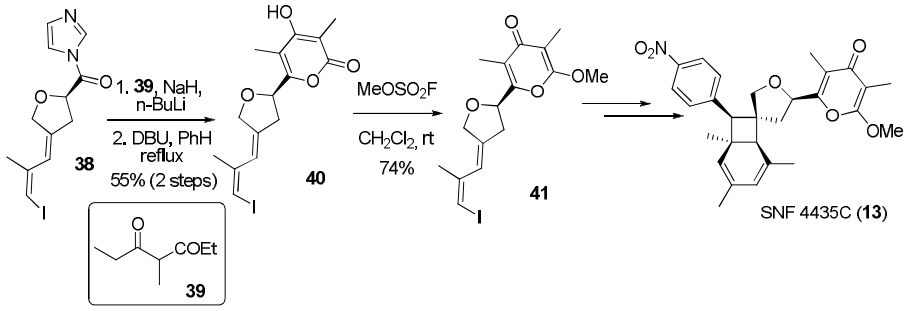
Scheme 10

Nevertheless, this strategy remained restricted for small scale synthesis as a way to handle small amounts of the toxic and poorly available reagent. In such cases, the methylation was planned as the last step of the route, the scaffold being already connected to the elaborated side chain of the desired target. For example, Trauner et al. prepared γ-pyrone **36**, an advanced intermediate in the synthesis of (–)-crispatene (**8**), by the regioselective methylation of α-pyrone **35** (Scheme 11). The process was accompanied by partial desilylation of the product giving the alcohol **37**. Although this side-reaction had no consequence to access **8**, the silylated protecting group had to be removed, this case illustrates the compatibility issue of such a reagent with functional groups.



Scheme 11

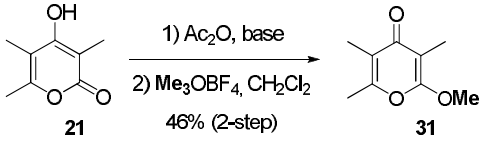
Methyl fluorosulfonate was found compatible with side chain bearing cycloether, a heterocycle found in several natural products of this class of molecules. Hence, Parker et al. constructed the α'-methoxy-γ-pyrone scaffold of SNF4435 C (**13**) from acyl imidazole **38** (Scheme 12).[15a] Condensation of **38** with the dianion of **39** was followed by treatment with DBU to give α-pyrone **40** in 55% yield (for two steps) that was subsequently methylated in **41** with $MeOSO_2F$ in 74% yield at room temperature.



Scheme 12

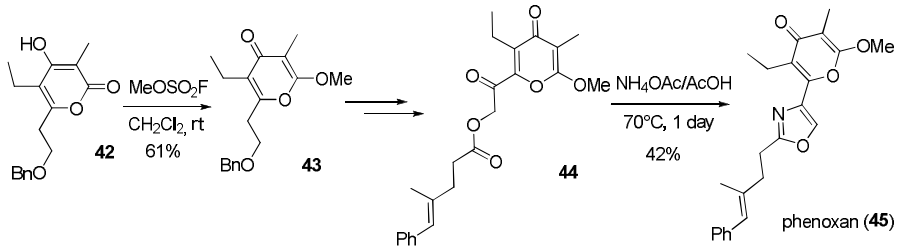
Seeking for an alternative to $MeOSO_2F$, Poulton and Cyr reported the regioselective installation of the methyl group as in **31** with Meerwein's reagent Me_3OBF_4 (46% yield for 2 steps) from **21** (Scheme 13). Of crucial importance was the prior acetylation of **21** with Ac_2O to inhibit the nucleophilicity of the oxygen in γ-position.[27]

Overall, this type of sequence involving 1) strongly basic conditions to construct the α-pyrone heterocycle and 2) an excess of toxic reagent to attain the α'-methoxy-γ-pyrone scaffold impacts the convergence of the synthetic routes that were mapped accordingly.



Scheme 13

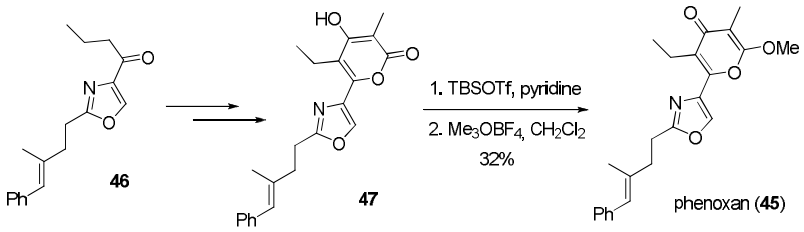
Moreover, the chemical compatibility of the side chain with such strong electrophiles has to be verified. For instance, sulfur and nitrogen containing side chain are likely to remain incompatible with $MeOSO_2F$ due to their nucleophilic characters. The case of phenoxan (**45**), a compound isolated form soil microorganism with anti-HIV properties, is interesting in this regard (Scheme 14).



Scheme 14

With a structure combining α'-methoxy-γ-pyrone heterocycle and oxazole, compound **45** provides an interesting case. As reported by Yamamura and Nishiyama et al., the construction of this framework began by the assemblage of the γ-hydroxy-α-pyrone **42** followed by regioselective methylation with $MeOSO_2F$ in 61% yield before pursuing the grafting of the side chain from **43**.[28] The preparation of the oxazole occurred as the last step by condensation of keto ester **44** with $NH_4OAc/AcOH$ (70 °C, 1 day) in 41% yield, the low efficiency of the step being possibly linked to the poor stability of α'-methoxy-γ-pyrone in these conditions.

Another approach to phenoxan (**45**) was reported by Peña et al. in which the route started with the construction of side chain **46** containing the oxazole ring (Scheme 15).[29] Then, assemblage of the α-pyrone **47** was followed by silylation with TBSOTf (instead of Ac_2O that was unsuccessful) prior treatment with Meerwein's salt to methylate the alleged silylenol ether.

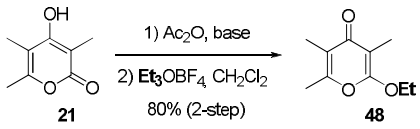


Scheme 15

This sequence produced phenoxan (**45**) in 32% yield from **47**, the paper giving no indications on the nature of the by-products.

Even though the scope of the reaction with other alkyl fluorosulfonate reagents was not explored, this strategy is probably limited to the methyl group. The expected low reactivity of such reagents and their poor availabilities could restrain de facto the synthesis of analogues of natural products to the α'-methoxy-γ-pyrone heterocycle. Although the synthesis of α'-alkoxy-γ-pyrone heterocycles with various substituents

was not investigated, the study of Poulton and Cyr provided an interesting solution to access α'-ethyloxy-γ-pyrone **48** from α-pyrone **21** (Scheme 16). After activation with anhydride acetic, treatment with Et_3OBF_4 delivered **48** in good yield and selectivity. Interestingly, several examples were reported.

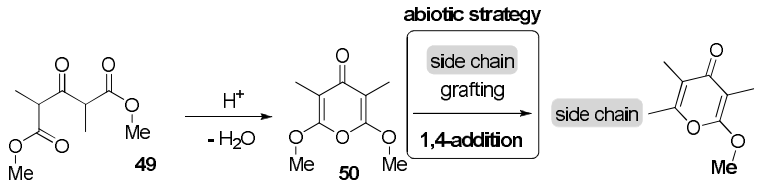


Scheme 16

3. Desymmetrization of α,α'-dimethoxy-γ-pyrone

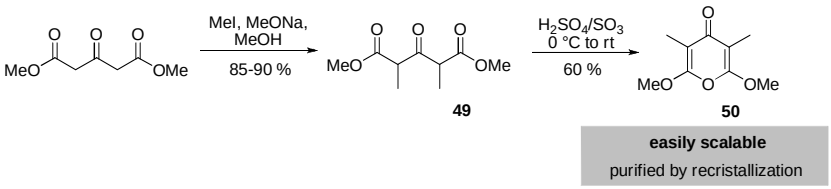
The α,α'-dimethoxy-γ-pyrone **50** was first mentioned early in the 20th century by Schroeter and the confirmation of the structure was later made by Woodward et al. in 1950 (Scheme 17).[30] Noting that the reactivity of this compound was unexplored for 60 years, we reasoned that a reaction of desymmetrization of compound **50** could bring simplicity and safety to the routes leading to α'-methoxy-γ-pyrone products.

Compared to the previous biomimetic approaches, this abiotic strategy provided new perspectives to graft the side chains of natural products, therefore improving the convergence of synthetic plans. In the initial reports, the preparation of **50** was described by treatment of keto diester **49** with a mixture of sulfuric acid and oleum. If the synthetic route appeared relatively simple and practical, the efficiency of the process was low, compound **50** being isolated in 12% yield.



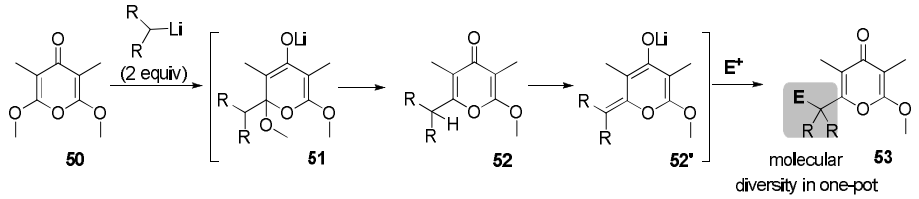
Scheme 17

To optimize the process, we screened Brønsted acids promoting the cyclisation of **49** (Scheme 18). While H_3PO_4 or triflic acid gave poor results, we found that treatment of ketodiester **49** with neat oleum and without solvent enhanced the yield of the cyclization, reaching values of 55-60%. Key to a successful cyclization/aromatization of **49** was the trapping of H_2O formed during the process with SO_3 contained in the oleum mixture.



Scheme 18

Anhydrous conditions were therefore reinforced with oleum acting as dehydrating reagent. Noteworthy, the purification of **50** was carried out by recrystallization. Hence, with an easily scalable process, compound **50** was simply and concisely assembled from readily available and modulable building blocks. Then, our plan to promote the desymmetrization of **50** comprised a nucleophilic 1,4-addition, enabling the synthesis of the α'-methoxy-γ-pyrone scaffold but also the grafting of the side chain (Scheme 19).



Scheme 19

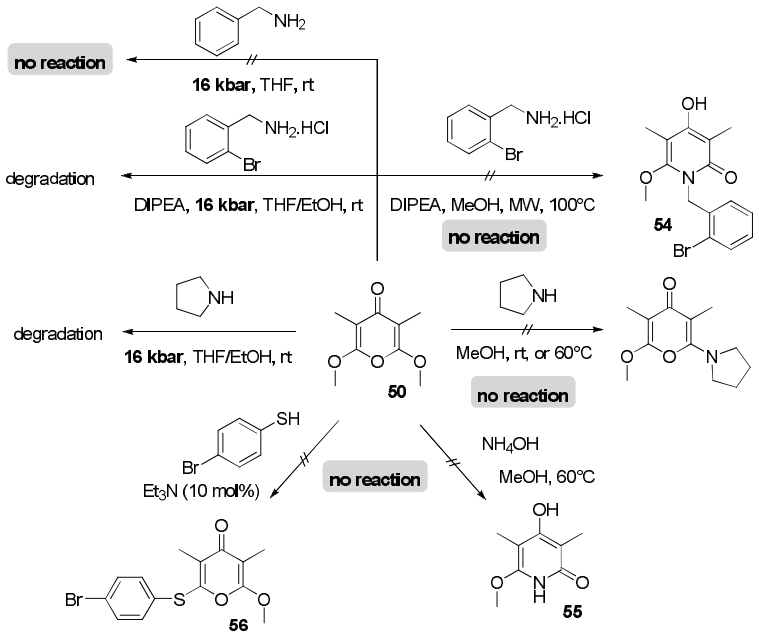
Following a conjugate addition to **50** and the elimination of lithium methoxide from intermediate **51**, the resulting adduct **52** acted as a pronucleophile containing the α'-methoxy-γ-pyrone scaffold. After deprotonation, vinylogous enolate **52'** was thus reacted with an electrophile, modulable according to the desired target, providing an elaborated compound such as **53** in one pot. Importantly, without subsequent deprotonation, **52** would risk a second nucleophilic attack of the reagent that performed the initial 1,4-addition. Being electron-rich, generated **52'** is thus protected against undesired 1,4-addition.

As an additional incentive, the process conveniently bypassed the need for regioselective methylation since the methoxy substituents originate from **49**. Incidentally, this sequence could provide a convenient access to α,α'-dialkoxy-γ-pyrone derivatives by cyclization of analogues of **49**.

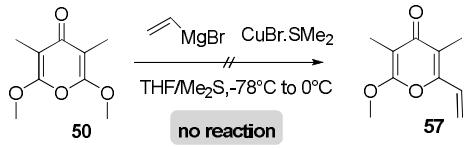
Compound **50** being aromatic, weak nucleophiles were less prone to react with the heterocyclic system. Hence, we observed that pyrrolidine did not react with **50** at room or elevated temperature unless high-pressure was applied, leading to the formation of several unidentified products (Scheme 20). Similarly, primary amine (ammonium hydroxide or 2-bromobenzylamine) did not react with **50** under thermic or microwave activation as the formation of α-pyridinones **54** and **55** was anticipated. Under high pressure, the decomposition of **50** was observed in the presence of 2-bromobenzylamine hydrochloride salt and diisopropylethylamine (DIPEA). Surmising that chloride ammonium salts accounted for this outcome, the desymmetrization of **50** was attempted with benzylamine under an activation of 16 kbar and resulted in the recovery of the starting material. Moreover, compound **50** was completely recovered after exposure to 4-bromothiophenol and a catalytic amount of Et_3N.

Cuprate reagents were also found ineffective to promote 1,4-addition to **50**. For instance, vinyl magnesium bromide in combination with a stoechiometric amount of $CuBr.SMe_2$ left compound **50** intact (Scheme 21).

The condensation of vinyltrimethylsilane to **50** upon activation with Lewis acid was also investigated but various outcomes were observed depending on the nature of the acid employed. At any rate, α-vinyl-α'methoxy-γ-pyrone **57** was not observed in the crude mixture of the experiments.

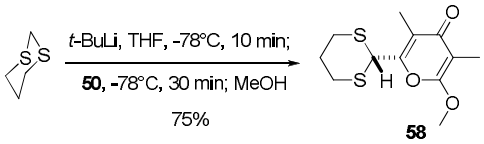


Scheme 20



Scheme 21

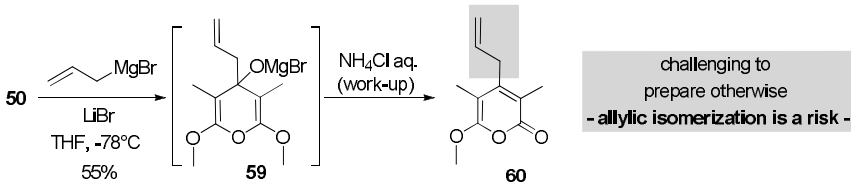
Pleasingly, the desymmetrization of **50** was effective with 2-lithium-1,3-dithiane (Scheme 22). Hence, treatment of **50** with such nucleophile (2 equiv) followed by treatment with MeOH resulted in the production of **58** combining both scaffolds.[31] Of note, 1,2-addition of 2-lithio-1,3-dithiane predominates with enones but 1,4-selectivity was exclusively observed with **50**.[32]



Scheme 22

In contrast, organolithium reagents such as *n*-BuLi, PhLi or Grignard reagents produced 1,2-adducts upon reaction with **50**. Hence, α-pyrone **60** was isolated in 55% yield from the reaction of **50** with

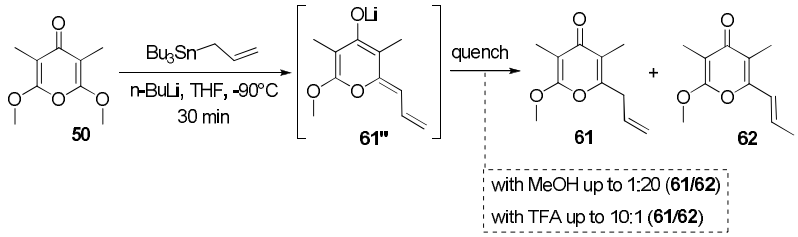
allylmagnesium bromide. The mechanism probably combined 1,2-addition, giving intermediate **59** (not characterizable), and spontaneous Stork-Danheiser rearrangement upon work-up (Scheme 23).[33]



Scheme 23

Incidentally, obtaining α-pyrone **60** by conventional approach would have been complicated with the required basic conditions that would likely conjugate the allylic moiety to the α-pyrone scaffold.

While allylmagnesium bromide reacted according to 1,2-pattern, the combination of reagents allyltributylstannane/*n*-BuLi was successfully employed to install the allyl group by 1,4-addition. Hence, treatment of **50** with allyltributylstannane/*n*-BuLi in THF at –90 °C led to the desired adduct in 60% yield (Scheme 24).

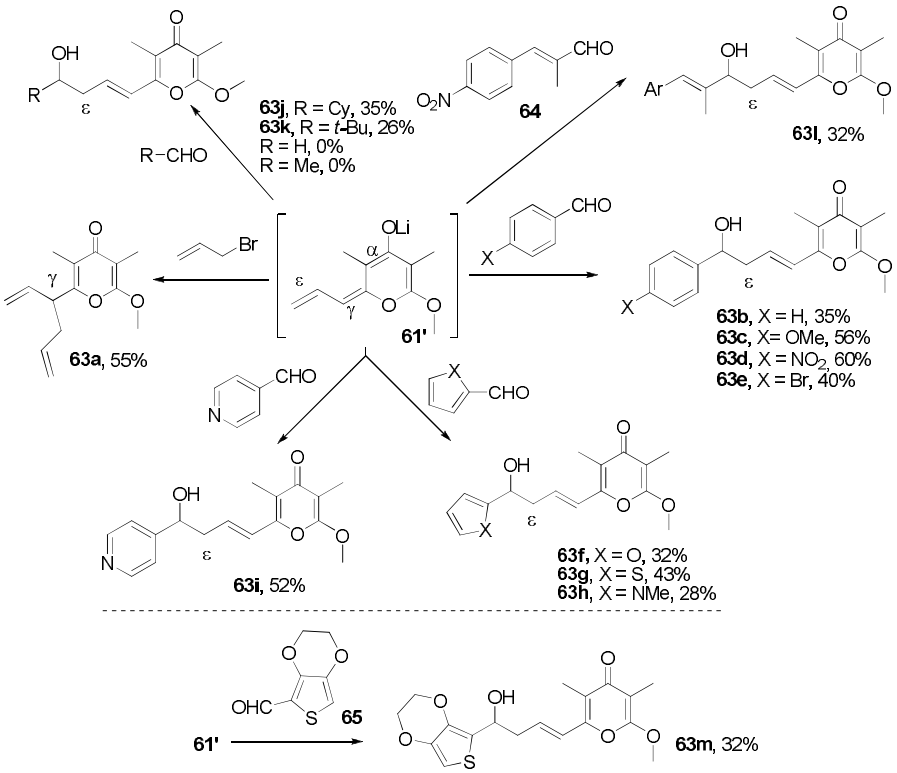


Scheme 24

The reaction was fast (30 min), producing a mixture of isomeric olefin depending on the details of the quenching. Hence with MeOH as the source of protons, compound **62** containing a conjugated olefin was obtained as the major isomer (**61**/**62** = 1:3). Actually, **62** can be obtained as the sole isomer (**61**/**62** > 1:20) after stirring the mixture **61**/**62** for 1 h at rt in the presence of MeOLi generated during the transformation. On the other hand, addition of aqueous HCl led to the preparation of **61** as the major isomer (**61**/**62** = 3:1) while a kinetic quenching of vinylogous enolate **61'** with TFA (in Et_2O at –90 °C) provided enhanced selectivity up to 10:1 (**61**/**62**) in favor of the allylic isomer.

From a mechanistic standpoint, it seems unlikely that the formation of **61** resulted from anionic oxy-Cope rearrangement of 1,2-adduct, a lithiated counterpart of **59**. Indeed, 1) such rearrangements typically occur between low and high temperatures, but not at very low temperatures, nor for a short time in contrast to the current reactions parameters (–90 °C, 30 min) and 2) 1,2-adduct such as **59** provided α-pyrone **60** after dehydration of the alcohol due to a very ionizable C-O bond and this outcome would have been similar with lithiated alcohol.

The versatility of vinylogous enolate **61'** was further demonstrated by reactions with carbon electrophiles.[33b] Hence, the reaction of **61'** with allyl bromide delivered compound **63a** as the sole isomer resulting from γ-alkylation (Scheme 25). On the other hand, treatment of **61'** with benzaldehyde furnished the aldol product **63b** in 35% yield as unique regio- and stereoisomer arising from aldolisation reaction with ε-selectivity. Noteworthy, this one-pot sequence encompasses five transformations including lithiation, 1,4-addition to **50**, MeOLi elimination, deprotonation and aldolisation.

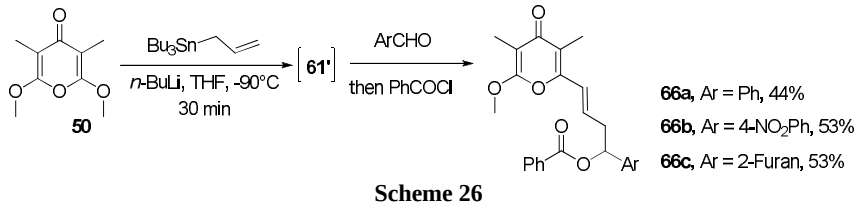


Scheme 25

To obtain more molecular diversity from readily available building blocks, the chemistry was further demonstrated with several carboxaldehydes. Electron-poor and electron-rich electrophiles were found compatible with the synthetic methodology delivering elaborated substrates **63c-e** in good yields (40-60% yield). Furan, thiophene and pyrrole carboxaldehyde proved compatible as the products **63f-h** were isolated in acceptable yields (28-43% yield) while 4-pyridine carboxaldehyde reacted efficiently with **61'** furnishing **63i** in 52% yield. Provided with some steric hindrance, aliphatic aldehydes were employed as electrophiles. Hence, cyclohexane and pivalyl carboxaldehyde reacted with **61'** in fair yield (**63j-k**, 26-35%) while no aldolisation occurred with formaldehyde and acetaldehyde as electrophiles. Increasing even further the complexity of the resulting aldol product, the reaction of **61'** with enal **64** furnished alcohol **63l** in 32%

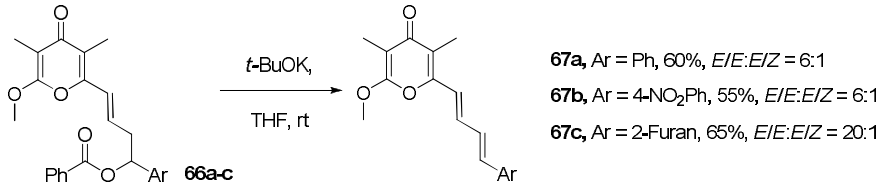
yield. Despite being strongly electronically rich as derived from thiophene, aldehyde **65** was assembled with the vinylogous enolate **61'** into **63m** 32% yield.

The sequence was extended to the synthesis of esters by introduction of acyl chloride reacting with hydroxylate products, adding another structural element of diversity to the side chain of the α'-methoxy-γ-pyrone scaffold and leading to **66a-c** in 38-53% yield (Scheme 26).[33b]



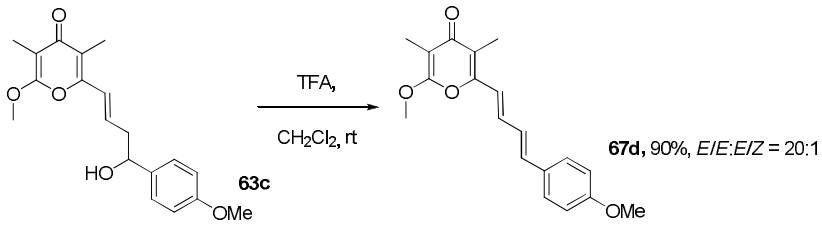
Scheme 26

As detailed in Scheme 27, esters **66a-c** were conveniently converted into 1,3-dienes **67a-c** by treatment with *t*-BuOK with good selectivity in favor of the *E*/*E* isomer (from 6:1 up to 20:1).[34] Without the use of transition metals, these elaborated molecules were therefore accessed as analogues of natural products, especially the cyercene family, in two steps from readily available **50** and commercially available reagents.



Scheme 27

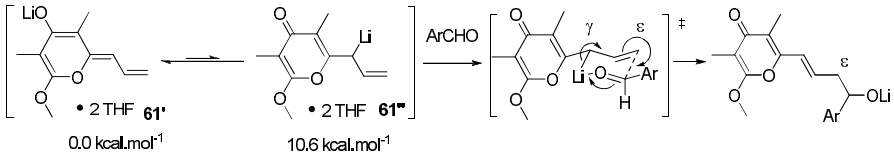
Connected to electron-rich aryl substituent, alcohol **63c** was transformed into 1,3-diene **67d** by a simple treatment with trifluoroacetic acid (TFA), this occurring with excellent efficiency and selectivity (90%, *E*/*E*:*E*/*Z* = 20:1) (Scheme 28).



Scheme 28

To investigate the excellent regio- and stereoselectivity observed for the reaction of **61'** with electrophiles such as alkylating reagent or carboxaldehydes, we calculated the stability of **61'** compared to

61'' (Scheme 29). With the negative charge localized on the oxygen, isomer **61'** logically appeared to be more stable compared to **61''** by DFT calculations (at B3LYP/6-31G** level with 2 molecules of THF).[33b]



Scheme 29

But a Zimmerman-Traxler transition state could be postulated with isomer **61''** and such an organized transition state, only possible with **61''**, would facilitate the reaction and explain the observed ε-selectivity.

Not only did the strategy of desymmetrization of **50** allow access (1-step) to elaborated molecules containing the α'-methoxy-γ-pyrone scaffold but the biological activity of these compounds was pertinent for evaluation as analogues of natural products. Verticipyrone (**2**), for instance, is an inhibitor of bovine heart mitochondrial respiratory chain function with NADH oxidase and NADH ubiquinone oxidoreductase activities.[4a] Of the analogues prepared, compound **63c** showed the greatest inhibition in the NADH oxidase assay (IC_{50} 44 ± 5 nM), a potency comparable to the best of the analogues such as **68** (IC_{50} 36 ± 1 nM) reported previously by Hecht et al. (Figure 3).[33b,23] For both compounds though, IC_{50} values for the NADH-ubiquinone oxidoreductase activity were higher: 2.5 and 0.101 μM respectively.

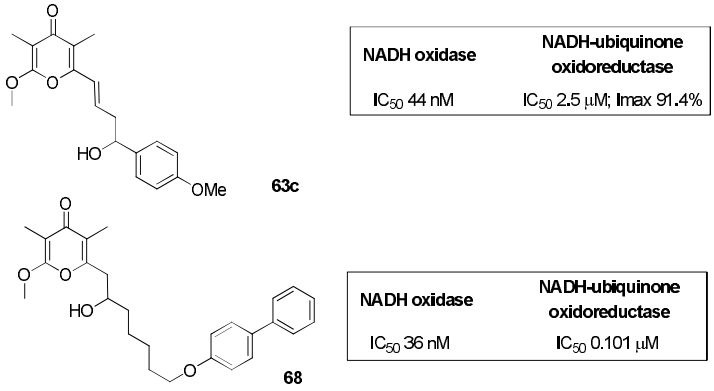
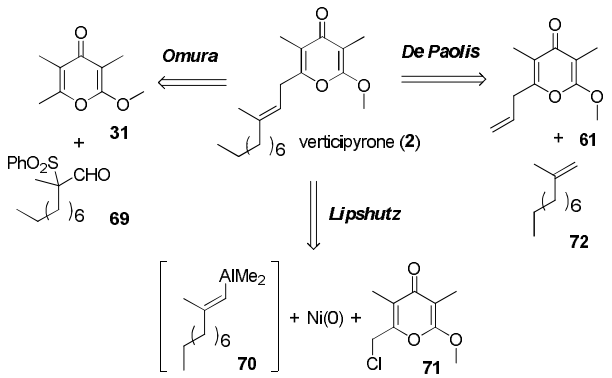


Figure 3

4. Synthetic approaches toward verticipyrone (2)

Initially isolated in 2004, verticipyrone (**2**) harbors the α'-methoxy-γ-pyrone scaffold connected to an allylic side chain (Scheme 30).[4a] As reported by Omura et al., the tendency of the double bond to isomerize in basic conditions jeopardized their initial strategy and connecting the side chain with the α'-methoxy-γ-pyrone group required adjustments. The route to **2** was consequently adapted and α-methyl-α'-methoxy-γ-pyrone **31** was reacted with aldehyde **69** after deprotonation.

For fashioning verticipyrone (**2**), Lipshutz et al. coupled the nucleophilic species **70** with chloromethylene pyrone **71** upon Ni(0)-catalysis, demonstrating incidentally the chemical compatibility of **2** with conditions involving the preparation of **70** by carboalumination of 1-decyne with Cp_2ZrCl_2 (10 mol%) and $AlMe_3$ (2 equiv).[4b]



Scheme 30

As an alternative route to verticipyrone (**2**), we envisaged the cross-metathesis of allylic pyrone **61**, prepared by desymmetrization of **50**, with olefin **72**. Not trivial, since a trisubstituted olefin was targeted, this transformation was complicated by the isomerization of **61** into crotylpyrone **62** promoted by the catalyst of the reaction of metathesis. Pleasingly, the coupling was successfully carried out in the presence of an excess of **72**, to favor its initial reaction with the catalyst. Hence, verticipyrone (**2**) was obtained in 55-60% yield while the excess of **72** was easily recovered by simple filtration.[31] In total, four steps were required for the synthesis of **2**.

5. Synthetic approaches toward aureothin

Isolated from *Streptomyces thioluteus*,[35] the unusual structure of aureothin (**9**) triggered investigations to elucidate its biogenesis and the notable presence of the nitroaryl substituent (Figure 4).[36] Our interest in **9** was fed by the peculiar structural elements of the target: the stereodefined 1,3-diene with nitroaryl and tetrahydrofuran substituents linked to α'-methoxy-γ-pyrone. With antitumoral, antifungal, antiparasitic and pesticidal activity, the molecule was also a pertinent target for biological evaluations,[37] even more so in view of the significant selectivity displayed against trypanosome strains.[38] As a matter of fact, we found that (+)-**9** exhibits potent and selective antiproliferative activity (IC_{50} respectively 17, 19.5, 4 and 5 nM) against four cancer cell lines: A2780 (ovarian), HCT116 (colon), HepG2 (liver) and MDAMB-468 (breast).[39]

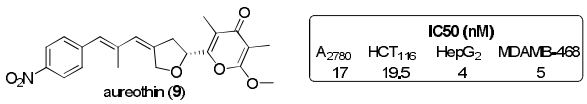
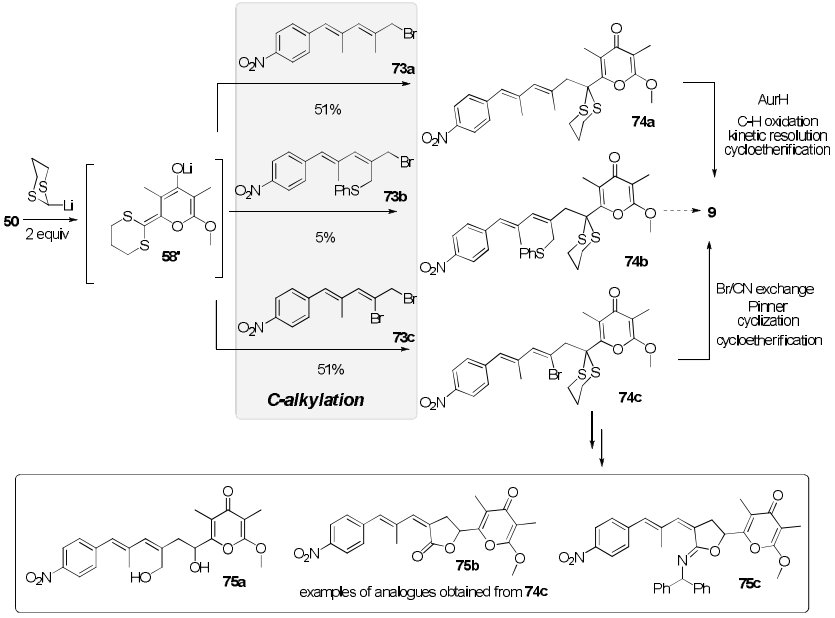


Figure 4

The pioneering studies of Yamamura,[40] Baldwin,[41] Trauner,[42] and Hertweck,[43] provided interesting and instructive approaches to **9** but practical access to enantiopure material remained to be devised. The strategy of desymmetrization of α,α'-dimethoxy-γ-pyrone **50** was initially conceived to provide a solution for the rapid assemblage of the carbon skeleton of **9**. Hence, as mentioned above, conjugate addition of 2-lithio-1,3-dithiane to **50** led to vinylogous enolate **58'**, an unexplored nucleophile (Scheme 31).

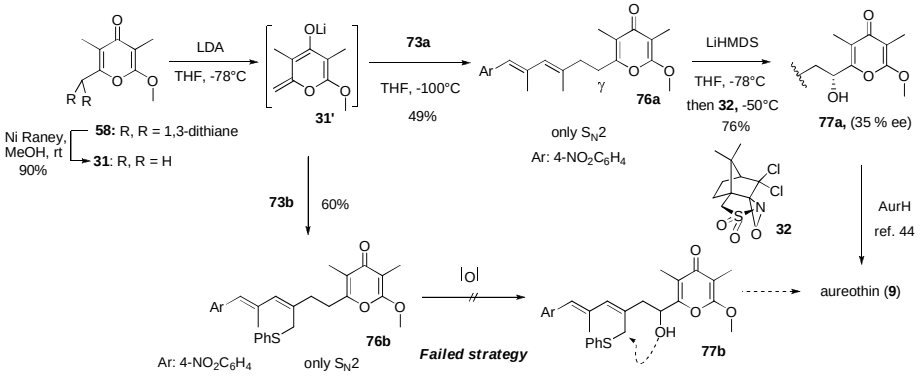


Scheme 31

Capitalizing on these results, we investigated the coupling of these species with **73a** to attain advanced intermediates en route to **9**. This one-pot strategy was successful with electrophiles such as bromo **73a** containing the side chain of the target. Hence, despite the risk of O-alkylation of **58'**, compound **74a** was isolated in 51% yield on gram-scale. As an advanced intermediate toward (+)-aureothin (**9**), compound **74a** was converted in 3 steps that included regioselective and parallel P450-mediated C-H oxidation of the corresponding alcohol masked as 1,3-dithiane moiety.[44]

On the other hand, vinylogous enolate **58'** was poorly reactive toward a more hindered electrophile such as **73b**, the condensed adduct being isolated in only 5% yield. However, a less hindered electrophile such as **73c** reacted smoothly with **58'**, delivering **74c** in 51% yield despite the sensitivity of bromoallyl bromide **73c** to strong bases. Interestingly, compound **74c** turned out to be a valuable intermediate en route to aureothin (**9**) and analogues such as **75a-c** containing versatile diols, lactone and imino ethers moieties. Palladium-mediated cyanation of sensitive 1,3-bromodiene and Pinner-type cyclization were among the transformations allowing the preparation of such targets.[45]

In an initial venture to reach (±)-aureothin (**9**) and analogues, our group also explored the reactivity of the less hindered pronucleophile **31** that was prepared by reductive deprotection of dithiane **58** with Raney Ni (Scheme 32).



Scheme 32

Previously described as a partner for aldolisation reactions, the vinylogous enolate **31'** was less studied for alkylation reactions. Pleasingly, elaborated side chains such as **73a** and **73b** were grafted to **31'** in fair yield without any noticeable O-alkylation reaction. For preparing aureothin (**9**), the condensed adduct **76a** was furthermore regioselectively oxidized into alcohol **77a** (76% yield) by treatment with LiHMDS and Davis oxazoridine reagent **32**. Despite the low enantioselectivity of this transformation, alcohol **76a** that was obtained in 35% ee can be converted into enantiopure (+)-aureothin (**9**) upon treatment with AurH.

Surprisingly, the same strategy was not effective with adduct **76b**. Probably due to an excessive steric hindrance, the formation of the enolate of **76b** or its oxidation into **77b** remained problematic and this strategy failed to provide access to aureothin (**9**).

6. Conclusions

An abiotic strategy of desymmetrization of α,α'-dimethoxy-γ-pyrone **50** was developed to access natural products and analogues containing the α'-methoxy-γ-pyrone heterocycle. Beginning by 1,4-addition to **50**, the sequence allowed the grafting of nucleophilic species and can potentially include the trapping of vinylogous enolate intermediates with electrophiles, ideally the side chain of the targets. Natural products containing α'-methoxy-γ-pyrone often display interesting and promising biological activities and such progress may help the design and preparation of analogues to understand and exploit their mode of action. In view of the strong and selective anti-proliferative activity of aureothin (**9**), analogues with enhanced photostability and similar activity would be highly desirable.

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