



Total Synthesis of γ -Indomycinone and Kidamycinone by Means of Two Regioselective Diels-Alder Reactions

Thibaud Mabit, Aymeric Siard, Mathilde Pantin, Doumadé Zon, Laura Foulgoc, Drissa Sissouma, Andre Guingant, Monique Mathé-Allainmat, Jacques Lebreton, François Carreaux, et al.

► To cite this version:

Thibaud Mabit, Aymeric Siard, Mathilde Pantin, Doumadé Zon, Laura Foulgoc, et al.. Total Synthesis of γ -Indomycinone and Kidamycinone by Means of Two Regioselective Diels-Alder Reactions. *Journal of Organic Chemistry*, 2017, 82 (11), pp.5710-5719. 10.1021/acs.joc.7b00544 . hal-01533331

HAL Id: hal-01533331

<https://univ-rennes.hal.science/hal-01533331>

Submitted on 6 Jun 2017

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Total synthesis of γ -indomycinone and kidamycinone by means of two regioselective Diels-Alder reactions.

Thibaud Mabit^{†i}, Aymeric Siard^{†i}, Mathilde Pantin[†], Doumadé Zon[†], Laura Foulgoc[†], Drissa Sissouma[†], André Guingant[†], Monique Mathé-Allainmat[†], Jacques Lebreton[†], François Carreaux[‡], Gilles Dujardin[§] and Sylvain Collet^{†*}

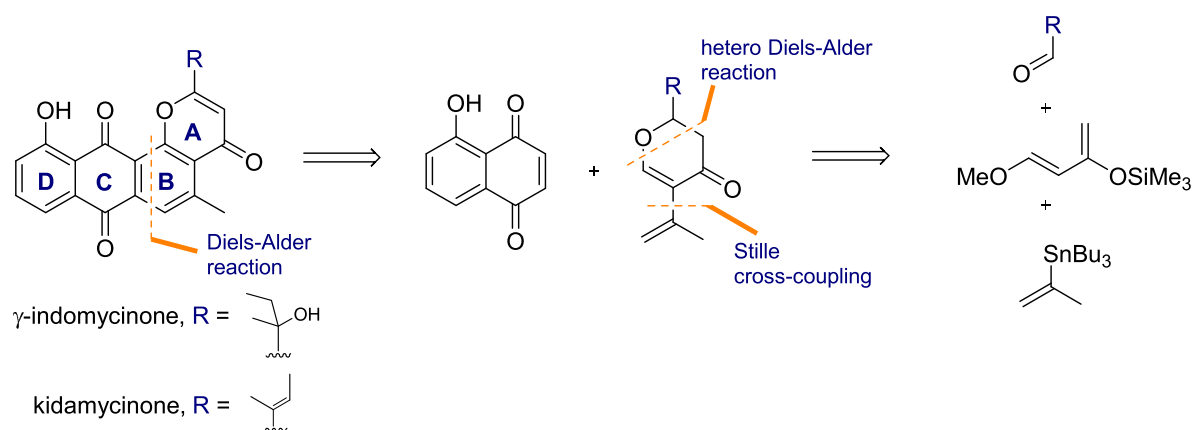
[†]Université de Nantes, CNRS, Chimie Et Interdisciplinarité: Synthèse, Analyse, Modélisation (CEISAM), UMR CNRS n° 6230, 2, chemin de la Houssinière – BP 92208 – 44322 NANTES Cedex 3 (France)

[‡] Institut des Sciences Chimiques de Rennes, UMR 6226 CNRS-Université de Rennes 1, 263, avenue du Général Leclerc, Campus de Beaulieu, Bâtiment 10A, 35042 Cedex Rennes, France

[§] Université du Maine, Institut des Molécules et Matériaux du Mans, UMR CNRS 6283, Faculté des Sciences, Avenue O. Messiaen, 72085 Le Mans cedex 9, France

sylvain.collet@univ-nantes.fr

Abstract



An efficient access for the synthesis of pluramycinones is described. Total syntheses of racemic γ -indomycinone and kidamycinone were achieved by means of two Diels-Alder reactions. A first Diels-Alder condensation followed by a Stille cross-coupling is used for the elaboration of the

ⁱ These authors contributed equally to this work

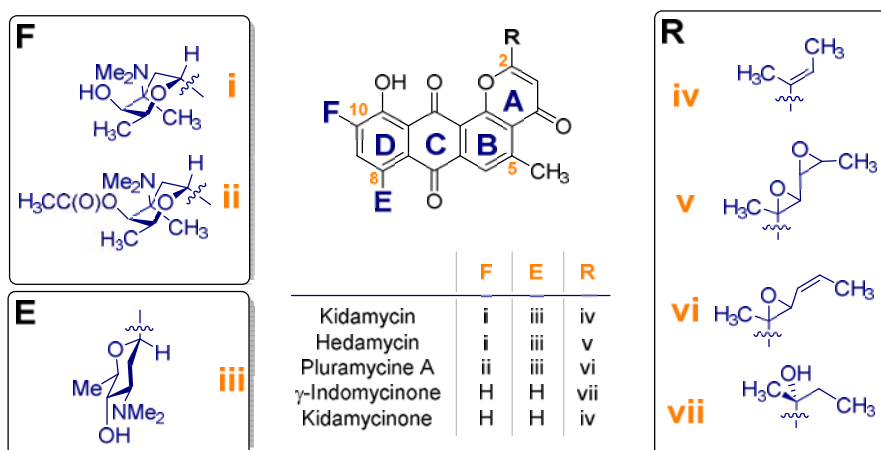
desired substituted dienes which will be involved in the second pericyclic reaction with juglone to construct the tetracyclic core of pluramycinones.

Introduction

The pluramycin family represents a group of natural compounds first isolated from *Streptomyces pluricologrescens* by Maeda and coworkers.¹ This class of molecules exhibits antimicrobial activity against Gram-positive bacteria and anticancer activity (especially against Ehrlich ascites carcinoma, leukemia L1210, Sarcoma-180 and Fukuoka's sarcoma).² Quite recently, Beerman *et al.* analyzed thoroughly the mode of action of hedamycin at the cellular scale (see Figure 1). A slowdown in cell growth was observed at subnanomolar concentrations. This phenomena was explained by a direct inhibition of DNA replication through the activation of several DNA damage checkpoint proteins (p53, chk1 and chk2) leading to a blocking in cell cycle progression in G2 or G1 phase, depending on the concentration of hedamycin.³ During the 1990s, Hurley and coworkers have widely investigated the molecular mode of action of pluramycins with NMR, X-ray and molecular modeling studies.⁴ As a result of this work, the antitumoral activity is now understood and explained through both reversible DNA intercalation and irreversible DNA alkylation. This singular dual-action is a result of the complex molecular structure of these compounds. As shown on Figure 1, the pluramycin skeleton is a 4*H*-anthra[1,2-*b*]pyran-4,7,12-trione, also called ABCD tetracycle, functionalized by two deoxy-aminosugars (referenced as rings E and F) by *C*-glycosidic linkages respectively at C-8 and C-10, and an unsaturated and/or oxygenated side-chain at C-2 (Figure 1).⁵ These carbohydrates moieties are responsible for DNA recognition and sequence selectivity as they form a hydrogen-bridge-bound complex in both minor and major grooves of the DNA double helix. In some cases, while E ring (angolosamine) is linked to the tetracyclic core of pluramycine by a β -anomeric linkage, NMR and X-ray studies have shown the F ring (*N,N*-dimethylvancosamine) to be in its unfavorable α -anomeric form which tends to epimerize to its thermodynamically preferred β -form in slightly

acidic or basic media.⁶ On account of this poor stability, the introduction of the aminosugars remains the last hurdle slowing down total syntheses of pluramycins. Indeed, whereas many methods have been described to build *C*-aryl glycosides,⁷ all attempts to link both β -angolosamine and α -*N,N*-dimethylvancosamine moieties on a pluramycin skeleton failed. The construction of this elaborated structure remains thus a challenge for synthetic organic chemists. Added to the intricate structure of pluramycins, the synthetic challenge resides in avoiding the annoying degradation behavior in acidic, basic and oxidative conditions⁶ in addition to their light sensivity in both aerobic and anaerobic solutions.⁸

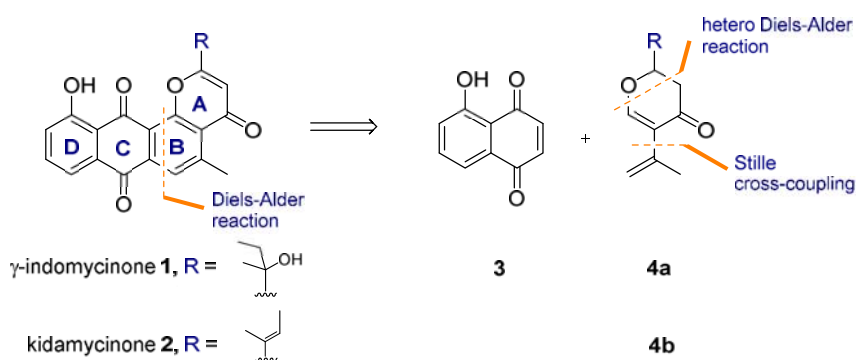
Figure 1 : Structures of pluramycins and pluramycinones



From a biosynthetic point of view, while the formation of the tetracyclic scaffold is well-known as it proceeds *via* subsequent Claisen-like condensations, the origin of the side chain at C-2 as well as the formation of *C*-glycosidic connections are not fully understood.⁹ As a proof of the synthetic interest of pluramycins, construction of the aglycon frame has been reported by many groups since the pioneering work of Hauser in 1979, describing the synthesis of the kidamycinone *O*-methyl ether.¹⁰ Following a biomimetic strategy, Mc Donald published in 2005 an interesting synthesis giving access to both kidamycin and altromycin aglycones from a common tetracyclic intermediate.¹¹ The same biomimetic approach was applied in 2007 to build the backbone of γ -indomycinone¹² which

was also synthesized by several groups through Diels-Alder reactions.¹³⁻¹⁵ Construction of aglycones is therefore well known but, to the best of our knowledge, despite many endeavors, interest and developments during the last decade,¹⁶⁻²¹ there is still no reported methodology to prepare natural pluramycin containing both β -angolosamine (see Figure 1, ring E) and α -*N,N*-dimethylvancosamine (see Figure 1, ring F) moieties. Two major problems can be highlighted: 1) the introduction of the glycosidic subunits at the first stages of a linear synthesis increases possible unwanted side reactions such as epimerization, 2) the introduction of the glycosidic subunits by direct glycosylation reactions in the last steps of the synthesis, on a properly functionalized and bulky tetracycle, may suffer from poor regio- and/or stereoselectivity in combination with poor yields. With the aim of developing a methodology which could overstep these barriers, we herein report a full account of the total syntheses of racemic γ -indomycinone and kidamycinone through a novel approach. The described strategy differs from the earlier described pathways by addition of the DC framework to the A ring while creating the B ring by means of a Diels-Alder reaction as depicted in retrosynthetic scheme 1.

Scheme 1. Retrosynthetic analysis of the tetracyclic core of γ indomycinone (1) and kidamycinone (2).



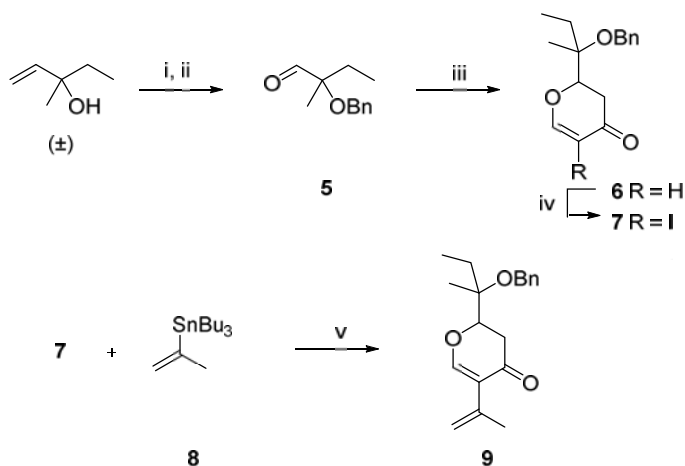
Dienes **4a** and **4b** could be synthesized through a Stille cross-coupling from the iodinated corresponding dihydropyranone, which in turn should result from a hetero Diels-Alder reaction between Danishefsky's diene and the well-suited aldehyde. This convergent strategy takes on its full

meaning as the R group on ring A, which is major responsible for the pluramycin diversity, can be easily changed at the beginning of the synthesis using the appropriate aldehyde in the first hetero Diels- Alder reaction. Thus, our flexible strategy could be applied to conveniently access a variety of pluramycins using glycosylated juglone at C-6 and C-8.

Results and Discussion

Our attention initially focused on the synthesis of γ -indomycinone.¹⁵ The racemic 2-benzyloxy-2-methylbutanal **5** was synthesized in two steps from commercially available 3-methylpenten-3-ol (Scheme 2). First, benzylation of the tertiary alcohol of the racemic 3-methylpenten-3-ol was achieved by treatment with NaH, benzylbromide and a substoichiometric amount of TBAI in DMF.²² Then, the resulting protected allylic alcohol was submitted to ozonolysis in a mixture of dichloromethane and methanol at -78 °C followed by a reductive workup with dimethyl sulfide to provide aldehyde **5** in 89% yield over two steps. It should be mentioned that attempts to carry out the first step of this sequence, using benzyl 2,2,2-trichloroacetimidate²³ as the benzylating agent and triflic acid as the catalyst, led to aldehyde **5** with lower overall yield (80%).

Scheme 2. Preparation of diene **9**^a



^aReagents and conditions : (i) NaH, BnBr, TBAI, DMF, 0 °C to rt, 20 h; (ii) O₃, CH₂Cl₂, MeOH, -78 °C then Me₂S, 89% (2 steps); (iii) Danishefsky's diene, ZnCl₂, THF, 40 °C, 18 h, then TFA, CH₂Cl₂, rt, 15 min, 71%; (iv) I₂, CCl₄/Pyr. (1/1), rt, 2 h, 81%; (v) Pd₂(dba)₃, AsPh₃, Cu(TC), THF, DMSO, 40 °C, 16 h, 92%.

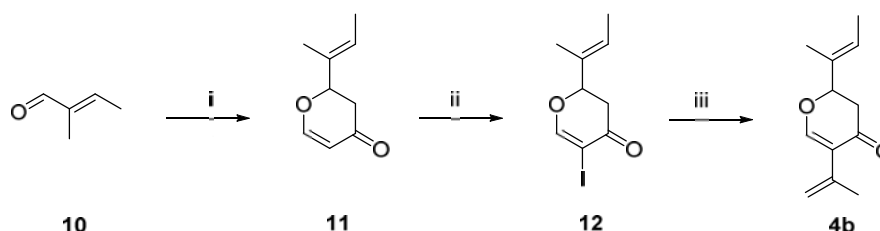
With aldehyde **5** in hand, we next focused our efforts on the formation of the dihydropyranone skeleton. In this way, Lewis acid-activated hetero-Diels-Alder condensation²⁴ of aldehyde **5** onto Danishefsky's diene afforded 2,3-dihydro-4*H*-pyran-4-one **6** as a mixture of both diastereomers. Best results in terms of yield and diastereoselectivity were obtained using ZnCl₂ as catalyst (rd 87/13). Even though the newly created stereogenic center will be destroyed in the penultimate state of our strategy (see scheme 4), in order to facilitate the purification procedures as well as NMR analysis of intermediates at each step, the major diastereomer **6** (unknown stereochemistry) has been isolated in pure form in 71% yield.

Prior to perform a palladium-catalyzed Stille cross-coupling reaction, dihydropyranone **6** was subjected to a direct Johnson-type α -iodination reaction, using iodine in a 1:1 pyridine/CCl₄ mixture,²⁵ to provide the corresponding α -iodoenone derivative **7** in 81% yield. Then, pivotal cross-coupling of 3-iodo-dihydropyran-4-one **7** with tributyl(isoprenyl)stannane **8**²⁶ was investigated to install the α -isoprenyl group on enone **9**. Following conditions developed by Fuwa and Sasaki,²⁷ using a combination of Pd₂(dba)₃ as precatalyst, Ph₃As as soft ligand to accelerate the rate-limiting transmetalation step, and copper(I) 2-thiophenecarboxylate (CuTC) as catalyst to promote transmetalation of vinyl stannane **8** into more reactive copper species,²⁸ the desired diene **9** was obtained in an excellent yield of 92%.

For the synthesis of kidamycinone **2**, the same strategy has been employed starting from the commercially available *trans*-2,3-dimethylacrolein **10** as depicted in scheme 3. BF₃.Et₂O mediated hetero Diels-Alder reaction of *trans*-2,3-dimethylacrolein **10** with Danishefsky's diene was conducted at -78 °C as reported in the literature for α,β -unsaturated aldehydes²⁴ to afford the desired adduct **11** in 89% yield. Next, α -iodination of **11** was performed using close conditions compared to

those used for compound **6** with iodine and pyridine in dry CH_2Cl_2 to give the desired 3-iodo-dihydropyranone **12** in 94% yield.²⁹ Finally, the latter intermediate **12** was subjected to previously described Stille cross-coupling reaction conditions to lead to the expected diene **4b** in 95% yield.

Scheme 3. Preparation of diene 4b^a

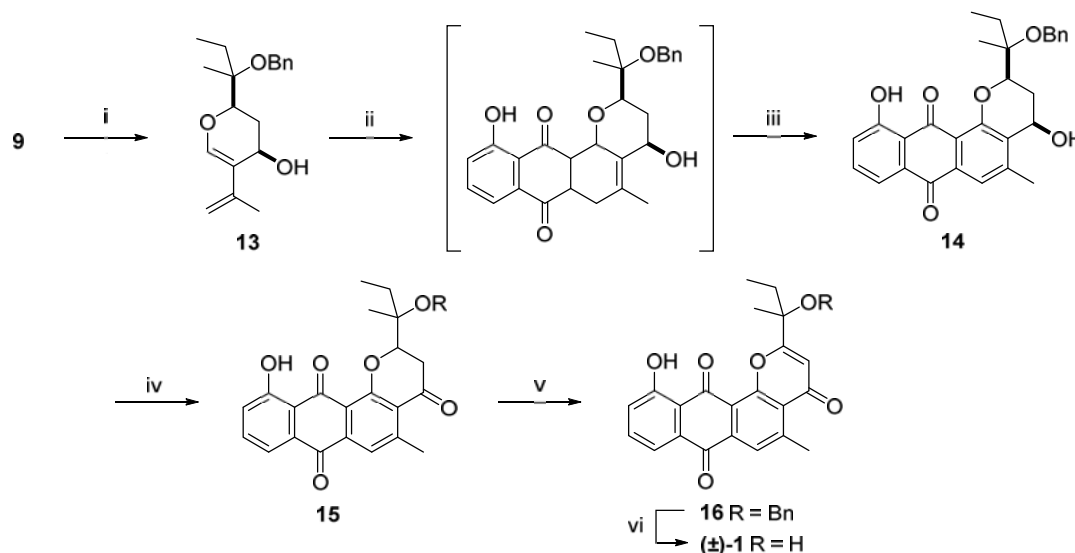


^aReagents and conditions : (i) Danishefsky's diene, $\text{BF}_3 \cdot \text{OEt}_2$, Et_2O , -78°C , 5 h, then TFA, CH_2Cl_2 , rt, 1 h, 89%; (ii) I_2 , Pyridine., CH_2Cl_2 , 0°C , 30 min then rt, 2.5 h, 94%; (iii) **8**, $\text{Pd}_2(\text{dba})_3$, AsPh_3 , CuTC, THF, DMSO, 40°C , 16 h, 95%.

Dienes **9** and **4b** bearing a deactivating electron withdrawing group in *C*-2 position were found not to be reactive toward dienophile such as juglone **3**.³⁰ Therefore, we decided to perform the reduction of the ketone function under Luche's conditions prior to the cycloaddition step (Scheme 4).³¹ Starting from diene **9**, the resulting crude secondary alcohol **13** was directly engaged in a Diels-Alder condensation with juglone **3**. While regioselectivity of cycloaddition could be easily determined using 2D HMBC NMR experiments on compound **14**, *endo* or *exo* selectivity could not be determined on this substituted tetracycle, but will be later discussed on a kidamycinone intermediate (*vide infra*). To promote the aromatization of ring B, the unstable primary cycloadduct was then engaged without purification in a one-pot two-step sequence involving the epoxidation of the newly created C-C double bond with *m*-CPBA followed by treatment of the resulting crude epoxide with an excess of triethylamine in the presence of air to provide intermediate **14** in 64% global yield from diene **9**. No trace of the other regioisomer was found in the crude mixture confirming that regioselectivity in cycloaddition of juglone with polar dienes such as **9** is based on the presence of a

strong internal hydrogen bond between phenolic proton and oxygen atom of the adjacent carbonyl group.³²

Scheme 4. Synthesis of racemic γ -indomycinone (1**)^a**

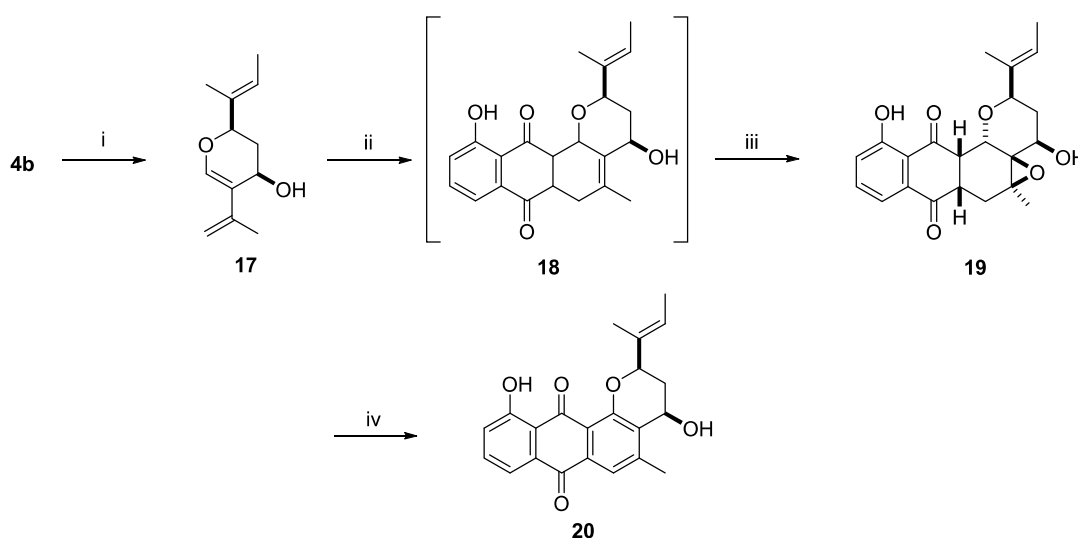


^aReagents and conditions : (i) $\text{CeCl}_3 \cdot 7 \text{H}_2\text{O}$, NaBH_4 , THF/MeOH , -78°C , 15 min then -30°C over 1 h; (ii) juglone **3**, CH_3CN , 40°C , 16 h; (iii) *m*-CPBA, CH_2Cl_2 , rt, 16 h then Et_3N , air, rt, 1 h, 64 % (3 steps); (iv) PCC, CH_2Cl_2 , 40°C , 24 h, 70%; (v) I_2 , DMSO, 95°C , 24 h, 78 %; (vi) DDQ, PhCl , 140°C , 1 h, 78%.

The last steps to access to γ -indomycinone **1** consisted in the recovering of the ketone moiety followed by oxidation of the chromanone moiety and debenzylation of the tertiary alcohol. Oxidation of the secondary alcohol **14** was performed with PCC in 70% yield.³³ Dehydrogenation of the resulting ketone **15** was accomplished in 78% yield by Patonay's procedure³⁴ using substoichiometric amount of I_2 in DMSO at 95°C . To avoid palladium catalyzed hydrogenolytic debenzylation conditions which are incompatible with the presence of a α,β -unsaturated ketone in ring A, cleavage of the hindered tertiary benzyl ether in intermediate **16** was performed using DDQ in refluxing chlorobenzene³⁵ to furnish racemic γ -indomycinone (\pm)-**1** in 78% yield.

Following the same multi-steps strategy (*vide supra*), but starting from diene **4b**, reduction of the carbonyl group using Luche's conditions afforded diene **17** (84%) and cycloaddition with juglone **3** gave the unstable cycloadduct **18** (Scheme 5). At this stage, the aromatization of ring B of primary adduct **18** was investigated, taking into account that the presence of an extracyclic electron-rich double bond could greatly complicate the epoxidation step of this sequence compared to the precedent synthesis with intermediate **14**. First attempts were performed using *m*-CPBA. Even if anchimeric assistance of the allylic hydroxyl moiety could exert a positive effect by directing the peracid to the desired double bond,³⁶ presence of the extracyclic 2-butenyl group unfortunately led to a mixture of epoxidized derivatives. In sharp contrast, vanadium-catalyzed epoxidation of **18** using vanadyl acetylacetonate and with *tert*-butylhydroperoxide³⁷ as primary oxidant afforded epoxy alcohol **19** as a single diastereoisomer with excellent chemo- and stereoselectivity. Subsequent treatment with triethylamine under aerobic conditions furnished compound **20** in 74% yield over the three steps. As for the previous case, no trace of the other regioisomer has been found in the crude mixture (*vide supra*).

Scheme 5. Synthesis of kidamycinone intermediate 20^a



^aReagents and conditions : (i) $\text{CeCl}_3 \cdot 7 \text{H}_2\text{O}$, NaBH_4 , THF/MeOH, -78°C to -30°C , 2 h, 84%; (ii) Juglone **3**, CH_3CN , 40°C , 14 h; (iii) $\text{VO}(\text{acac})_2$, $t\text{BuOOH}$, CH_2Cl_2 , rt, 2 h; (iv) Et_3N , air, CH_2Cl_2 , rt, 14 h, 74% (3 steps).

The structure of the epoxy alcohol **19** was established by NMR data. Further confirmation was achieved by single crystal X-ray analysis³⁸ (Figure 2), and the relative configuration of all stereocenters helped us to rationalize the stereochemical course of each single step of this carbonyl reduction – hetero Diels-Alder condensation - epoxidation sequence.

Relative *syn*-relation of 2-butenyl and hydroxyl groups confirmed that reduction of the carbonyl group under Luche's conditions occurred on the less hindered face of the dihydropyranone ring. The stereoselectivity of the vanadium-catalyzed olefin epoxidation was also confirmed by the relative *syn*-relation between the oxiran ring and the hydroxyl group with respect to the regiocontrol effect by this hydroxyl group. Regarding the relative configurations of the three other stereocenters, the complete stereoselectivity of the cycloaddition could be accounted by an *endo* transition state with minimization of steric interactions (Figure 3). These results in hand, we decided to study the expected transition state by computational methods. In order to adapt the conditions for both kidamycinone and γ -indomycinone, DFT computations were carried out on simplified diene **A** (Figure 3). Starting from juglone **3** and diene **A**, a reasonable reaction profile has been calculated.³⁹ The Diels-Alder sequence passes through an asynchronous concerted mechanism highlighted by a dissymmetric approach of diene towards dienophile. Despite this asynchronicity, only one transition state (TS) has been found in free activation energy of 25.5 kcal/mol leading to cycloadduct **B**.

Figure 2. X-ray structure of intermediate 19. The thermal ellipsoid contour probability levels is 30 %.

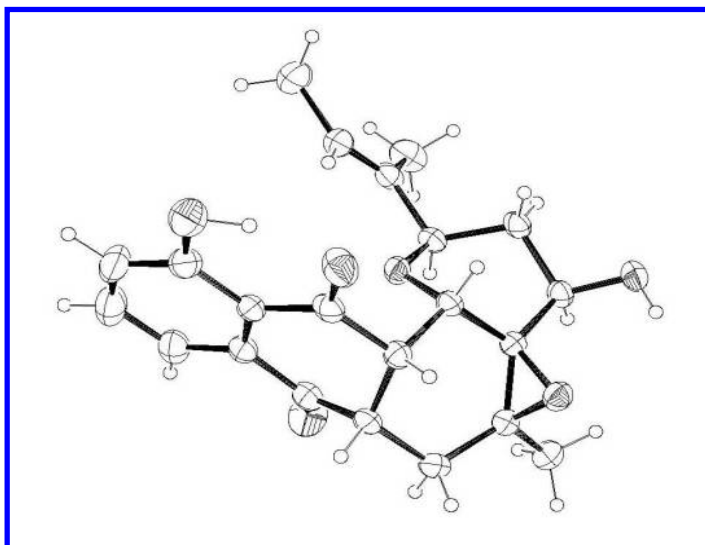
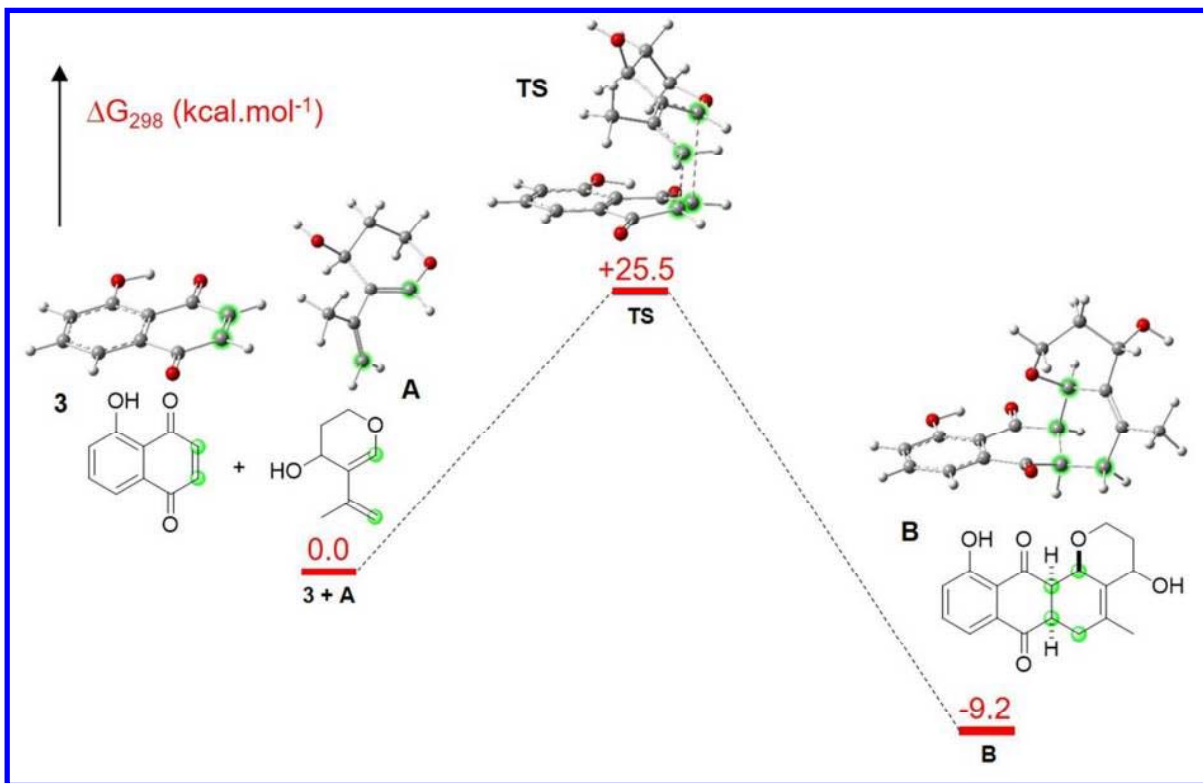


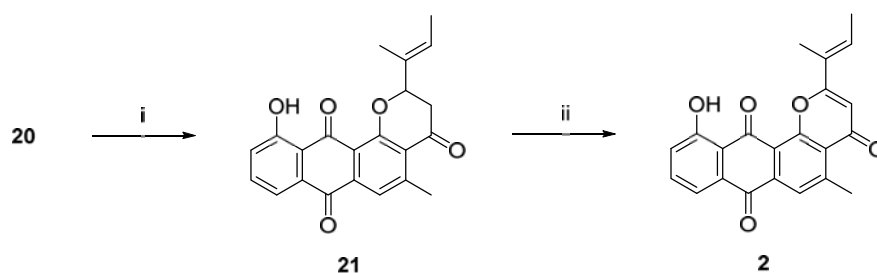
Figure 3. Computed reaction profile leading to intermediate 18 *via* an *endo* transition state. DFT method: B3LYP/ 6-31G(d) PCM in acetonitrile at the same level theory. ΔG values are given in kcal.mol⁻¹. Carbon atoms involved in ring B formation have been highlighted in green..



The final stage of the synthesis of kidamycinone required oxidation of the secondary alcohol and dehydrogenation of the resulting ketone into the corresponding α,β -unsaturated carbonyl moiety to implant the flavone unit. It is worth noting that this sequence should be operated under mild reaction conditions to offer a high functional group tolerance as it could be required for the preparation of more complex members of this family, such as kidamycin with angolosamine and *N,N*-dimethylvancosamine moieties linked on ring D (see Figure 1).

Therefore, oxidation of alcohol **20** was evaluated under various conditions.

Scheme 6. Final steps of the kidamycinone synthesis^a



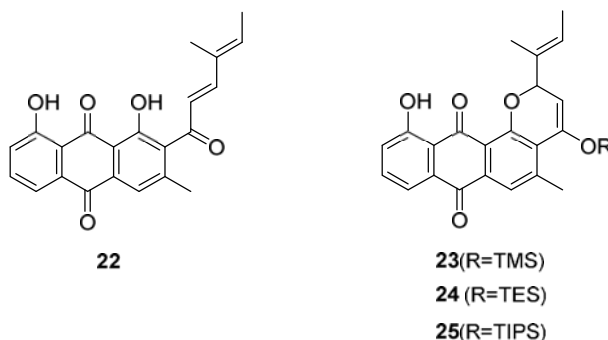
^aReagents and conditions : (i) DMP, $\text{CH}_2\text{Cl}_2/\text{DMSO}$ (2:1), rt, 2 h, 88% ;) I_2 , DMSO, 95 °C, 14 h, 68%.

First attempts were performed using MnO_2 as oxidizing agent.⁴⁰ Unfortunately, a large amount of agent (more than 50 eq.) was necessary to reach satisfactory conversions. Use of tetrapropylammonium perruthenate (TPAP) with *N*-methylmorpholine oxide (NMO) as co-oxidant⁴¹ also required more than 50 mol% of catalyst to give satisfactory result. In other hand, oxidation of alcohol **20** with a catalytic amount of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO)⁴² and [bis(acetoxy)iodo]benzene (BAIB) as a stoichiometric oxidant gave a low conversion. Fortunately, the use of two equivalents of Dess-Martin periodinane⁴³ in a mixture of dimethylsulfoxide and dichloromethane led to an excellent conversion and a satisfactory 88% yield of **21** (Scheme 6).

It was then expected to achieve the synthesis of the targeted molecule **2** by dehydrogenation of intermediate **21**. In contrast with reports from the literature,⁴⁴ initial attempts using IBX in DMSO

failed. A mixture of chalcone derivative **22** (Figure 4) formed by dihydropyranone ring opening, and starting material **21** in 6:4 ratio was obtained in which the desired adduct **2** was detected as traces. In the other hand, all efforts to carry on this transformation employing the well-known $\text{Pd}(\text{OAc})_2$ promoted Ito-Saegusa oxidation⁴⁵ of the corresponding TMS-, TES- and TIPS-silyl enol ethers, respectively **23**, **24** and **25** (Figure 4), to afford enone **2** were unsuccessful leading to complex mixtures. Next, we turned our attention to DDQ oxidation⁴⁶ and various conditions were screened. At the best, treatment of flavone **21** with 5 equivalents of DDQ in dioxane/DMSO (3:1) at 40 °C provided a mixture of the desired targeted compound **2**, chalcone **22** and starting material **21** in 45:30:25 ratio. Fortunately, treatment of **21** in DMSO with substoichiometric amount of iodine at 95 °C cleanly provided kidamycinone **2** which was isolated in 68% yield (Scheme 6).³⁴

Figure 4. By-product (22) and desired intermediates (23-25) in dehydrogenation attempts



In summary, we have developed a general strategy for the synthesis of anthrapyranic skeletons which allowed us to synthesize racemic γ -indomycinone (**1**) in 11 steps and kidamycinone (**2**) in 9 steps with overall yields of 13% and 28%, respectively. Efforts are currently focused on the preparation of suitably substituted juglones in order to propose convergent synthesis of natural pluramycins.

Experimental section

General information. Anhydrous reactions were carried out under an atmosphere of argon using flame-dried glassware and standard syringe/septa techniques. Tetrahydrofuran was distilled over sodium and benzophenone, dichloromethane, toluene and diethyl ether were dried using a solvent purification system. Petroleum ether refers to the petroleum fraction bp 40–60 °C. Commercial reagents were used as supplied, unless otherwise indicated. Flash chromatography was performed with silica gel Kieselgel SI60 40-63 μm . Combi-Flash chromatography was performed using 40 μm silica pre-packed cartridges. Mobile phases are reported in relative composition (*e.g.* 1:1 EtOAc/Petroleum ether v/v). Melting points were determined using a melting point apparatus and are uncorrected/calibrated. ^1H NMR spectra were recorded on a 300 MHz spectrometer. ^{13}C NMR spectra were recorded on a 75 MHz spectrometer. ^{119}Sn NMR spectra were recorded on a 112 MHz spectrometer. Spectra were fully assigned using DEPT, COSY, HSQC and HMBC. Chemical shifts are reported relative to CDCl_3 (δ 7.26 ppm), C_6D_6 (δ 7.16 ppm) or $\text{DMSO}-d_6$ (δ 2.50 ppm) for ^1H NMR and CDCl_3 (δ 77.16 ppm), C_6D_6 (δ 128.06 ppm) or $\text{DMSO}-d_6$ (δ 29.5 ppm) for ^{13}C NMR. High-resolution mass spectra (HRMS) were recorded on ESI or MALDI with Q-ToF analysers within a tolerance of 5 ppm of the theoretically calculated value and measurements are given in Da.

2-benzyloxy-2-methylbutanal (5). A 60% sodium hydride dispersion in mineral oil (3.20 g, 80.0 mmol) was washed twice with pentane under argon at 0 °C before being taken in DMF (200 mL) and 3-methylpenten-3-ol (4.80 mL, 40.0 mmol) was added. After 30 min stirring, benzyl bromide (7.20 mL, 60.0 mmol) was added followed by *tetra*-butyl ammonium iodide (1.74 g, 4.80 mmol). After 30 min stirring, the mixture was allowed to warm up to room temperature. After 20 h the mixture was cooled to 0 °C and quenched by addition of a saturated solution of NH_4Cl (150 mL) and was extracted with EtOAc (2 \times 200 mL). The combined organic layers were washed with water (2 \times 200 mL) and brine (2 \times 200 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was directly used in the next step without any further purification. A

solution of freshly formed alkene (7.61 g, 40.0 mmol) in CH₂Cl₂/MeOH (170 mL/12 mL) at -78 °C under argon was ozonised until a blue color persisted. The mixture was purged with argon until complete disappearance of the color. At this point, Me₂S (32 mL, 400 mmol) was added and the mixture was allowed to warm to room temperature overnight. A saturated solution of NaHCO₃ was added (60 mL) and the aqueous phase was extracted with CH₂Cl₂ (2 × 100 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (Petroleum Ether/Et₂O 95:5) to afford *the title compound 5* (6.84 g, 35.6 mmol, 89%) as a colorless oil. *R_f* 0.80 (Petroleum ether/Et₂O 80:20), *v*_{max} (neat)/cm⁻¹ 2977, 1718, 1497, 1167; *δ*_H (300 MHz; CDCl₃) 9.67 (s, 1H, CHO), 7.37–7.28 (m, 5H, H_{aromatic}), 4.49 and 4.44 (part of an AB system, *J* = 11.2 Hz, 2H, CH₂O), 1.88 and 1.65 (AB part of an ABX system, *J* = 14.6 Hz, *J* = 7.5 Hz, 2H, CH₃CH₂), 1.32 (s, 3H, CH₃), 0.94 (t, *J* = 7.5 Hz, 3H, CH₃CH₂); *δ*_C (75 MHz, CDCl₃) 205.2 (CHO), 138.4 (C_{aromatic}), 128.4 (2 × CH_{aromatic}), 127.7 (CH_{aromatic}), 127.4 (2 × CH_{aromatic}), 82.9 (C), 66.1 (CH₂O), 27.7 (CH₃CH₂), 17.7 (CH₃), 7.3 (CH₃CH₂); *m/z* (ESI+) [M+H]⁺ 193.1223 calcd for C₁₂H₁₇O₂ 193.1226.

2-(2-(benzyloxy)butan-2-yl)-2,3-dihydro-4H-pyran-4-one (6). To a solution of zinc chloride (freshly fused under *vacuum*) (4.04 g, 29.6 mmol) in THF (120 mL), was added aldehyde **5** (5.70 g, 29.6 mmol) dissolved in THF (50 mL). After 10 min stirring, Danishefsky's diene (11.5 mL, 59.2 mmol) was added. After 18 h at 40 °C, the solution was quenched by addition of a saturated solution of NaHCO₃ and extracted with Et₂O (3 × 100 mL). The combined organic layers were washed with brine (150 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was diluted in CH₂Cl₂ (40 mL) and trifluoroacetic acid (0.90 mL, 11.8 mmol) was added. The solution was stirred for 15 min at room temperature and then concentrated. The crude product was purified by silica gel column chromatography (Petroleum Ether/EtOAc 95:5 to 90:10) to afford *the title compound 6* (5.47 g, 21.0 mmol, 71%) as a pale yellow oil. *R_f* 0.37 (Petroleum ether/EtOAc 85:15); *v*_{max} (neat)/cm⁻¹ 2970, 1678, 1567, 1257; *δ*_H (300 MHz; CDCl₃) 7.38 (d, *J* = 5.9 Hz, 1H,

CH=CHO), 7.37–7.29 (m, 5H, H_{aromatic}), 5.42 (dd, $J = 5.9$ Hz, $J = 1.2$ Hz, 1H, $\underline{\text{CH}}=\text{CHO}$), 4.50 and 4.45 (AB system, $J = 11.2$ Hz, 2H, CH_2O), 4.42 (X part of an ABX system, $J = 14.5$ Hz, $J = 3.8$ Hz, 1H, $-\text{CHO}$), 2.74–2.41 (AB part of an ABX system, $J = 16.9$ Hz, $J = 14.5$ Hz, $J = 3.8$ Hz, $J = 1.2$ Hz, 2H, $\text{CH}_2\text{C}=\text{O}$), 1.81 and 1.71 (AB part of an ABX system, $J = 14.8$ Hz, $J = 7.4$ Hz, 2H, CH_3CH_2), 1.33 (s, 3H, CH_3), 0.94 (t, $J = 7.4$ Hz, 3H, CH_3CH_2); δ_{C} (75 MHz, CDCl_3) 193.4 (CO), 162.9 ($\text{CH}=\text{CHO}$), 138.9 ($\text{C}_{\text{aromatic}}$), 128.3 ($2 \times \text{CH}_{\text{aromatic}}$), 127.4 ($\text{CH}_{\text{aromatic}}$), 127.1 ($2 \times \text{CH}_{\text{aromatic}}$), 107.3 ($\text{CH}=\text{CHO}$), 81.5 (CHO), 77.2 (COBn), 63.8 (PhCH_2O), 36.5 (CH_2CO), 27.5 (CH_3CH_2), 18.5 (CH_3), 7.3 (CH_3CH_2). m/z (MALDI) $[\text{M}+\text{Na}]^+$ 283.1294 calcd for $\text{C}_{16}\text{H}_{20}\text{O}_3\text{Na}$ 283.1305.

2-(2-(benzyloxy)butan-2-yl)-5-iodo-2,3-dihydro-4H-pyran-4-one (7). Iodine (8.22 g, 32.4 mmol) dissolved in a CCl_4 /pyridine mixture (1:1, 30 mL) was added dropwise at 0 °C to a solution of starting ketone **6** (4.22 g, 16.2 mmol) in CCl_4 /pyridine (1:1, 30 mL). The mixture was stirred for 2 h at room temperature, then diluted with CH_2Cl_2 (100 mL) and washed with water (50 mL), HCl 1 M (2×50 mL) and 20% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (2×50 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (Petroleum Ether/ Et_2O 80:20) to afford the *title compound* **7** (5.13 g, 13.3 mmol, 82%) as a pale yellow solid. R_f 0.31 (Petroleum ether/ Et_2O 90:10); Mp 72–73 °C; ν_{max} (neat)/ cm^{-1} 2971, 1671, 1595, 1273, 512; δ_{H} (300 MHz; CDCl_3) 7.81 (d, $J = 0.6$ Hz, 1H, $\text{IC}=\text{CHO}$), 7.37–7.27 (m, 5H, H_{aromatic}), 4.47 (X part of an ABX system, $J = 14.5$ Hz, $J = 3.8$ Hz, 1H, CHO), 4.55 and 4.46 (AB system, $J = 11.2$ Hz, 2H, PhCH_2O), 2.97 and 2.83 (AB part of an ABX system, $J = 16.9$ Hz, $J = 14.5$ Hz, $J = 3.8$ Hz, $J = 1.2$ Hz, 2H, $\text{CH}_2\text{C}=\text{O}$), 1.72–1.64 (AB part of an ABX_3 system, $J = 14.8$ Hz, $J = 7.4$ Hz, 2H, CH_3CH_2), 1.32 (s, 3H, CH_3), 0.96 (t, $J = 7.4$ Hz, 3H, CH_3CH_2); δ_{C} (75 MHz, CDCl_3) 187.3 (CO), 165.7 ($\text{IC}=\text{CHO}$), 138.7 ($\text{C}_{\text{aromatic}}$), 128.5 ($2 \times \text{CH}_{\text{aromatic}}$), 127.5 ($\text{CH}_{\text{aromatic}}$), 127.2 ($2 \times \text{CH}_{\text{aromatic}}$), 82.4 (CHO), 77.1 (C), 76.9 ($\text{IC}=\text{CHO}$), 63.9 (CH_2O), 36.3 (CH_2CO), 27.5 (CH_3CH_2), 18.6 (CH_3), 7.4 (CH_3CH_2); m/z (MALDI) $[\text{M}+\text{Na}]^+$ 409.0286 calcd for $\text{C}_{16}\text{H}_{19}\text{IO}_3\text{Na}$ 409.0271.

2-(2-(benzyloxy)butan-2-yl)-5-(prop-1-en-2-yl)-2,3-dihydro-4H-pyran-4-one (9). To a solution of vinyl iodide **7** (2.00 g, 5.20 mmol) in a deoxygenated mixture of THF and DMSO (1:1, 250 mL) under argon atmosphere were added successively isopropenyltributyltin **8**²⁶ (3.44 g, 10.4 mmol), tris(dibenzylideneacetone)dipalladium (476 mg, 0.52 mmol), triphenylarsine (1.27 g, 4.16 mmol) and copper(I)-thiophene-carboxylate (1.28 g, 6.76 mmol). The mixture was stirred at 40 °C overnight, then treated by addition of a saturated solution of NaF (150 mL). The resulting mixture was vigorously stirred for 1 h. The residue was filtered through a pad of Celite[®], extracted with Et₂O. The combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (Petroleum Ether/Et₂O 95:5) to afford *the title compound 9* (1.44 g, 4.78 mmol, 92%) as a colourless oil. *R_f* 0.50 (Petroleum Ether/Et₂O 90:10); *v*_{max} (neat)/cm⁻¹ 2970, 1677, 1568, 1256; *δ*_H (400 MHz; CDCl₃) 7.43 (d, *J* = 0.6 Hz, 1H, C=CHO), 7.43–7.32 (m, 5H, H_{aromatic}), 5.23 (dd, *J* = 2.0 Hz, *J* = 0.6 Hz, 1H, C=CHH), 4.98 (dd, *J* = 2.0 Hz, *J* = 1.5 Hz, 1H, C=CHH), 4.51 and 4.46 (AB system, *J* = 11.3 Hz, 2H, CH₂O), 4.40 (X part of an ABX system, *J* = 15.2 Hz, *J* = 3.0 Hz, 1H, CHO), 2.74 and 2.60 (AB part of an ABX system, *J* = 16.6 Hz, *J* = 15.2 Hz, *J* = 3.0 Hz, 2H, CH₂C=O), 1.93 (s, 3H, CH₃ propenyl), 1.81 and 1.69 (AB part of an ABX₃ system, *J* = 15.0 Hz, *J* = 7.5 Hz, 2H, CH₃CH₂), 1.33 (s, 3H, CH₃), 0.94 (t, *J* = 7.5 Hz, 3 H, CH₃CH₂); *δ*_C (100 MHz, CDCl₃) 192.0 (CO), 159.8 (C=CHO), 139.0 (C_{aromatic}), 137.4 (CH₃C=CH₂), 128.4 (2 × CH_{aromatic}), 127.4 (CH_{aromatic}), 127.2 (2 × CH_{aromatic}), 121.0 (C=CHO), 115.2 (C=CH₂), 81.6 (CHO), 77.2 (OCMe(Et)), 63.9 (CH₂O), 37.1 (CH₂C=O), 27.7 (CH₃CH₂), 22.3 (CH₃C=CH₂), 18.6 (CH₃), 7.5 (CH₃CH₂); *m/z* (MALDI) [M+H]⁺ 301.1789 calcd for C₁₉H₂₅O₃ 301.1798.

2-(2-(benzyloxy)butan-2-yl)-4,11-dihydroxy-5-methyl-3,4-dihydro-2H-anthra[1,2-*b*]pyran-7,12-dione (14). To a solution of diene **9** (1.33 g, 4.43 mmol) in THF/MeOH (1:1, 80 mL) was added cerium chloride heptahydrate (1.65 g, 4.43 mmol). After dissolution of the cerium salts, the solution

was cooled to -78 °C and sodium borohydride (335 mg, 8.86 mmol) was added in one portion. The mixture was stirred at -78 °C for 15 min, then the temperature was raised to -50 °C and left to warm up to -30 °C over an hour. The mixture was concentrated under reduced pressure and the product extracted from the salts with CH₂Cl₂ (3 × 100 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The resulting diene was dissolved in acetonitrile (30 mL) and juglone (926 mg, 5.32 mmol) was added. The resulting mixture was stirred at 40 °C overnight. Solvent was evaporated, the residue dissolved in CH₂Cl₂ (50 mL) and *m*-CPBA acid (2.95 g, 12.0 mmol) was added. The mixture was stirred at room temperature overnight and then triethylamine (6.18 mL, 44.3 mmol) was added, the mixture was stirred for an extra hour. The residue was concentrated under reduced pressure and purified by silica gel column chromatography (Petroleum Ether/EtOAc 70:30) to afford *the title compound* **14** (1.34 g, 2.84 mmol, 64%) as a yellow solid. *R*_f 0.60 (Petroleum Ether/EtOAc 60:40); Mp 179-181 °C (dec.); *v*_{max} (neat)/cm⁻¹ 3392, 2966, 1667, 1633, 1582, 1261; *δ*_H (300 MHz; CDCl₃) 13.28 (s, 1H, Ar-OH), 7.76 (X part of an AMX system, *J* = 7.6 Hz, *J* = 1.1 Hz, 1H, H_{aromatic}), 7.70 (s, 1H, H_{aromatic}), 7.42 (M part of an AMX system, *J* = 8.3 Hz, *J* = 7.6 Hz, 1H, H_{aromatic}), 7.28 (A part of an AMX system, *J* = 8.3 Hz, *J* = 1.1 Hz, 1H, H_{aromatic}), 7.15–7.06 (m, 3H, H_{aromatic}), 6.82–6.75 (m, 2H, H_{aromatic}), 4.74 (M part of an ABMX system, *J* = 10.9 Hz, *J* = 5.9 Hz, *J* = 4.0 Hz, 1H, CH(OH)), 4.45–4.37 (X part of an ABX system, 1H, CH(O)), 4.41 and 4.33 (AB system, *J* = 10.5 Hz, 2H, CH₂O), 3.97 (d, *J* = 10.9 Hz, 1H, CH(OH)), 2.53 and 2.42 (AB part of an ABMX system, *J* = 15.0 Hz, *J* = 5.9 Hz, *J* = 5.8 Hz, *J* = 4.0 Hz, 2H, CH₂(CHOH)), 2.42 (s, 3H, CH₂=CCH₃), 2.05–1.79 (AB part of an ABX₃ system, *J* = 15.2 Hz, *J* = 7.5 Hz, 2H, CH₃CH₂), 1.67 (s, 3H, CH₃), 1.01 (t, *J* = 7.5 Hz, 3H, CH₃CH₂); *δ*_C (75 MHz, CDCl₃) 188.6 (CO), 183.0 (CO), 162.5 (C(OH)_{aromatic}), 157.2 (C_{aromatic}), 148.0 (CCH_{3aromatic}), 137.5 (C_{aromatic}), 135.6 (C_{aromatic}), 133.9 (C_{aromatic}), 132.9 (C_{aromatic}), 131.3 (C_{aromatic}), 128.4 (2 × CH_{aromatic}), 127.7 (3 × CH_{aromatic}), 124.7 (CH_{aromatic}), 121.9 (CH_{aromatic}), 118.6 (CH_{aromatic}), 117.9 (C_{aromatic}), 117.4 (C_{aromatic}), 80.8 (COBn), 78.0 (CH(O)), 65.4 (PhCH₂O), 60.5 (CH(OH)), 30.5 and 29.5 (CH₂CHOH

and CH_3CH_2), 20.2 and 19.2 ($\text{Ar}-\text{CH}_3$ et CH_3), 8.4 (CH_3CH_2); m/z (MALDI) $[\text{M}+\text{Na}]^+$ 495.1763 calcd for $\text{C}_{29}\text{H}_{28}\text{O}_6\text{Na}$ 495.1778.

2-(2-(benzyloxy)butan-2-yl)-11-hydroxy-5-methyl-3,4-dihydro-2H-anthra[1,2-*b*]pyran-4,7,12-trione (15). To a solution of alcohol **14** (300 mg, 0.63 mmol) in anhydrous CH_2Cl_2 (20 mL) under argon atmosphere, was added pyridinium chlorochromate (0.41 g, 1.90 mmol). Resulting mixture was refluxed overnight then concentrated under reduced pressure. The crude product was purified on silica gel column chromatography (Petroleum Ether/EtOAc 80:20) to afford *the title compound 15* (210 mg, 0.44 mmol, 70%) as a yellow solid. R_f 0.76 (Petroleum Ether/EtOAc 80:20); Mp 179-180 °C ; ν_{max} (neat)/ cm^{-1} 3072, 2971, 1678, 1641, 1568, 1257; δ_{H} (300 MHz; CDCl_3) 13.11 (s, 1H, Ar-OH), 7.77 (dd, X part of an AMX system, $J = 7.6$ Hz, $J = 1.1$ Hz, 1H, $\text{H}_{\text{aromatic}}$), 7.75 (s, 1H, $\text{H}_{\text{aromatic}}$), 7.64 (dd, M part of an AMX system, $J = 8.3$ Hz, $J = 7.6$ Hz, 1H, $\text{H}_{\text{aromatic}}$), 7.34 (dd, A part of an AMX system, $J = 8.3$ Hz, $J = 1.1$ Hz, 1H, $\text{H}_{\text{aromatic}}$), 7.32–7.26 (m, 5H, $\text{H}_{\text{aromatic}}$), 4.69–4.62 (X part of ABX system, 1H, CHO), 4.58 and 4.54 (AB system, $J = 10.5$ Hz, 2H, CH_2O), 3.01 and 2.91 (AB part of an ABX system, $J = 15.0$ Hz, $J = 5.8$ Hz, 2H, $\text{CH}_2(\text{C}=\text{O})$), 2.77 (s, 3H, Ar- CH_3), 2.14 and 1.82 (AB part of an ABX₃ system, $J = 15.2$ Hz, $J = 7.5$ Hz, 2H, CH_3CH_2), 1.62 (s, 3H, CH_3), 1.01 (t, $J = 7.5$ Hz, 3H, CH_3CH_2); δ_{C} (75 MHz, CDCl_3) 193.9 (CO), 187.6 (CO), 182.5 (CO), 163.4 (C(OH)), 162.6 ($\text{C}_{\text{aromatic}}$), 150.0 ($\text{CCH}_3\text{aromatic}$), 139.3 ($\text{C}_{\text{aromatic}}$), 137.2 ($\text{C}_{\text{aromatic}}$), 136.0 ($\text{CH}_{\text{aromatic}}$), 132.6 ($\text{C}_{\text{aromatic}}$), 128.5 ($2 \times \text{CH}_{\text{aromatic}}$), 127.4 ($\text{CH}_{\text{aromatic}}$), 127.3 ($2 \times \text{CH}_{\text{aromatic}}$), 125.2 ($\text{CH}_{\text{aromatic}}$), 124.5 ($\text{C}_{\text{aromatic}}$), 123.2 ($\text{CH}_{\text{aromatic}}$), 119.1 ($\text{C}_{\text{aromatic}}$), 119.0 ($\text{CH}_{\text{aromatic}}$), 117.2 ($\text{C}_{\text{aromatic}}$), 81.3 (COBn), 78.2 ($\text{CH}(\text{O})$), 64.6 (CH_2O), 38.8 ($\text{CH}_2(\text{C}=\text{O})$), 28.1 (CH_3CH_2), 24.0 (Ar- CH_3), 18.7 (CH_3), 7.7 (CH_3CH_2); m/z (ESI+) $[\text{M}+\text{Na}]^+$ 493.1635 calcd for $\text{C}_{29}\text{H}_{26}\text{O}_6\text{Na}$ 493.1622.

2-(2-(benzyloxy)butan-2-yl)-11-hydroxy-5-methyl-anthra[1,2-*b*]pyran-4,7,12-trione (16). To a solution of ketone **15** (150 mg, 0.32 mmol) in DMSO (14 mL) was added iodine (30 mg, 0.13 mmol). The resulting mixture was stirred under argon atmosphere at 95 °C overnight. After cooling to room temperature, the reaction mixture was quenched by addition of brine (15 mL),

extracted with CH_2Cl_2 (3×20 mL). Combined organic layers were washed with a solution of $\text{Na}_2\text{S}_2\text{O}_3$ (20%), dried over Na_2SO_4 , and concentrated under reduced pressure. The crude product was purified on silica gel column chromatography (Petroleum Ether/EtOAc 95:5) to afford *the title compound* **16** (0.117g, 0.249 mmol, 78%) as a yellow solid. R_f 0.31 (Petroleum Ether/EtOAc 90:10); Mp 201-202 °C ; ν_{max} (neat)/ cm^{-1} 3069, 2975, 1685, 1672, 1650, 1581, 1551, 1265; δ_{H} (300 MHz; CDCl_3) 12.91 (s, 1H, Ar-OH), 8.06 (d, $J = 0.6$ Hz, 1H, $\text{H}_{\text{aromatic}}$), 7.83–7.80 (X part of an AMX system, $J = 7.6$ Hz, $J = 1.2$ Hz, 1H, $\text{H}_{\text{aromatic}}$), 7.73–7.65 (M part of an AMX system, $J = 8.3$ Hz, $J = 7.6$ Hz, 1H, $\text{H}_{\text{aromatic}}$), 7.41–7.26 (m, 6H, $\text{H}_{\text{aromatic}}$), 6.64 (s, 1H, OC=CH), 4.59 and 4.53 (AB system, $J = 10.5$ Hz, 2H, CH_2O), 3.02 (d, $J = 0.6$ Hz, 3H, ArCH_3), 2.22 and 2.14 (AB part of an ABX₃ system, $J = 15.2$ Hz, $J = 7.5$ Hz, 2H, CH_3CH_2), 1.81 (s, 3H, CH_3), 0.94 (t, $J = 7.5$ Hz, 3H, CH_3CH_2); δ_{C} (75 MHz, CDCl_3) 187.2 (CO), 181.9 (CO), 179.3 (CO), 170.7 (OC=CH), 162.6 (C(OH)), 156.4 ($\text{C}_{\text{aromatic}}$), 149.8 ($\text{CCH}_3_{\text{aromatic}}$), 138.3 ($\text{C}_{\text{aromatic}}$), 136.3 ($\text{CH}_{\text{aromatic}}$), 136.0 ($\text{C}_{\text{aromatic}}$), 132.2 ($\text{C}_{\text{aromatic}}$), 128.4 ($2 \times \text{CH}_{\text{aromatic}}$), 127.5 ($\text{CH}_{\text{aromatic}}$), 127.1 ($2 \times \text{CH}_{\text{aromatic}}$), 126.5 ($\text{C}_{\text{aromatic}}$), 125.6 ($\text{CH}_{\text{aromatic}}$), 125.3 ($\text{CH}_{\text{aromatic}}$), 119.9 ($\text{C}_{\text{aromatic}}$), 119.3 ($\text{CH}_{\text{aromatic}}$), 116.8 ($\text{C}_{\text{aromatic}}$), 111.3 (OC=CH), 79.1 (COBn), 64.8 (CH_2O), 31.7 (CH_3CH_2), 24.6 (Ar- CH_3), 22.0 (CH_3), 8.0 (CH_3CH_2); m/z (ESI+) [$\text{M} + \text{Na}$]⁺ 491.1476 calcd for $\text{C}_{29}\text{H}_{24}\text{O}_6\text{Na}$ 491.1465.

2-(2-(hydroxy)butan-2-yl)-11-hydroxy-5-methyl-anthra[1,2-*b*]pyran-4,7,12-trione (1). To a solution of benzyl-protected alcohol **16** (84 mg, 0.18 mmol) in chlorobenzene (9 mL), under argon atmosphere, was added DDQ (163 mg, 0.72 mmol), and the resulting mixture heated up to 140 °C. After 1 hour stirring, the reaction mixture was concentrated under reduced pressure and the crude product was purified on silica gel column chromatography (Toluene/EtOAc 80:20) to afford γ -indomycinone **1** (53 mg, 0.14 mmol, 78%) as a yellow solid. All spectroscopic data for **1** are identical in all respects with those of the natural product described in literature.^{12a, 47} R_f 0.19 (Toluene/EtOAc 80:20); Mp 289-290 °C ; ν_{max} (neat)/ cm^{-1} 3359, 2959, 2925, 2873, 1674, 1639,

1582, 1446, 1262, 1184, 765, 750; δ_H (700 MHz; DMSO) 12.69 (s, 1H, Ar–OH), 7.94 (s, 1H, H_{aromatic}), 7.78 (br. t, X part of an AMX system, $J = 7.6$ Hz, $J = 1.2$ Hz, 1H, H_{aromatic}), 7.69 (dd, M part of an AMX system, $J = 8.3$ Hz, $J = 7.6$ Hz, 1H, H_{aromatic}), 7.39 (dd, A part of an AMX system, $J = 8.3$ Hz, $J = 1.1$ Hz, 1H, H_{aromatic}), 6.48 (s, 1H, OC=CH), 5.55 (s, 1H, OH), 2.91 (s, 3H, Ar–CH₃), 2.07 and 1.84 (AB part of an ABX₃ system, $J = 15.2$ Hz, $J = 7.5$ Hz, 2H, CH₃CH₂), 1.61 (s, 3H, CH₃), 0.84 (t, $J = 7.5$ Hz, 3H, CH₃CH₂); δ_C (175 MHz, DMSO) 187.0 (CO), 181.4 (CO), 178.3 (CO), 173.9 (OC=CH), 161.4 (C(OH)_{aromatic}), 155.6 (C_{aromatic}), 148.3 (CCH_{3aromatic}), 136.7 (C_{aromatic}), 135.8 (C_{aromatic}), 132.1 (C_{aromatic}), 125.5 (CH_{aromatic}), 124.7 (2 × CH_{aromatic}), 119.8 (CH_{aromatic}), 118.7 (C_{aromatic}), 116.8 (C_{aromatic}), 109.0 (OC=CH), 72.7 (C(OH)), 32.9 (CH₃CH₂), 26.7 (Ar–CH₃), 23.4 (CH₃), 7.8 (CH₃CH₂); m/z (ESI+) [M+H]⁺ 379.1183 calcd for C₂₂H₁₉O₆ 379.1176.

(E)-2-(but-2-en-2-yl)-2H-pyran-4(3H)-one (11). To a solution of Danishefsky's diene (11.3 mL, 52.2 mmol) in diethyl ether at -78 °C was added *trans*-1,3-dimethylacrolein (14.0 mL, 145.1 mmol) under argon atmosphere. After 15 min stirring, trifluoride boron etherate (9.32 mL, 75.5 mmol) was added in one portion and the resulting mixture stirred for 5 h at -78 °C. The reaction was quenched by a dropwise addition of a saturated solution of NaHCO₃ (200 mL) after letting the reaction mixture to warm up for 30 min. The mixture was then extracted with diethyl ether (3 × 250 mL), organic layers were gathered, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was dissolved in dry CH₂Cl₂ (300 mL). Trifluoroacetic acid (4.00 mL, 75.5 mmol) was added dropwise and the mixture stirred for 1 hour at room temperature under argon atmosphere before being quenched by addition of a saturated solution of NaHCO₃ (200 mL). The aqueous phase was extracted with diethyl ether (3 × 250 mL), and combined organic layers dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by distillation under vacuum (81 °C, 0.39 mbar) using a Kugelrohr apparatus to afford *the title compound 11* (7.03 g, 46.3 mmol, 89%) as a yellow oil. ν_{max} (neat)/cm⁻¹ 2919, 1672, 1588, 1404, 1268, 1217, 1037, 985, 910, 825, 787; δ_H (300 MHz ; CDCl₃) 7.39 (d, $J = 6.1$ Hz, 1 H, OCHCH), 5.63 (q quint, $J = 6.8$ Hz, $J = 1.2$ Hz, 1 H,

CH₃CH), 5.39 (dd, $J = 6.1$ Hz, $J = 1.2$ Hz, 1 H, CHCHC(O)), 4.71 (X part of an ABXY system, $J = 14.5$ Hz, $J = 3.4$ Hz, 1 H, OCH), 2.76 (A part of an ABXY system, $J = 16.6$ Hz, $J = 14.5$ Hz, 1 H, (O)CCHH'), 2.35 (B part of an ABXY system, $J = 16.6$ Hz, $J = 3.4$ Hz, $J = 1.2$ Hz, 1 H, (O)CCHH'), 1.71 (quint, $J = 1.2$ Hz, 3 H, CH₃) 1.66 (br. d, $J = 6.8$ Hz, 3 H, CH₃); δ_C (75 MHz, CDCl₃) 193.0 (CO), 163.5 (CHCHO), 132.4 (C), 124.9 (CHCH₃), 106.9 (CHCO), 84.7 (CH₂CHO), 40.7 (CH₂), 13.4 (CHCH₃), 11.8 (CCH₃); m/z (ESI+) [M + Na]⁺ 175.0729 calcd for C₉H₁₂O₂Na 175.0730.

(E)-2-(but-2-en-2-yl)-5-iodo-2H-pyran-4(3H)-one (12). To a solution of iodine (15.00 g, 59.1 mmol) in anhydrous CH₂Cl₂ (100 mL) at 0 °C, under argon atmosphere, was added freshly-dried pyridine (10.2 mL, 131.4 mmol). A solution of **11** (4.00 g, 26.2 mmol) in anhydrous CH₂Cl₂ (100 mL) was then added dropwise. The resultant reaction mixture was maintained under stirring for 30 min at 0 °C protected from light before being allowed to warm up to room temperature for 2.5 h. The reaction was then quenched with a saturated solution of Na₂S₂O₃ (200 mL), partitioned between a saturated solution of NaHCO₃ (300 mL) and CH₂Cl₂ (250 mL), and was then extracted with CH₂Cl₂ (3 × 250 mL). The combined organic layers were dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The crude product was then purified by combi-flash chromatography (Petroleum Ether/EtOAc 100:0 to 92:8) to afford *the title compound 12* (6.87 g, 24.7 mmol, 94%) as a pale yellow solid. R_f 0.63 (Petroleum Ether/EtOAc 85:15); Mp 48-50 °C; ν_{\max} (neat)/cm⁻¹ 3028, 2914, 1661, 1552, 1370, 1352, 1264, 1112, 964, 931, 812, 490; δ_H (300 MHz; CDCl₃) 7.80 (s, 1 H, OCHCH), 5.65 (q quint, $J = 6.5$ Hz, $J = 1.2$ Hz, 1 H, CH₃CH), 4.88 (X part of an ABX system, $J = 14.2$ Hz, $J = 3.5$ Hz, 1 H, OCH), 2.91 (A part of an ABX system, $J = 16.6$ Hz, $J = 14.2$ Hz, 1 H, (O)CCHH'), 2.72 (B part of an ABX system, $J = 16.6$ Hz, $J = 3.5$ Hz, 1 H, (O)CCHH'), 1.69 (quint, $J = 1.2$ Hz, 3 H, CH₃), 1.67 (dq, $J = 6.5$ Hz, $J = 1.2$ Hz, 3 H, CH₃); δ_C (75 MHz, CDCl₃) 186.7 (CO), 166.3 (ICCHO), 131.5 (C), 125.9 (CHCH₃), 85.5 (CI) 77.3 (CH₂CHO), 40.1 (CH₂), 13.3 (CHCH₃), 11.7 (CCH₃); m/z (ESI+) [M + Na]⁺ 300.9696 calcd for C₉H₁₁O₂INa 300.9696.

(E)-2-(but-2-en-2-yl)-5-(prop-1-en-2-yl)-2H-pyran-4(3H)-one (4b). Iodide derivative **12** (4.00 g, 14.4 mmol), isopropenyltributyltin **8**²⁶ (9.52 g, 28.8 mmol), triphenylarsine (1.76 g, 5.75 mmol), tris(dibenzylideneacetone)dipalladium(0) (1.32 g, 1.44 mmol) and copper(I) thiophenecarboxylate (3.56 g, 18.7 mmol) were dissolved in a THF/DMSO (1:1, 200 mL) mixture and stirred at 40 °C under argon atmosphere for 16 h. The reaction mixture was then treated at room temperature by addition of a saturated solution of sodium fluoride (150 mL) and stirred for one extra hour with Celite[®]. The residue was filtered through a pad of Celite[®], extracted with diethyl ether. The combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo*. The resulting crude product was purified on combi-flash chromatography (Petroleum Ether/EtOAc 100:0 to 98:2) to afford the *title compound* **4b** (2.64 g, 13.7 mmol, 95%) as a yellow oil. *R*_f 0.67 (Petroleum Ether/EtOAc 90:10); *v*_{max} (neat)/cm⁻¹ 2921, 1672, 1578, 1358, 1311, 1254, 1125, 1057, 894, 824; *δ*_H (300 MHz; CDCl₃) 7.43 (d, *J* = 0.6 Hz, 1 H, OCH), 6.64 (q quint, *J* = 6.6 Hz, *J* = 1.3 Hz, 1 H, CH₃CH), 5.19 (dq, *J* = 2.3 Hz, *J* = 0.9 Hz, 1 H, CHH'), 4.96 (dq, *J* = 2.3 Hz, *J* = 1.4 Hz, 1 H, CHH'), 4.72 (X part of an ABX system, *J* = 14.4 Hz, *J* = 3.3 Hz, 1 H, OCH), 2.79 (A part of an ABX system, *J* = 16.4 Hz, *J* = 14.4 Hz, 1H, CHH'C(O)), 2.40 (B part of an ABX system, *J* = 16.4 Hz, *J* = 3.3 Hz, 1H, CHH'C(O)), 1.92 (dd, *J* = 1.4 Hz, *J* = 0.9 Hz, 3 H, CH₃), 1.70 (quint, *J* = 1.3 Hz, 3 H, CH₃), 1.66 (br. d, *J* = 6.6 Hz, 3 H, CH₃); *δ*_C (75 MHz, CDCl₃) 191.7 (CO), 160.4 (CCHO), 137.5 (CH₂CCH₃), 132.4 (CH₃CCH), 124.9 (CH₃CH), 120.6 (CH₂CCH₃), 115.1 (CCO), 85.5 (OCHCH₂), 41.1 (COCH₂), 22.3 (CH₂CCH₃), 13.4 (CHCH₃), 11.8 (CHCCH₃); *m/z* (ESI+) [M + Na]⁺ 215.1043 calcd for C₁₂H₁₆O₂Na 215.1043.

(E)-2-(but-2-en-yl)-5-(prop-1-en-2-yl)-3,4-dihydro-2H-pyran-4-ol (17). To a solution of diene **4b** (0.54 g, 2.81 mmol) in THF/MeOH (1:1, 50 mL) was added cerium chloride heptahydrate (1.15 g, 3.09 mmol). After complete dissolution of cerium salts, the solution was cooled down to -78 °C.

Sodium borohydride (0.24 g, 6.32 mmol) was then added in one portion. The resulting mixture was stirred at the same temperature for 30 min before being warmed up to -50 °C and left to warm up to -30 °C over 45 min. Solvents were evaporated under reduced pressure and the residue was dissolved in the least amount of CH₂Cl₂ possible before being filtered through a pad of Celite[®], washed with CH₂Cl₂ (3 × 100 mL), and concentrated under reduced pressure. The crude product was then purified on Combi-Flash chromatography (Petroleum Ether/EtOAc 100:0 to 95:5) to afford *the title compound 17* (0.44 g, 2.3 mmol, 81%) as a clear colourless oil. *R_f* 0.45 (Petroleum Ether/EtOAc 90:10); ν_{max} (neat)/cm⁻¹ 3401, 2922, 1724, 1630, 439; δ_{H} (300 MHz; CDCl₃) 6.68 (s, 1 H, OCH), 5.58 (q quint, *J* = 6.8 Hz, *J* = 1.2 Hz, 1 H, CH₃CH), 4.95 (m, 1 H, CHH'C), 4.87 (quint, *J* = 1.3 Hz, 1 H, CHHC), 4.66 (ddd, *J* = 7.2 Hz, *J* = 6.3 Hz, *J* = 5.8 Hz, 1 H, OCH), 4.32 (br. dd, *J* = 8.9 Hz, *J* = 3.0 Hz, 1 H, CHOH), 2.20 (ddd, *J* = 13.6 Hz, *J* = 6.3 Hz, *J* = 3.0 Hz, 1 H, CHH'CHOH), 2.08 (ddd, *J* = 13.6 Hz, *J* = 8.9 Hz, *J* = 7.2 Hz, 1 H, CHH'CHOH), 2.03 (dd, *J* = 5.8 Hz, 1 H, CHH'CHOH), 1.87 (dd, *J* = 1.3 Hz, *J* = 0.6 Hz, 3 H, CH₃), 1.67 (quint, *J* = 1.2 Hz, 3 H, CH₃), 1.64 (dq, *J* = 6.8 Hz, *J* = 1.2 Hz, 3 H, CH₃); δ_{C} (75 MHz, CDCl₃) 144 (OCH), 139.1 (CCOH), 134.2 (CH₃CCH), 121.7 (CH₃CH), 118.0 (CH₂CCH₃), 109.6 (CH₂CCH₃), 78.9 (CHOH), 62.3 (OCH), 35.3 (CH₂CHOH), 20.6 (CH₃CCH₂), 13.2 (CH₃CH), 12.3 (CH₃C); *m/z* (ESI+) [M -H]⁺ 193.1222 calcd for C₁₂H₁₇O₂ 193.1223.

((*E*)-but-2-en-2-yl)-4,11-dihydroxy-5-methyl-3,4,6,6a,12q,12b-hexahydroanthra[2,3-*h*]oxireno [1, 2-*b*]pyrene-7,12(2*H*,6*H*)-dione (19). To a solution of diene **17** (650 mg, 3.35 mmol) in CH₃CN (40 mL) was added 5-hydroxynaphthalene-1,4-dione **3** (583 mg, 3.35 mmol), the resulting mixture was stirred at 40 °C overnight. Solvent was evaporated and the residue, identified as being **18**, was dissolved in CH₂Cl₂ (80 mL) under argon atmosphere, vanadyl acetylacetonate (134 mg, 0.53 mmol) was added in one portion and the resulting mixture stirred for 45 min. A solution of *tert*-butyl hydroperoxide (5.5 M in decane, 0.92 mL, 5.25 mmol) was added dropwise *via* a syringe pump

system and the resulting mixture was stirred for 2 h at room temperature. The reaction was quenched by addition of a saturated solution of $\text{Na}_2\text{S}_2\text{O}_3$ (30 mL), extracted with CH_2Cl_2 (3×50 mL), dried over MgSO_4 and concentrated under reduced pressure. The crude product was purified on combi-flash chromatography ($\text{CHCl}_3/\text{MeOH}$ 99.8:0.2) to afford *the title compound 19* (990 mg, 2.58 mmol, 77%) as a yellow solid. R_f 0.18 ($\text{CHCl}_3/\text{MeOH}$ 99.8:0.2); Mp 139-140 °C; ν_{max} (neat)/ cm^{-1} 3510, 2993, 2822, 1701, 1631, 1578, 1455, 1245, 1162, 1075, 754; δ_{H} (300 MHz; CDCl_3) 12.09 (s, 1H, Ar-OH), 7.56 (dd, $J = 8.4$ Hz, $J = 7.6$ Hz, 1H, $\text{H}_{\text{aromatic}}$), 7.40 (dd, $J = 7.6$ Hz, $J = 1.2$ Hz, 1H, $\text{H}_{\text{aromatic}}$), 7.16 (dd, $J = 8.4$ Hz, $J = 1.2$ Hz, 1H, $\text{H}_{\text{aromatic}}$), 5.23 (br. quint, $J = 1.5$ Hz, $J = 6.8$ Hz, 1H, CH_3CHC), 4.62 (d, $J = 3.4$ Hz, 1H, OCH), 3.96 (br. t, X part of an ABXY system, $J = 6.4$ Hz, 1H, CHOH), 3.83 (br. t, Y part of an ABXY system $J = 6.4$ Hz, 1H, OCH), 3.33 (dd, $J = 3.4$ Hz, $J = 5.8$ Hz, 1H, C(O)CHCH), 3.07 (ddd, $J = 1.0$ Hz, $J = 8.0$ Hz, $J = 5.8$ Hz, 1H, C(O)CHCH_2), 2.94 and 2.11–2.01 (m and AB part of an ABXY system, $J = 16.0$ Hz, $J = 8.0$ Hz, $J = 1.0$ Hz, 4H, $\text{CHCH}_2\text{CO} + \text{CH}_2\text{CHOH}$), 1.53 (s, 3H, CCH_3), 1.45 (br. dq, $J = 1.3$ Hz, $J = 6.8$ Hz, 3H, CH_3CH), 1.18 (s, 3H, CCH_3); δ_{C} (75 MHz, CDCl_3) 204.7 (CO), 195.4 (CO), 161.5 ($\text{C}_{\text{aromatic}}$), 137.5 (C), 136.6 ($\text{C}_{\text{aromatic}}$), 134.2 ($\text{C}_{\text{aromatic}}$), 122.6 ($\text{CH}_{\text{aromatic}}$), 120.7 (CH_3CH), 119.2 ($\text{C}_{\text{aromatic}}$), 117.0 ($\text{CH}_{\text{aromatic}}$), 74.9 (OCH), 66.5 (C epoxide), 64.9 (C epoxide), 64.7 (OCH), 63.6 (CHOH), 49.1 (C(O)CH), 41.9 (C(O)CH), 33.0 (CH_2CHOH), 26.3 (CH_2CCH_3), 21.1 (CH_3CO), 13.3 (CH_3CH), 12.5 (CH_3C); m/z (ESI+) $[\text{M} + \text{Na}]^+$ 407.1452 calcd for $\text{C}_{22}\text{H}_{24}\text{O}_6\text{Na}$ 407.1465.

(E)-2-(but-2-en-2-yl)-4,11-dihydroxy-5-methyl-3,4-dihydro-2H-anthra[1,2-b]pyran-7,12-dione (20). To a solution of epoxide **19** (990 mg, 2.58 mmol) was added Et_3N (3.40 mL, 25.8 mmol) at room temperature under air atmosphere. The resulting reaction mixture was stirred for 1 h, then concentrated under reduced pressure and purified by Combi-flash chromatography ($\text{CHCl}_3/\text{MeOH}$ 99.8:0.2) to afford *the title compound 20* (845 mg, 2.32 mmol, 90%) as a yellow solid. R_f 0.22 (Petroleum ether/EtOAc 80:20); Mp 159-161 °C (dec.); ν_{max} (neat)/ cm^{-1} 3258, 2924, 1673, 1632,

1583, 1405, 1318, 1285, 1260, 1188, 1037, 875, 794, 751; δ_{H} (300 MHz; CDCl_3) 13.11 (s, 1H, Ar–OH), 7.77 (s, 1H, $\text{H}_{\text{aromatic}}$), 7.76 (dd, $J = 7.4$ Hz, $J = 1.2$ Hz, 1H, $\text{H}_{\text{aromatic}}$), 7.61 (dd, $J = 7.4$ Hz, $J = 8.2$ Hz, 1H, $\text{H}_{\text{aromatic}}$), 7.28 (dd, $J = 8.2$ Hz, $J = 1.2$ Hz, 1H, $\text{H}_{\text{aromatic}}$), 5.63 (quint, $J = 1.5$ Hz, $J = 6.7$ Hz, 1H, CH_3CH), 4.98–4.89 (m, 2 H, 2 OCH), 2.58 (s, 3H, CH_3), 2.5–2.35 (m, 2H, OCHCH_2), 1.75 (s, 3H, CH_3), 1.60 (d, $J = 6.7$ Hz, 3H, CH_3CH); δ_{C} (75 MHz, CDCl_3) 188.4 (CO), 182.9 (CO), 162.5 ($\text{C}_{\text{aromatic}}$), 156.6 ($\text{C}_{\text{aromatic}}$), 147.9 ($\text{C}_{\text{aromatic}}$), 135.7 ($\text{CH}_{\text{aromatic}}$), 134.7 ($\text{C}_{\text{aromatic}}$), 134.5 (C), 133.0 ($\text{C}_{\text{aromatic}}$), 130.6 ($\text{C}_{\text{aromatic}}$), 124.9 ($\text{CH}_{\text{aromatic}}$), 122.0 ($\text{CH}_{\text{aromatic}}$), 120.8 (CHCH_3), 119.0 ($\text{CH}_{\text{aromatic}}$), 118.4 ($\text{C}_{\text{aromatic}}$), 117.1 ($\text{C}_{\text{aromatic}}$), 77.9 (OCH), 62.3 ($\text{CH}(\text{OH})$), 34.3 (CH_2CHOH), 20.6 (Ar– CH_3), 13.6 (CCH_3), 13.3 (CHCH_3); m/z (ESI+) $[\text{M} + \text{Na}]^+$ 387.1208 calcd for $\text{C}_{22}\text{H}_{20}\text{O}_5\text{Na}$ 387.1208.

(*E*)-2-(but-2-en-2-yl)-11-hydroxy-5-methyl-3,4-dihydro-2*H*-anthra[1,2-*b*]pyran-4,7,12-

trione (21). To a solution of benzylic alcohol **20** (500 mg, 1.37 mmol) in a mixture $\text{CH}_2\text{Cl}_2/\text{DMSO}$ (4:2, 6 mL) was added Dess-Martin Periodinane (1.16 g, 2.74 mmol) at room temperature. The resulting mixture was stirred for 2 h, then quenched by addition of a saturated solution of $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL) and a saturated solution of NaHCO_3 (10 mL) and extracted with CH_2Cl_2 until the organic phase became colourless. The combined organic layers were concentrated under reduced pressure, dissolved in EtOAc and washed with cold brine. After having been dried over MgSO_4 , the crude mixture was concentrated and purified on Combi-flash chromatography ($\text{CHCl}_3/\text{MeOH}$ 99.8:0.2) to afford the title compound **21** (447 mg, 1.23 mmol, 88%) as a yellow solid. R_f 0.18 (Petroleum ether/EtOAc 90:10); Mp 204-205°C ; ν_{max} (neat)/ cm^{-1} 3367, 2919, 1676, 1631, 1579, 1550, 1476; δ_{H} (300 MHz; CDCl_3) 13.01 (s, 1H, Ar–OH), 7.79 (dd, $J = 7.4$ Hz, $J = 1.2$ Hz, 1H, $\text{H}_{\text{aromatic}}$), 7.67 (s, 1H, $\text{H}_{\text{aromatic}}$), 7.55 (dd, $J = 7.4$ Hz, $J = 8.4$ Hz, 1H, $\text{H}_{\text{aromatic}}$), 7.23 (dd, $J = 8.4$ Hz, $J = 1.2$ Hz, 1H, $\text{H}_{\text{aromatic}}$), 5.76 (quint, $J = 1.0$ Hz, $J = 6.7$ Hz, 1H, CH_3CH), 4.91 (br. d, X part of an ABX system, $J = 12.5$ Hz, $J = 3.0$ Hz, 1H, 2 OCHCH_2), 2.96 and 2.80 (AB part of an ABX

system, $J = 12.5$ Hz, $J = 3.0$ Hz, 1H, 2 OCHCH₂), 2.73 (s, 3H, Ar-CH₃), 1.81 (br. quint, $J = 1.0$ Hz, 3H, CH₃CH), 1.67 (dq, $J = 6.7$ Hz, $J = 1.0$ Hz, 3H, CCH₃); δ_C (75 MHz, CDCl₃) 193.3 (CO), 187.7 (CO), 182.5 (CO), 163.6 (C_{aromatic}), 162.6 (C_{aromatic}), 150.0 (C_{aromatic}), 137.4 (C_{aromatic}), 136.0 (CH_{aromatic}), 132.6 (C_{aromatic}), 132.4 (C), 125.3 (CH_{aromatic}), 124.3 (C_{aromatic}), 124.0 (CHCH₃), 123.1 (CH_{aromatic}), 119.7 (C_{aromatic}), 119.1 (CH_{aromatic}), 82.3 (OCH), 42.6 (CH₂), 24.1 (Ar-CH₃), 13.6 (CHCH₃), 12.7 (CCH₃); m/z (ESI+) [M - H]⁺ 361.1078 calcd for C₂₂H₁₇O₅ 361.1076.

(E)-2-(but-2-en-2-yl)-11-hydroxy-5-methyl-4H-anthra[1,2-b]pyran-4,7,12-trione (2).

To a solution of saturated ketone **21** (40 mg, 0.11 mmol) in DMSO (5 mL) under argon atmosphere, iodine (12 mg, 50 μ mol) was added in one portion and the mixture was stirred overnight at 95 °C. Then, the reaction was quenched by addition of brine (30 mL), extracted with CH₂Cl₂ (3 \times 30 mL) and the combined organic layers were washed with a saturated solution of Na₂S₂O₃ (40 mL) and brine (40 mL) before being dried over MgSO₄, and concentrated under reduced pressure. The crude product was purified by Combi-Flash chromatography (Petroleum Ether/EtOAc from 90:10 to 80:20) to afford kidamycinone **2** (27 mg, 80 μ mol, 68%) as a yellow solid. All spectroscopic data for **2** are identical in all respects with those described in literature.¹¹ R_f 0.14 (Petroleum ether/EtOAc 85:15); Mp 255-256 °C ν_{\max} (neat)/cm⁻¹ 3070, 2961, 2851, 1670, 1628, 1457, 1316, 1259, 1078, 1014, 839, 790; δ_H (300 MHz; CDCl₃) 12.89 (s, 1H, Ar-OH), 7.99 (d, $J = 0.7$ Hz, 1H, H_{aromatic}), 7.79 (dd, $J = 7.5$ Hz, $J = 1.3$ Hz, 1H, H_{aromatic}), 7.66 (dd, $J = 7.5$ Hz, $J = 8.2$ Hz, 1H, H_{aromatic}), 7.46 (qq, $J = 1.0$ Hz, $J = 7.1$ Hz, 1H, CHCH₃), 7.33 (dd, $J = 8.2$ Hz, $J = 1.3$ Hz, 1H, H_{aromatic}), 6.35 (s, 1H, (O)CH), 2.99 (d, $J = 0.7$ Hz, 3H, Ar-CH₃), 2.02 (qd, $J = 7.1$ Hz, 3H, CHCH₃), 1.99-1.91 (m, 3H, CCH₃); δ_C (75 MHz, CDCl₃) 187.5 (CO), 182.0 (CO), 179.8 (CO), 164.2 (C_{aromatic}), 162.7 (C_{aromatic}), 156.3 (C_{aromatic}), 150.0 (C), 136.5 (C_{aromatic}), 136.1 (CH_{aromatic}), 134.6 (CHCH₃), 132.4 (C_{aromatic}), 127.4 (CCH₃), 126.5 (C_{aromatic}), 125.6 (CH_{aromatic}), 125.4 (CH_{aromatic}), 119.7 (C_{aromatic}), 119.5 (CH_{aromatic}),

116.9 (C_{aromatic}), 108.9 ($O\text{CCH}$), 24.3 ($\text{Ar}-\text{CH}_3$), 15.2 (CHCH_3), 12.3 (CCH_3); m/z (ESI+) $[\text{M} + \text{H}]^+$
361.1068 calcd for $\text{C}_{22}\text{H}_{17}\text{O}_5$ 361.1076.

1,8-dihydroxy-3-methyl-2-((2E,4E)-4-methylhexa-2,4-dienoyl)anthracen-9,10-dione (22). To a solution of ketone **21** (100 mg, 0.27 mmol) in a mixture 1,4-dioxane/DMSO/phosphate buffer pH=7 (3:1:1, 5 mL) was added DDQ (313 mg, 1.38 mmol) under argon atmosphere. The resulting mixture was heated up to 40 °C and stirred for 18 h. Then, the reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography ($\text{CHCl}_3/\text{MeOH}$ 99.8:0.2) to afford *the title compound 22* (58mg, 0.16 mmol, 60%) as an orange powder. R_f 0.21 ($\text{CHCl}_3/\text{MeOH}$ 99.9:0.1); Mp 160-162 °C (dec.); ν_{max} (neat)/ cm^{-1} 3045, 2923, 1723, 1670, 1620, 1577, 1449, 1262, 753, 730; δ_{H} (300 MHz; CDCl_3) 12.23 (s, 1H, Ar-OH), 12.01 (s, 1H, Ar-OH), 7.84 (dd, $J = 7.5$ Hz, $J = 1.1$ Hz, 1H, $\text{H}_{\text{aromatic}}$), 7.71 (s, 1H, $\text{H}_{\text{aromatic}}$), 7.70 (dd, $J = 7.5$ Hz, $J = 8.4$ Hz, 1H, $\text{H}_{\text{aromatic}}$), 7.31 (dd, $J = 8.4$ Hz, $J = 1.1$ Hz, 1H, $\text{H}_{\text{aromatic}}$), 6.97 (d, $J = 15.9$ Hz, 1H, $\text{CHCHC}(\text{O})$), 6.40 (d, $J = 15.9$ Hz, 1H, $\text{CHCHC}(\text{O})$), 6.00 (qd, $J = 7.1$ Hz, $J = 1.0$ Hz, 1H, CH_3CH), 2.35 (s, 3H, Ar- CH_3), 1.85 (br. quint, $J = 1.0$ Hz, 3H, CH_3C), 1.82 (br. d, $J = 7.1$ Hz, 3H, CH_3CH); δ_{C} (75 MHz, CDCl_3) 195.6 (CO), 192.7 (CO), 181.7(CO), 162.8 (C_{aromatic}), 159.6 (C_{aromatic}), 152.3 (CHCHC), 146.4 ($\text{C}_{\text{aromatic}}\text{CH}_3$), 139.8 (CHCH_3), 137.4 ($\text{CH}_{\text{aromatic}}$), 135.6 (C_{aromatic}), 134.6 (CCH_3), 133.7 (C_{aromatic}), 133.2 (C_{aromatic}), 125.3 ($\text{C}(\text{O})\text{CHCH}$), 125.0 ($\text{CH}_{\text{aromatic}}$), 122.1 ($\text{CH}_{\text{aromatic}}$), 120.3 ($\text{CH}_{\text{aromatic}}$), 116.0 (C_{aromatic}), 114.2 (C_{aromatic}), 20.3 (Ar- CH_3), 15.0 (CHCH_3), 12.0 (CCH_3); m/z (ESI+) $[\text{M}+\text{H}]^+$ 363.1230 calcd for $\text{C}_{22}\text{H}_{19}\text{O}_5$ 363.1232 .

Associated content

Supporting information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Crystal data for **19** (CIF)

IRC animation (MPG)

^1H and ^{13}C NMR spectra for products **1**, **2**, **4b**, **5-7**, **9**, **11**, **12**, **14-17**, **19-22**.

Acknowledgments

The authors would like to thank ANR for financial support (ANR-14-CE06-0008-01).

References and notes

- (1) Maeda, K.; Takeuchi, T.; Nitta, K.; Yagishita, K.; Utahara, R.; Osato, T.; Ueda, M.; Kondo, S.; Okami, Y.; Umezawa, H. *J. Antibiot.* **1956**, *9*, 75.
- (2) Kanda, N.; Kono, M.; Asano, K. *J. Antibiot.* **1972**, *25*, 553.
- (3) Tu, L. C.; Melendy, T.; Beerman, T. A. *Mol. Cancer Ther.* **2004**, *3*, 577.
- (4) Hansen, M. R.; Hurley, L. H. *Acc. Chem. Res.* **1996**, *29*, 249.
- (5) Séquin, U. In *Fortschritte der Chemie organischer Naturstoffe / Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Tamm, C., Eds.; Springer Vienna: 1986; Vol. 50, p 57.
- (6) Furukawa, M.; Hayakawa, I.; Ohta, G.; Iitaka, Y. *Tetrahedron* **1975**, *31*, 2989.
- (7) Nishikawa, T.; Adachi, M.; Isobe, M. In *Glycoscience*; Fraser-Reid, B., Tatsuta, K., Thiem, J., Eds.; Springer Berlin Heidelberg: 2008, p 755.
- (8) Fredenhagen, A.; Séquin, U. *Helv. Chim. Acta* **1985**, *68*, 391.
- (9) Bililign, T.; Hyun, C.-G.; Williams, J. S.; Czisny, A. M.; Thorson, J. S. *Chem. Biol.* **2004**, *11*, 959.
- (10) Hauser, F. M.; Rhee, R. P. *J. Am. Chem. Soc.* **1979**, *101*, 1628.
- (11) Fei, Z.; McDonald, F. E. *Org. Lett.* **2005**, *7*, 3617.
- (12) a) Krohn, K.; Tran-Thien, H. T.; Vitz, J.; Vidal, A. *Eur. J. Org. Chem.* **2007**, 1905. b) Krohn, K.; Tran-Thien, H. T.; Ahmed I. *Eur. J. Org. Chem.* **2011**, 2223.

- (13) Hsu, D.-S.; Matsumoto, T.; Suzuki, K. *Chem. Lett.* **2006**, 35, 1016.
- (14) Tietze, L. F.; Singidi, R. R.; Gericke, K. M. *Org. Lett.* **2006**, 8, 5873.
- (15) Pantin, M.; Zon, D.; Vomiandry, R.; Foulgoc, L.; Sissouma, D.; Guingant, A.; Collet, S. *Tetrahedron Lett.* **2015**, 56, 2110.
- (16) Fei, Z.; McDonald, F. E. *Org. Lett.* **2007**, 9, 3547.
- (17) O'Keefe, B. M.; Mans, D. M.; Kaelin, D. E.; Martin, S. F. *J. Am. Chem. Soc.* **2010**, 132, 15528.
- (18) O'Keefe, B. M.; Mans, D. M.; Kaelin, D. E.; Martin, S. F. *Tetrahedron* **2011**, 67, 6524.
- (19) Hartung, J.; J. D. Wright, B.; Danishefsky, S. J. *Chem. Eur. J.* **2014**, 20, 8731.
- (20) a) Shigeta, M.; Hakamata, T.; Watanabe, Y.; Kitamura, K.; Ando, Y.; Suzuki, K.; Matsumoto, T. *Synlett*, **2010**, 2654. b) Kitamura, K.; Ando, Y.; Matsumoto, T.; Suzuki, K. *Angew. Chem. Int. Ed.* **2014**, 53, 1258. c) Kitamura, K.; Maezawa, Y.; Ando, Y.; Kusumi, T.; Matsumoto, T.; Suzuki, K. *Angew. Chem. Int. Ed.* **2014**, 53, 1262.
- (21) Kitamura, K.; Ando, Y.; Maezawa, Y.; Matsumoto, T.; Suzuki, K. *Heterocycles* **2015**, 90, 1240.
- (22) Chin, Y.-J.; Wang, S.-Y.; Loh, T.-P. *Org. Lett.* **2009**, 11, 3674.
- (23) Widmer, U. *Synthesis* **1987**, 568.
- (24) a) Danishefsky, S. J.; Larson, E.; Askin, D.; Kato, N. *J. Am. Chem. Soc.* **1985**, 107, 1246. b) Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F.; Maring, C. J.; Springer, J. P. *J. Am. Chem. Soc.* **1985**, 107, 1256.
- (25) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W.; Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron Lett.* **1992**, 33, 917.
- (26) Seyferth, D.; Stone, F. G. A. *J. Am. Chem. Soc.* **1957**, 79, 515.
- (27) Fuwa, H.; Ebine, M.; Bourdelais, A. J.; Baden, D. G.; Sasaki, M. *J. Am. Chem. Soc.* **2006**, 128, 16989.

- (28) a) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905. b) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748.
- (29) Barcelos, R. C.; Pastre, J. C.; Caixeta, V. ; Vendramini-Costa, D. B. ; De Carvalho, J. E. ; Pilli, R. A. *Bioorg. Med. Chem.* **2012**, *20*, 3635.
- (30) Foulgoc, L.; Sissouma, D.; Evain, M.; Collet, S.; Guingant, A. *Synlett* **2012**, *23*, 768.
- (31) Danishefsky, S. J.; Bednarski, M. *Tetrahedron Lett.* **1985**, *26*, 3411.
- (32) Boeckman, R. K.; Dolak, T. M. ; Culos, K. O. *J. Am. Chem. Soc.* **1978**, *100*, 7098.
- (33) Corey, E.; Suggs, W. *Tetrahedron Lett.* **1975**, *16*, 2647.
- (34) Patonay, T.; Cavaleiro, J.; Lévai, A.; Silva, A. *Heterocycl. Commun.* **1997**, *3*, 223.
- (35) For selected examples of benzylethers cleavage with DDQ, see : a) Oikawa, Y. Horita, K. , Yonemitsu, O. *Tetrahedron Lett.* **1985**, *26*, 1541. b) Sviridov, A. F. ; Ermolenko, M. S. ; Yashunsky, D. V. ; Borodkin, V. S. ; Kotchetkov, N. K. *Tetrahedron Lett.* **1987**, *28*, 3839. c) Vedejs, E. ; Buchanan, R. A. ; Watanabe, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8430.
- (36) Murakate, H. ; Natsume, M. *Tetrahedron*, **2006**, *62*, 7071.
- (37) Doi, T. ; Fuse, S. ; Miyamoto, S. ; Nakai, K. ; Sasuga, D. ; Takahashi, T. *Chem. Asian J.* **2006**, *1*, 370.
- (38) CCDC 1527990 (**19**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
- (39) Frisch, M. J. et al. Gaussian 09, Revision A.02; Gaussian, Inc.:Wallingford, CT, 2009.
- (40) a) Fatiadi, A. J. *Synthesis* **1976**, *65*. b) Wu, D. ; Shea, D. F. *Org Lett.* **2013**, *15*, 3392.
- (41) Ley, S.V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

- (42) De Mico, A. ; Margarita, R. ; Parlanti, L. ; Vescovi, A. ; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974.
- (43) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
- (44) Beekman, A. M.; Martinez, E. C.; Barrow, R. A. *Org. Biomol. Chem.* **2013**, *11*, 1109 and cited literature.
- (45) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
- (46) Chorley, D. F.; Furkert, D. E.; Brimble, M. A. *Eur. J. Org. Chem.* **2016**, 314.
- (47) Schumacher, R. W.; Davidson, B. S. ; Montenegro, D. A.; Bernan, V. S. *J. Nat. Prod.* **1995**, *58*, 613.