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A New Route to γ-Arylidenebutyrolactones via a tandem carbopalladation-heterocyclisation sequence : a formal synthesis of U-68,215.

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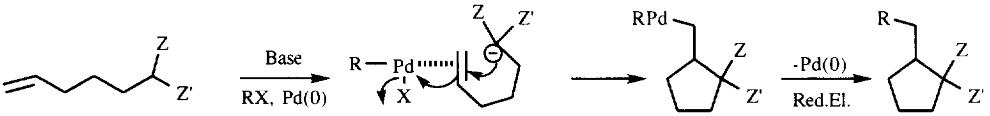
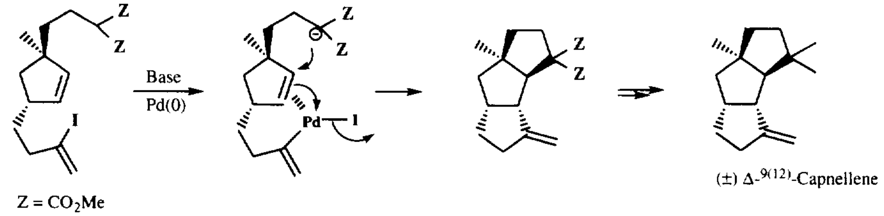
Abstract : Benzo-annulated enol lactones are obtained in good yields from pentynoic acids 3- or 5-substituted with an iodo-aryl moiety by palladium-catalyzed cyclization of their potassium carboxylates. Using this approach, an efficient new route to U-68,215 is described.

In 1989, we reported[1] the first example of an intramolecular nucleophilic attack on an unsaturation electrophilically activated by the σ-aryl or σ-vinylpalladium complexes generated *in situ* . In the last step, a reductive elimination gives the cyclic derivative and regenerates the palladium (0) catalyst (Scheme 1).



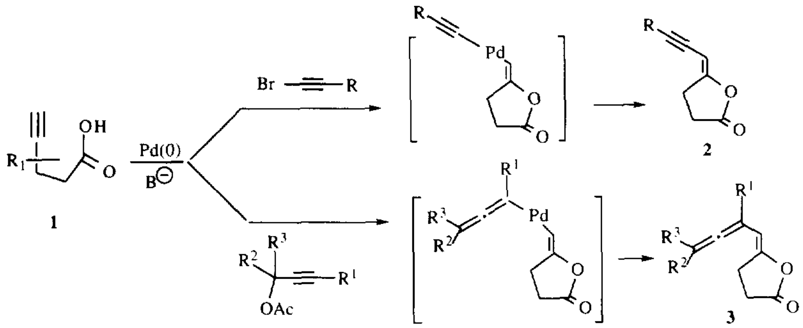
Scheme 1

More recently [2], we presented the intramolecular version of this strategy that led to the synthesis of the triquinane terpenoid (±)$\Delta^{(9,12)}$ capnellene **via a novel tandem carbopalladation-cyclisation sequence** (Scheme 2).



Scheme 2

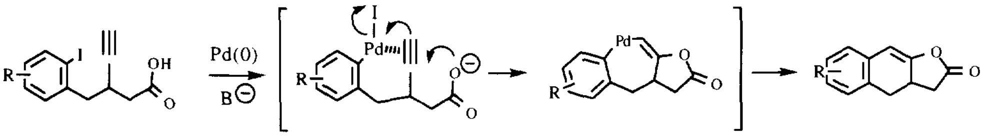
This cyclisation catalysed by an organopalladium species was then applied by us and other groups to alkynes bearing carbon[3], oxygen[4] and nitrogen[5] nucleophiles to give stereodefined exocyclic compounds. In this area, we recently reported that biologically active ynenol[6] and allenenollactone[7] **2** and **3** are easily and stereoselectively obtained by reaction of γ-acetylenic carboxylates with 1-bromo 1-alkynes or propargylacetates (Scheme 3).



Scheme 3

Simultaneously, Cacchi's group[8] reported the acyloxypalladation of 4-alkynoic acids with σ-aryl and σ-alkenyl palladium species to produce γ-alkylidenebutyrolactones.

As part of our ongoing studies on the construction of tricyclic system[2], we report here a concise synthesis of alkylidenebutyrolactone using a **novel tandem carbopalladation heterocyclisation process**[9] (Scheme 4). These compounds are of interest as synthetic intermediates[10].



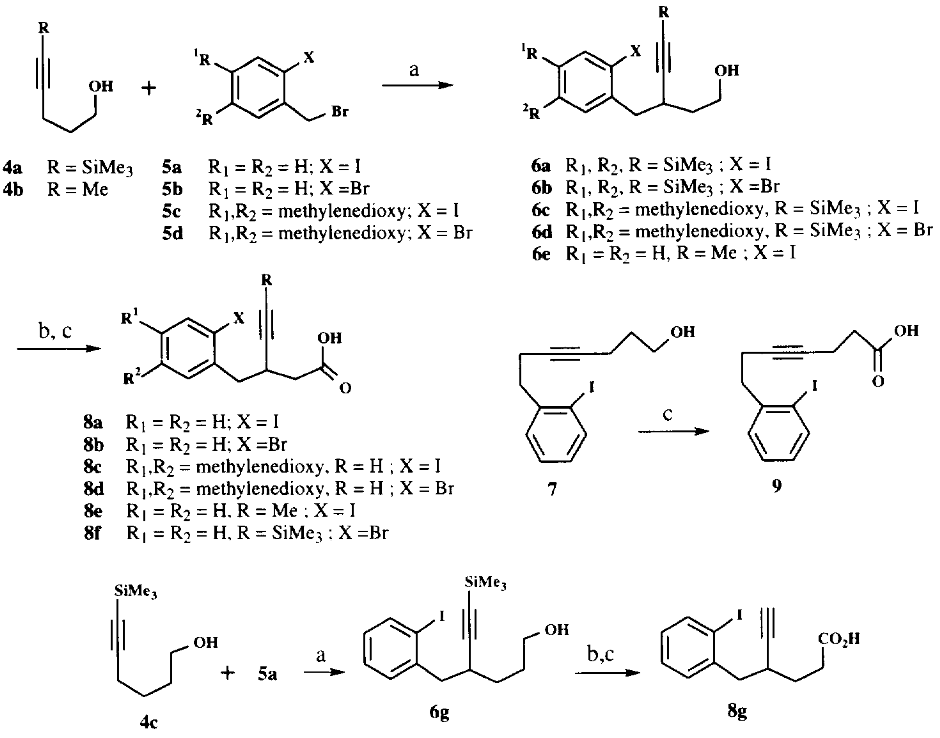
Scheme 4

Preparation and cyclisation of aryl pentynoic and hexynoic derivatives.

Scheme 5 summarizes the preparation of pentynoic and hexynoic acids that we used in this study.

The dimetallation of 5-trimethylsilyl-4-pentyn-1-ol **4a** with butyllithium (1 equiv.) t-butyllithium (1 equiv.) in presence of TMEDA (2 equiv.) followed by the introduction of 1 equivalent of **5a-d** led to the corresponding alkynols of type **6**. When the same dimetallation was effected on hex-4-yn-1-ol **4b** followed by addition of **5a**, we obtained a mixture of **6e** and **7** in a 1/1 ratio, both compounds being separated by flash chromatography. Where necessary, subsequent desilylation of alkynols **6** with KF, H_2O followed by oxydation with Jones reagent provided the acids **8a-f** and **9**.

The same three step sequence a→c was applied to 6-trimethylsilyl-5-hexyn-6-ol **4c** and 2 iodo benzylbromide **5a** to afford hexynoic acid **8g**.



4a R = $SiMe_3$
4b R = Me

5a $R_1 = R_2 = H$; X = I
5b $R_1 = R_2 = H$; X =Br
5c R_1,R_2 = methylenedioxy; X = I
5d R_1,R_2 = methylenedioxy; X = Br

6a R_1, R_2, R = $SiMe_3$; X = I
6b R_1, R_2, R = $SiMe_3$; X =Br
6c R_1,R_2 = methylenedioxy, R = $SiMe_3$; X = I
6d R_1,R_2 = methylenedioxy, R = $SiMe_3$; X = Br
6e $R_1 = R_2$ = H, R = Me ; X = I

8a $R_1 = R_2 = H$; X = I
8b $R_1 = R_2 = H$; X =Br
8c R_1,R_2 = methylenedioxy, R = H ; X = I
8d R_1,R_2 = methylenedioxy, R = H ; X = Br
8e $R_1 = R_2$ = H, R = Me ; X = I
8f $R_1 = R_2$ = H, R = $SiMe_3$; X =Br

a) 1eq BuLi, 1eq tBuLi, TMEDA, 5a,5b,5c,5d ; b) when 4a and 4c is used : KF, H_2O, DMF ; c) Jones reagent

Scheme 5

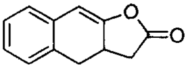
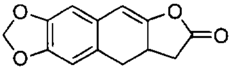
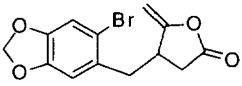
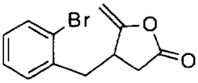
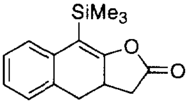
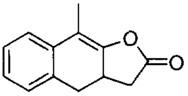
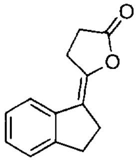
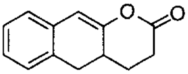
In the first attempt, the derivative **8a** underwent palladium catalyzed cyclisation under the conditions previously described by our group for the transformation **1**→**2** (entry 1). Thus, when treated with a catalytic amount of palladium acetate (5 mol %) and tri(2-furyl)phosphine (10 mol %) in DMSO, (room temperature, 30 min) in the presence of t-BuOK as base, a rapid and clean reaction occurred leading to **10a** as a single product in 78% yield (conditions A). Substitution of tBuOK for KF[11] afforded exclusively **10a** in 60% yield (conditions B).

Replacement of tri(2-furyl)phosphine by triphenylphosphine resulted in a very low conversion to **10a**.

The use of phase transfer catalysis[12] was also investigated. It was found that with the use of palladium acetate (5 mol %), triphenylphosphine (10 mol %) and benzyltriethyl ammonium chloride (TEBA) in DMSO in the presence of Et_3N as base (conditions C), the reaction could be carried out at room temperature but with significant decrease in chemical yield (entry 4).

Using conditions A, the aryl iodide **8c** cyclised to **10b** (50%) within 30 min at room temperature (entry 5). We were surprised by the results of the cyclisation experiments with the corresponding arylbromide **8d**. Under conditions A, **8d** gave essentially the same result as for **8c** (entry 6). In contrast, under conditions C, **8d** produced only trace amounts of the bis annulation product **10b** along with the product **11a** (47%) resulting from the direct cyclisation of the acid on the triple bond (entry 7).By switching

Table I : Palladium catalyzed cyclization of substituted pentynoic acids^a

entry	pentynoic acid	reaction conditions ^{b}	catalyst	reaction time (h)	product	yield (%)^c
1	**8a**	A	TFP^f	0.5	 **10a**	78
2	**8a**	A	PPh_3			traces^e
3	**8a**	B	TFP	0.5		60
4	**8a**	C	PPh_3			60
5	**8c**	A	TFP	0.5	 **10b**	50
6	**8d**	A	TFP	1		50
7	**8d**	C	TFP	24^g	 **11a**	47
8	**8d**	C	PPh_3	24^g		27
9		A^d	TFP	6		8
10	**8b**	A	TFP	24	**10a** +  **11b**	59 10a/11b (1/3)
11	**8f**	A	TFP	0.5	**10a** +  **10 c**	(10a/10c) 65 (50/50)
12	**8f**	B	TFP	0.5		64 (0/100)
13	**8e**	A	TFP	1	 **10d**	70
14	**9**	A	TFP	1	 **12**	77
15	**9**	B	TFP	1		64
16	**8g**	A	TFP	24^g		no reaction
17	**8g**	B	TFP	24^g		

a) Unless otherwise stated the reactions were carried out at room temperature ; b) Conditions A : $Pd(OAc)_2$ (5 mol %) and ligand (10 mol %) in the presence of tBuOK as base (1.1 eq) Conditions B : $Pd(OAc)_2$ (5 mol %) and ligand (10 mol %) in the presence of KF as base (1.1 eq) Conditions C : $Pd(OAc)_2$ (5 mol %) and PPh_3 (10 mol %) benzyltriethylammonium chloride (1.1 eq) in presence of Et_3N as base (1 eq.) ;
c) isolated yields ; d) Reaction carried out in presence of K_2CO_3 (eq.) as base ; e) Starting **8a** was recovered in this experiment in 80% yield ; f) TFP tri-2-(furyl)phosphine ; g) reaction was carried out at 50 °C.

to a catalyst derived from palladium acetate (5 mol %) and PPh_3 (10 mol %) **11a** was obtained in only 27% yield (entry 8). When the reaction was performed under conditions A in presence of K_2CO_3 as base in place of tBuOK, only a moderate conversion of the starting material was observed and compound **10b** was formed in only 8% yield (entry 9). The mechanism of formation of **11a** is unclear but this compound is not an intermediate in the formation of **10b** since **11a** is unchanged when treated under conditions A. To investigate the role played by the halide, the bromoderivative **8b**, homologue of **8a**,was synthesised and subjected to conditions A. The corresponding bis-annulated product **10a** was isolated in only 15% yield after one day at room temperature. Direct cyclisation of the carboxylate on the triple bond was again found to be faster than the palladium catalyzed bis cyclisation reaction as the lactone **11b** was isolated in 44 % yield (entry 10).

This difference in reactivity between the aryliodide **8a** and the corresponding bromide **8b** is not understandable since, on the basis of our earlier results obtained in the palladium catalyzed cyclisation of unsaturated malonates[13], we observed that the reactivity of an aryl iodide is only slightly higher than that of the corresponding bromide. The present study shows that a generalisation is not possible and that the difference in reactivity between both types of halide is dependent upon the nature of the unsaturation (double and triple bond)and on the nature of the nucleophile.

We then hoped to apply this bis-cyclisation reaction to the silylated pentynoic acid **8f** expecting the formation of the vinylsilane enol lactone **10c**.

In our earlier work with silyl acetylenic derivatives[3a], we found that such a group is often labile towards palladium mediated reactions under basic conditions and this was also observed in the present case when we used potassium t-butoxyde as base (conditions A). Under these conditions, **8f** was converted into a mixture of **10a** and the desired silylated product **10c** in a 1:1 ratio (entry 11). However, the reaction is remarkably clean with KF as base and the expected product **10c** was isolated in 64% yield (conditions B). (entry 12).

The present reaction was also applicable to the disubstituted alkyne **8e** and gave the corresponding enol lactone **10d** in 70% yield (condition A) (entry 13).

Next, we investigated the extent of this new palladium tandem heterocyclisation towards the synthesis of the benzoannulated enol lactone **12** from the linear pentynoic acid **9**. When the reaction was carried out using conditions A, bis cyclization took place to give **12** in 77% yield (entry 14). Using KF as base, the yield was 64% (condition B). The enol butyrolactone was identified by its characteristic IR absorbances at 1800 cm^{-1} and 1680 cm^{-1} which are consistent with reported frequencies for five membered exocyclic enol lactone carbonyls [14] and with frequencies for **10a**, **10b** and **10d.**

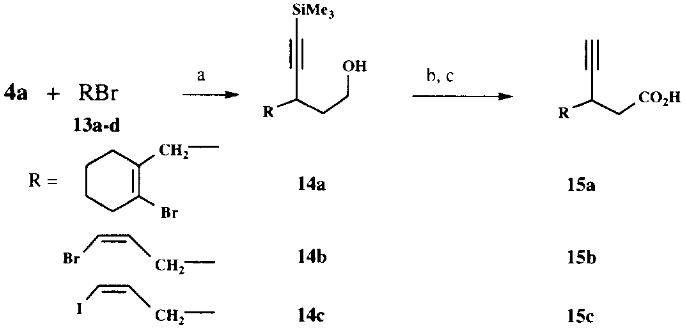
These indan enol lactones of type **12** are of great interest because they are easily transformed into spiro cyclic diketones via DiBAl reduction followed by an in situ aldol condensation and subsequent oxidation[15]. Consequently, they may be used for the construction of the BCD ring system of Fredericamycin A, a potent quinone antitumour antibiotic[16,17].

Some unsuccessful attempts in the cyclisation of vinylpentynoic and of aryl hexenoic derivatives

Attempts were made to extend the reaction to the synthesis of unsaturated valerolactones. Unfortunately, unsatisfactory results were obtained. Indeed, reaction of hexynoic acid **8g** using conditions A or B did not give any cyclised coupling product. The starting material was recovered, and no improvement was observed with an increase in reaction temperature.

Vinyl pentynoic derivatives.

The use of vinyl halides as precursors of organopalladium intermediates has been briefly investigated. We initially examined the issue of the palladium-catalysed cyclisation with the readily available vinylbromides **13a** and **13b**. Thus, alkylation of the dimetallated alkynol **4a** by the known 1-bromo-2-bromomethylcyclohexene **13a**[18] and (Z)-1,3-dibromoprop-1-ene **13b**[19] led respectively to alcohols **14a** and **14b** which were converted to acids **15a** and **15b** by a two step process as shown in scheme 6.



Scheme 6

However, the results of the reaction of **15a** and **15b** under the conditions used for conversion of **8a**→**10a** were disappointing. Only a moderate transformation of the starting material was observed and in all cases (conditions A, C) undesired compounds **11c** or **11d**, were obtained accompanied by traces of the expected lactones **16** and **17** (table II). **11c**-**11d** were again the result of direct cyclisation of the carboxylate on the triple bond.

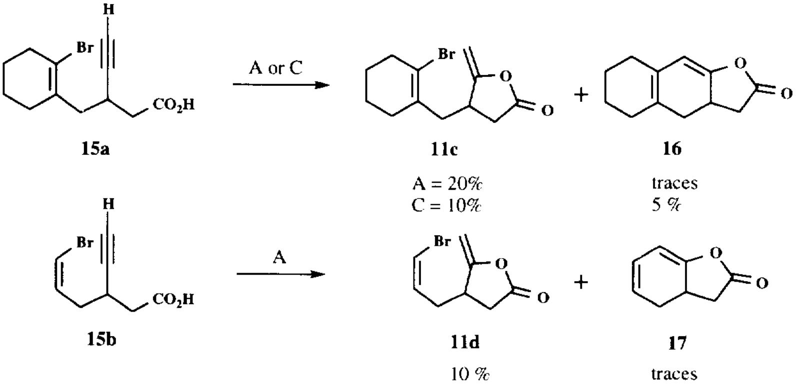
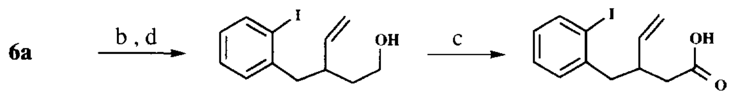


Table II

In order to avoid this competing reaction, we tried to synthesise the more reactive vinyl iodide derivative **15c**. However, when the alkynol **4a** was dimetalated and treated by the known (Z)-1-iodo-3-bromo-prop-1-ene **13c**[20] under the conditions used for the preparation of alcohols **15a-b**, the starting dihalide **13c** was consumed but the formation of the expected adduct **15c** was never observed. In all trials, the starting alcohol **4a** was recovered accompanied by many polymers which may result from elimination of HI from the sensitive substrate **13d** in basic medium. In order to suppress the competitive presumed elimination we decided to synthesise the unknown 1-iodo-2-bromomethylcyclohexene **13b**, homologue of **13a**, but all efforts towards this goal were fruitless. As a consequence the study of the reactivity of vinyl halides in this tandem carbopalladation-heterocyclisation was abandoned.

aryl hexenoic derivative

Although there are a number of examples of the intramolecular acyloxypalladation by means of Pd^{II} salts [21] of alkenoic acids to give unsaturated lactones, there are no examples of an intramolecular nucleophilic attack of a carboxylate anion on a double bond activated by an organopalladium species [22]. The pentenoic acid **19** was readily synthesised in a three step process from **6a** as shown in scheme 7.

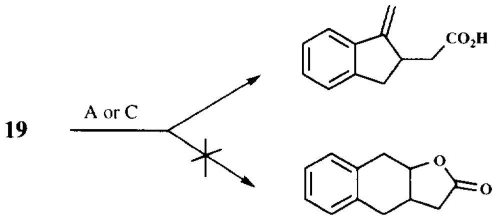


18 **19**

b) KF, H_2O, DMF ; d) H_2, Pd / $BaSO_4$; c) Jones reagent

Scheme 7

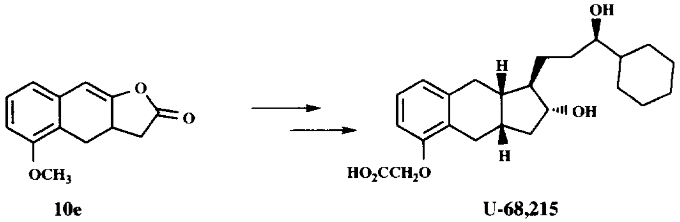
Under the standard reaction conditions (A or C) **19** gave only the product of the addition of phenylpalladium iodide to the olefin (classical Heck reaction) without the formation of the desired tricyclic butyrolactone (scheme 8).



Scheme 8

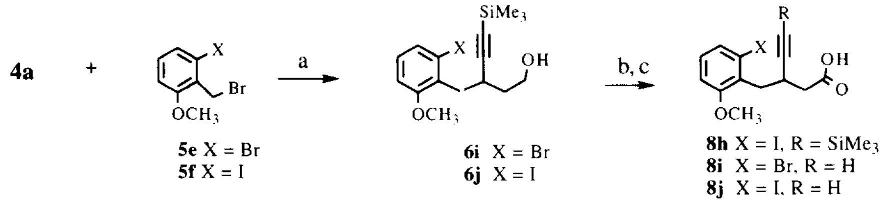
An application of the tandem-carbopalladation-cyclisation sequence of arylpentynoic acids : formal synthesis of anti-ulcer agent U-68,215

The palladium catalysed bis cyclisation reaction presented herein constitutes a novel route to the interesting class of γ-arylidenebutyrolactones. Now, as an application of this methodology, we describe a synthesis of the enol lactone **10e**, an advanced intermediate in the synthesis of a potent anti-ulcer agent U-68,215.[23] (scheme 9)



Scheme 9

For comparative purposes, we decided to prepare the two acyclic precursors **8i** and **8j** which differ by the nature of the halide. These two compounds were synthesised from alcohol **4a** and the appropriate aryl dihalides **5e** or **5f** as previously described for the synthesis of compounds **8a-d.** (scheme 10)



a) 1eq BuLi, 1eq tBuLi, TMEDA ; b) if necessary KF, H_2O, DMF ; c) Jones reagent

Scheme 10

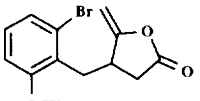
3-bromo-2-bromomethyl anisole **5e** was readily obtained from 2-methyl cyclohexane-1,3-dione according to Ganem's method[24] whereas 3-iodo-2-bromomethyl anisole **5f** was obtained by N-bromosuccinimide bromination of the known 2-iodo-6-methoxy toluene [25].

The cyclisation of the two acyclic precursors **8i** and **8j** was then investigated. Attempts to cyclise **8i** under conditions A or B failed to produce bis annulation product **10e**; only compound **11f** resulting from the direct cyclisation of the carboxylate on the triple bond was isolated in low yields.

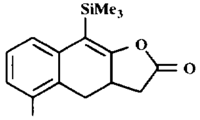
However, under the same conditions A or B the more reactive iodo compound **8j** gave the expected enol lactone **10e** respectively in 60 and 68 % yield, after purification by flash column chromatography. This compound has previously been converted to anti-ulcer U-68,215 by Aristoff's group [23].

This study demonstrates again the importance of the nature of the aryl halide in this tandem carbopalladation-cyclisation reaction.

We also cyclised the silylated derivative **8h** using conditions C and obtained the enol lactone **10f** in 73% yield. The desilylation of this compound could provide an alternative for the preparation of **10e**.



11f



10 f

In conclusion, the palladium-catalysed bis-cyclisation reaction presented herein constitutes a novel route to γ-arylidenebutyrolactones. Using this approach, an efficient new route to U-68,215 is described.

This new reaction is dependant upon the nature of the reactant since when aryl iodides are used as precursors of arylpalladium complexes, the expected bis-annulated products are efficiently synthesised in excellent yields, whereas the use of arylbromides or vinylbromides affords mixtures of two compounds resulting from mono and bis cyclisation reaction.

We are currently investigating an extension of this work for the preparation of more complex systems and natural product syntheses[17].

Acknowledgment: M.C. thanks the EC for the award of a postdoctoral fellowship under the framework of the Human Capital and Mobility Initiative.

EXPERIMENTAL

General methods. All reactions were carried out under a positive pressure of dry N_2 using freshly distilled solvents under anhydrous conditions. Reagents and solvents were handled by using standard syringe techniques. THF was distilled from sodium and benzophenone ; DMSO was distilled from calcium hydride. All other solvents were reagent grade commercial. Butyllithium (solution in hexane) was purchased from Acros and t-butyllithium (solution in pentane) from Aldrich. Flash chromatography was performed using Merck 200-400 mesh silica gel according to Still procedure. Infrared spectra were obtained on a Perkin-Elmer 337 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 200 instrument using $CDCl_3$ as a solvent with TMS as an internal standard reference (^1H : 200MHz or ^{13}C : 75MHz). GC-MS was mesured on a NERMAG R10-10 spectrograph (ionisation potential Ec=70eV) coupled to a DELSI DI 700 chromatograph (equiped with a OV-1 (25m column). The following abbreviations will be used : PE = petroleum ether bp : 40-60; Et_2O = diethyl ether; DMSO = dimethylsulfoxyde; EtOAc = ethylacetate; TMEDA = tetramethylenediamine.

3-(2-Iodobenzyl)-4-pentyl-1-ol-5-trimethylsilyl derivative (6a). To a solution of **4a** [26] (156 mg, 1 mmol) in THF (5 ml), TMEDA (332 ml, 2.2 mmol) was added and the solution was cooled at -30°C. *n*BuLi (1.1 mmol) and *t*-BuLi (1.1 mmol) were sequentially added dropwise. After 2 hours at -30°C the reaction mixture was cooled at -78°C and **5a** (312 mg, 1.05 mmol) in THF (5 ml) was added. The reaction was gently warmed until room temperature during 3 hours. The reaction was quenched with a satured NH_4Cl solution and the products extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product. Flash chromatography (PE/Et_2O : 8/2) yielded 235 mg (68%) of **6a** as a yellow oil.

IR (neat) : 3400 (broad) 2980, 2160, 1590, 1570 cm^{-1}. ^1H NMR : δ 7.8 (d, 1H, J = 7.8) ; 7.2-7.3 (m, 2H) ; 6.8-7.0 (m, 1H) ; 3.8 (t, 2H, J = 6.2) ; 2.8-3.0 (m, 3H) ; 2.0 (br. s, 1H) ; 1.7-1.9 (m, 2H) ; 0.1 (s, 9H). ^{13}C NMR (75 MHz) : 141.9, 139.5, 131.2, 128.2, 128.0, 108.7, 101.1, 87.9, 61.3, 45.9, 37.3, 30.6, 0.2.

3-(2-Bromobenzyl)-4-pentyn-1-ol-5-trimethylsilyl derivative (6b) was prepared as described for **6a** starting from **4a** and **5b**. Purification by flash chromatography (PE/Et_2O : 8/2). Yield 65%. IR (neat) : 3350, 2960, 2180, 1570 cm^{-1}. ^1H NMR : δ 7.56 (d, 1H, J = 7.8) ; 7.34 (m, 2H) ; 7.14 (m, 1H) ; 3.89 (t, 2H, J = 6.2) ; 2.96 (m, 3H) ;

1.83 (m, 3H) ; 0.1 (s, 9H). ^{13}C NMR : δ 138.4, 132.6, 131.9, 128.1, 126.9, 124.7, 108.7, 87.5, 61.1, 41.3, 37.1, 30.1, 0.2. Mass spectrum (m/e) : 324-322 (M$^{+\cdot}$) 155, 73.

3-(2-Iodo-4,5-methylendioxybenzyl)-4-pentyn-1-ol-5-trimethylsilylsilyl derivative (6c) was prepared as described for **6a** starting from **4a** and **5c**. Purification by flash chromatography (PE/Et$_2$O 8/2). Yield 67%. IR (neat): 3400, 2960, 2180, 1500, 1480 cm^{-1}. ^{1}H NMR : δ 7.3 (s, 1H) ; 6.8 (s, 1H) ; 6.0 (s, 2H), 3.8 (t, 2H, J = 6.2) ; 2.7-2.9 (m, 3H) ; 1.9 (br. s, 1H) ; 1.7-1.9 (m, 2H), 0.1 (s, 9H).

3-(2-Bromo-4,5-methylendioxybenzyl)-4-pentyn-1-ol-5-trimethylsilylsilyl derivative (6d) was prepared as described for **6a** starting from **4a** and **5d**. Purification by flash chromatography (PE/Et$_2$O: 8/2). Yield 86%. IR (neat) : 3400, 2960, 2180, 1500, 1480 cm^{-1}. ^{1}H NMR : δ 7.0 (s, 1H) ; 6.8 (s, 1H) ; 5.9 (s, 2H), 3.8 (m, 2H) ; 2.7-2.9 (m, 2H) ; 2.1 (br. s, 1H) ; 1.6-1.8 (m, 2H); 0.1 (s; 9H). ^{13}C NMR : δ 147.0, 146.9, 131.5, 114.7, 112.5, 111.4, 108.8, 101.5, 87.7, 61.1, 41.1, 37.0, 30.4, 0.1. Mass spectrum (m/e) : 370 (M$^{+\cdot}$) 213, 73.

3-(2-Iodobenzyl)-4-hexyn-1-ol (6e) was prepared as described for **6a** starting from **4b** and **5e**. Purification by flash chromatography (PE/Et$_2$O : 7/3). Yield 32% (+ 34% of **7**). IR (neat) : 3300, 2980, 1590, 1570, cm^{-1}. ^{1}H NMR : δ 7.8 (d, 1H) ; 7.23 (m, 2H) ; 6.8-7.0 (m, 1H), 3.7-3.9 (m, 2H) ; 2.7-2.9 (m, 1H) ; 2.4 (br. s, 1H) ; 2.2-2.4 (m, 2H), 1.8 (s, 3H). ^{13}C NMR : 142.1, 139.3, 131.6, 128.4, 128.2, 100.9, 89.4, 80.7, 75.0, 61.1, 31.5, 17.2, 3.4. Mass spectrum (m/e) : 314 (M$^{+\cdot}$) 217, 159, 143, 90, 67, 41.

7-(2-Iodophenyl)-4-heptyn-1-ol (7) was prepared as described for **6a** starting from **4b** and **5a**. Purification by flash chromatography (PE/Et$_2$O : 7/3). Yield 34% (+ 32% of **6e**). IR (neat) : 3400, 2940, 1590, 1570, cm^{-1}. ^{1}H NMR : δ 7.7 (d, 1H, J = 7.8) ; 7.2 (m, 2H) ; 6.7-6.3 (m, 1H), 3.6 (t, 2H, J = 6.5) ; 2.8 (t, 2H, J = 7.3) ; 2.4 (m, 2H) ; 2.2 (m, 2H), 1.9 (br. s, 1H), 1.55 (m, 2H). ^{13}C NMR : 143.1, 139.4, 129.7, 128.2, 128.1, 100.4, 80.5, 79.4, 61.7, 40.1, 31.5, 19.4, 15.3. Mass spectrum (m/e) : 314 (M$^{+\cdot}$) 217, 59, 141, 115, 90.

3-(2-Bromo-6-methoxybenzyl)-4-pentyn-1-ol-5-trimethylsilyl derivative (6i) was prepared as described for **6a** starting from **4a** and **5e**. Purification by flash chromatography (PE/Et$_2$O : 65/35). Yield 52%. IR (neat) : 3400, 2960, 2160, 1590, 1570 cm^{-1}. ^{1}H NMR : 7.15 (dd, 1H, J = 8.0; 1.1) ; 7.1 (t, 1H) ; 6.8 (dd, 1H, J = 8.0; 1.1), 3.8 (brs, 5H) ; 2.9-3.1 (m, 2H) ; 2.0 (br. s; 1H) ; 1.7-1.8 (m, 2H) ; 0.1 (s, 9H). ^{13}C NMR : 158.8, 128.4, 127.9, 126.3, 125.0, 109.4, 86.6, 68.8, 61.7, 55.8, 36.7, 35.0, 29.2, 0.2. Mass spectrum (m/e) : 356, 354 (M$^{+\cdot}$), 244, 201, 199, 171, 90, 73.

3-(2-Iodo-6-methoxybenzyl)-4-pentyn-1-ol-5-trimethylsilyl derivative (6j) was prepared as described for **6a** starting from **4a** and **5f**. Purification by flash chromatography (PE/Et$_2$O : 75/25). Yield 54%. IR (neat) : 3400, 2960, 2160, 1590, 1570 cm^{-1}. ^{1}H NMR : 7.45 (d, 1H, J = 7.4) ; 6.9-6.7 (m, 2H) ; 3.75 (br. s, 5H), 2.9-3.1 (m, 3H) ; 2.05 (br. s, 1H) ; 1.65-1.8 (m, 2H) ; 0.1 (s, 9H). ^{13}C NMR : 157.8, 131.7, 131.0, 129.0, 110.4, 109.4, 103.0, 86.8, 61.7, 55.7, 39.6, 36.8, 29.4, 0.2. Mass spectrum (m/e) : 330 (M$^{+\cdot}$) 247, 217, 175, 90.

4-(2-Bromo-1-cyclohexenyl)-3-(trimethylsilylethynyl)-butan-1-ol (14a) was prepared as described for **6a** starting from **4a** and **13a**. Purification by flash chromatography (PE/Et$_2$O : 8/2). Yield 92%. IR (neat) : 3400, 2960, 2160, 1650 cm^{-1}. ^{1}H NMR : 3.85 (t, 2H, J = 6.3) ; 2.85 (m, 1H) ; 2.2-2.6 (m, 6H), 1.9 (br. s, 1H) ; 1.6-1.8 (m, 6H) ; 0.1 (s, 9H). ^{13}C NMR : 133.9, 121.3, 109.4, 86.8, 61.3, 42.2, 37.2, 36.8, 31.9, 28.1, 24.8, 22.6, 0.1.

3-(trimethylsilylethynyl)-6-bromo-(E)-hex-5-en-1-ol (14b) was prepared as described for **6a** starting from **4a** and **13b**. Purification by flash chromatography (PE/Et$_2$O : 75/25). Yield 41%. IR (neat) : 3350, 2960, 2160, 1620 cm^{-1}. ^{1}H NMR : δ 6.3 (m, 2H) ; 3.8 (t, 2H, J = 6.3) ; 2.7 (m, 1H), 2.4 (m, 2H) ; 1.75 (m, 2H) ; 0.2 (s, 9H). ^{13}C NMR : 131.8, 109.4, 87.0, 71.0, 61.0, 36.9, 35.0, 28.6, 0.1.

Analytical data of all desilylated products derived from alcohols of type 6.

The yields were in all cases >90%.

Desilylation of 6a : To a stirred solution of **6a** (372 mg ; 1 mmol) in wet DMF, KF (87 mg, 1.5 mmol) was added. After 3 h at room temperature, the reaction was diluted with Et$_2$O. The layers were separated and the aqueous layer was extracted with Et$_2$O (3 times). The combined organic extracts were dried over Na$_2$SO$_4$ and concentrated to give the crude product. Flash chromatography (PE/Et$_2$O : 6/4) yielded 270 mg (90%) of pure desilylated corresponding product as a white solid. IR : 3350, 3300, 1570, 1470, 1440, 750 cm^{-1}. ^{1}H NMR : δ 7.8 (d, 1H, J = 7.8) ; 7.3 (m, 2H) ; 6.9 (m, 1H), 3.8 (t, 2H, J = 6.1) ; 2.9 (m, 3H) ; 2.1 (s, 1H) ; 1.8 (m, 2H). Mass spectrum (m/e) : 300 (M^{+}.) 217, 145, 90.

Desilylated product derived from 6b. IR : 3350, 3300, 2960, 1570, 1470, 750 cm^{-1}. ^{1}H NMR : δ 7.5 (dd, 1H, J = 7.8 ; 1.2) ; 7.3 (m, 2H) ; 7.1 (m, 1H), 3.9 (t, 2H, J = 6.1) ; 2.9 (m, 3H) ; 2.1 (s, 1H) ; 1.8 (m, 2H). ^{13}C NMR : 138.4, 132.9, 131.8, 128.3, 127.3, 124.8, 86.2, 71.1, 61.0, 41.5, 37.1, 28.8. Mass spectrum (m/e) : 254/ 252 (M^{+}.) 233, 145, 83, 43.

Desilylated product derived from 6c . IR : 3400, 3300, 2960, 1500, 1480 cm^{-1} . ^{1}H NMR : δ 7.2 (s, 1H) ; 6.9 (s, 1H) ; 5.9 (s, 2H) ; 3.9 (t, 2H,J = 6.2) ; 2.7-2.9 (m, 3H) ; 2.1 (s, 1H) ; 1.6-1.8 (m, 2H).

Desilylated product derived from 6d . IR : 3400, 3300, 2960, 1500, 1480 cm^{-1}. ^{1}H NMR : δ 7.0 (s, 1H) ; 6.8 (s, 1H) ; 5.9 (s, 2H) ; 3.8 (t, 2H, J = 6.2) ; 2.7-2.9 (m, 3H) ; 2.1 (d, 1H, J = 2.3) ; 1.6-1.8 (m, 2H). ^{13}C NMR : 147.0, 146.9, 131.3, 114.7, 112.5, 111.1, 101.5, 86.0, 71.0, 60.6, 41.1, 36.8, 28.8. Mass spectrum (m/e) : 298 (M$^{+\cdot}$) 213, 189, 135, 75, 43.

Desilylated product derived from 6i . IR : 3400, 3300, 1590, 1570 cm^{-1} . ^{1}H NMR : δ 7.0-7.3 (m, 2H) ; 6.8 (d, 1H, J = 6.2) ; 3.8 (m, 5H), 2.9-3.2 (m, 3H) ; 2.1 (s, 1H) ; 1.9 (br. s, 1H) ; 1.7 (m, 2H). ^{13}C NMR : 158.6, 128.3, 127.5, 126.0, 124.9, 109.4, 86.7, 70.0, 61.0, 55.7, 36.4, 34.8, 27.6.

Desilylated product derived from 6j . IR : 3400, 3300, 1590, 1570 cm^{-1}. ^{1}H NMR : δ 7.45 (d, 1H) ; 6.7-6.9 (m, 2H) ; 3.8 (br. s, 5H), 2.9-3.2 (m, 3H) ; 2.1 (s, 1H) ; 1.85 (br s, 1H) ; 1.65-1.8 (m, 2H). ^{13}C NMR : 157.8, 131.7, 130.8, 129.1, 110.5, 102.8, 86.7, 70.4, 61.3, 55.7, 39.5, 36.6, 28.0. Mass spectrum (m/e) : 330 (M$^{+\cdot}$) 247, 217, 175, 90.

Desilylated product derived from 14a . IR : 3400, 3300, 2940, 1660, 1450, 750 cm^{-1}. ^{1}H NMR : δ 3.9 (t, 2H, J = 6.18) ; 2.8 (m, 1H) ; 2.5 (m, 2H), 2.1-2.4 (m, 5H) ; 2.1 (s, 1H) ; 1.6-1.8 (m, 6H). ^{13}C NMR : 133.7, 121.5, 86.8, 70.4, 60.9, 42.2, 37.0, 36.8, 31.8, , 26.6, 24.8, 22.6.

Desilylated product derived from (14b) .IR : 3400, 3300, 2920, 1625, 1440, 1050 cm^{-1} . ^{1}H NMR : δ 6.2 (m, 2H) ; 3.6 (t, 2H, J = 6.2) ; 2.6 (m, 1H), 2.3 (m, 2H) ; 2.1 (s, 1H) ; 1.9 (br. s, 1H) ; 1.6 (m, 2H). ^{13}C NMR : 131.7, 109.6, 86.0, 70.6, 60.5, 36.4, 34.8, 27.2.

3-(2-Iodobenzyl)-4-pentynoic acid (8a) : To a stirred solution of desilylated **6a** (300 mg : 1 mmol) in acetone (5 ml) the Jones reagent was added dropwise until the orange coloration was persistant. Then *i* PrOH was added to decolor the solution and it was filtered over celite pad. The acetone was evaporated to give the crude product. Flash chromatography (PE/AcOEt : 7/3) yielded (221 mg (70%) of pure **8a** as a white solid. IR : 3500 , 3300, 1710, 1590, 1570 cm^{-1} . ^{1}H NMR : δ 8.5-9.0 (br. s, 1H) ; 7.9 (d, 1H, J = 7.8) ; 7.3 (m, 2H), 6.9 (m, 1H) ; 3.3 (m, 1H) ; 3.0 (d, 2H, J = 7.3) ; 2.6 (dd, 2H, J = 7.5 ; 2.1) ; 2.1 (d, 1H, J = 2.3). ^{13}C NMR : 177.1, 140.9, 139.7, 130.9, 128.7, 128.2, 100.9, 84.5, 71.2, 44.9, 39.0, 28.4. Mass spectrum (m/e) : 314 (M$^{+\cdot}$, 15) ; 254 (20) ; 217 (100) ; 145 (32) ; 90 (52).

3-(2-Iodobenzyl)-4-pentynoic acid-5-trimethylsilyl derivative (8f) was prepared as described for **8a** starting from **6a**. Purification by flash chromatography (PE/Et$_2$O : 7/3). Yield 71%. IR : 3500, 2180, 1710, 1590, 1570 cm^{-1} .

^{1}H NMR : δ 7.8 (d, 1H, J = 7.6) ; 7.2-7.3 (m, 2H) ; 6.8-7.0 (m, 1H) ; 3.1-3.3 (m, 1H) ; 2.8-3.0 (m, 2H) ; 2.5-2.7 (m, 2H) ; 0.1 (s, 9H). ^{13}C NMR : 177.3, 141.3, 139.6, 131.2, 128.6, 128.1, 106.8, 101.1, 87.7, 45.0, 33.4, 29.7, 0.1.

3-(2-Bromobenzyl)-4-pentynoic acid (8b) was prepared as described for **8a** starting from the desilylated **6b**. Purification by flash chromatography (PE/AcOEt : 7/3). Yield 62%. IR : 3500, 3300, 1710, 1590, 1570 cm^{-1}. ^{1}H NMR : δ 7.55 (d, 1H, J = 7.6) ; 7.3 (m, 2H) ; 7.05 (m, 1H) ; 3.25 (m, 1H) ; 3.00 (d, 2H, J = 6.8) ; 2.6 (dd, 2H, J = 7.6 ; 2.3) ; 2.1 (d, 1H, J =2.3). ^{13}C NMR : 185.5, 137.6, 133.0, 131.7, 128.6, 127.3, 124.8, 84.7, 71.0, 40.5, 39.9, 28.1.

3-(2-Iodo-4.5-methylendioxy-benzyl)-4-pentynoic acid (8c) was prepared as described for **8a** starting from the desilylated **6c** Purification by flash chromatography (PE/AcOEt : 1/1). Yield 57%. IR : 3500 , 3300, 1710, 1500, 1480 cm^{-1}. ^{1}H NMR : δ 7.2 (s, 1H) ; 6.9 (s, 1H) ; 6.0 (s, 2H) ; 3.1-3.2 (m, 1H) ; 2.8-2.9 (m, 2H) ; 2.5 (d, 2H, J = 7.4) ; 2.1 (d, 1H, J = 2.3). Mass spectrum (m/e) : 358 (M$^+$) 189, 135, 43.

3-(2-Bromo-4.5-methylendioxy-benzyl)-4-pentynoic acid (8d) was prepared as described for **8a** starting from the desilylated **6d**. Purification by flash chromatography (PE/AcOEt : 1/1). Yield 54%. IR : 3500 , 3300, 1710, 1500, 1480 cm^{-1}. ^{1}H NMR : δ 9.0-9.5 (br. s, 1H) ; 6.9 (s, 1H) ; 6.7 (s, 1H) ; 5.9 (s, 2H) ; 3.1 (m, 1H) ; 2.7-2.9 (m, 2H) ; 2.5 (m, 2H) ; 2.1 (d, 1H, J = 2.3). ^{13}C NMR : 177.3, 147.4, 147.2, 130.6, 115.2, 112.7, 111.2, 101.8, 84.7, 71.2, 41.1, 38.9, 28.9.

3-(2-Iodobenzyl)-4-hexynoic acid (8e) was prepared as described for **8a** starting from **6e**. Purification by flash chromatography (PE/AcOEt : 1/1). Yield 62%. IR : 3500, 1710, 1590, 1570 cm^{-1}. ^{1}H NMR : δ 9.5 (br. s, 1H) ; 7.8 (d, 1H, J = 7.8) ; 7.3 (d, 2H, J = 4.3) ; 6.8-7.0 (m, 1H) ; 3.2-3.3 (m, 1H) ; 2.4-2.6 (m, 4H) ; 1.8 (s, 3H). ^{13}C NMR : 178.5, 141.6, 139.7, 130.9, 128.7, 128.6, 128.2, 101.2, 79.5, 77.4, 45.5, 14.6, 3.6. Mass spectrum (m/e) : 328 (M$^{+\cdot}$, 10) ; 217 (100) ; 155 (79) ; 141 (32) ; 90 (61) ; 43 (42).

7-(2-Iodophenyl)-4-heptynoic acid (9) was prepared as described for **8a** starting from **7**. Purification by flash chromatography (PE/AcOEt 1:1). Yield 66%. IR : 3500, 1710, 1590, 1570 cm^{-1}. ^{1}H NMR : δ 10.5 (br. s, 1H) ; 7.8 (d, 1H, J = 7.8) ; 7.3 (m, 2H) ; 6.8-6.9 (m, 1H) ; 2.9 (t, 2H, J = 7.3) ; 2.4-2.7 (m, 6H). ^{13}C NMR : 178.4, 143.1, 139.4, 128.4, 128.2, 128.1, 100.4, 79.9, 79.0, 40.0, 33.4, 19.4, 14.5.

3-(2-Bromo-6-methoxy-benzyl)-4-pentynoic acid (8i) was prepared as described for **8a** starting from desilylated **6i**. Purification by flash chromatography (PE/AcOEt : 4/6). Yield 53%. IR : 3500, 3300, 1720, 1590, 1570 cm^{-1}. ^{1}H NMR : δ 9.5 (br. s, 1H) ; 7.1-7.3 (m, 2H) ; 6.85 (d, 1H, J = 7.9) ; 3.8 (s, 3H) ; 3.2-3.4 (m, 1H) ; 3.0-3.2 (m, 2H) ; 2.8-3.2 (m, 2H) ; 2.1 (s, 1H). ^{13}C NMR : 177.9, 158.8, 128.9, 126.8, 126.3, 125.1, 109.6, 85.7, 69.9, 55.8, 38.8, 34.4, 27.2.

3-(2-Iodo-6-methoxy-benzyl)-4-pentynoic acid (8j) was prepared as described for **8a** starting from desilylated **6j**. Purification by flash chromatography (PE/AcOEt : 4/6). Yield 65%. IR : 3500, 3300, 1720, 1590, 1570 cm^{-1}. ^{1}H NMR : δ 7.45 (d, 1H, J = 7.6) ; 6.7-6.9 (m, 2H) ; 3.85 (br. s, 3H) ; 3.2-3.4 (m, 1H) ; 3.05-3.2 (m, 2H) ; 2.35-2.7 (m, 2H) ; 2.1 (d, 1H, J = 2.3). ^{13}C NMR : 177.6, 157.8, 131.8, 129.8, 129.4, 110.4, 102.8, 85.4, 70.1, 55.6, 39.0, 38.6, 27.2. Mass spectrum (m/e) : 344 (M$^{+\cdot}$, 22) ; 247 (100) ; 217 (26) ; 90 (33) ; 51 (16).

3-(2-Iodo-6-methoxy-benzyl)-4-pentynoic acid-5-trimethylsilyl derivative (8k) was prepared as described for **8a** starting from desilylated **6k**. Purification by flash chromatography (PE/AcOEt : 1/2). Yield 66%. IR : 3500, 2180, 1710, 1530, 1510cm^{-1} .

4-(2-Bromo-1-hexenyl)-ethynyl butanoic acid (15a) was prepared as described for **8a** starting from desilylated **14a**. Purification by flash chromatography (PE/AcOEt : 1/1). Yield 61%. IR : 3500, 3300, 1710cm^{-1} . ^{1}H NMR

: δ 3.1-3.3 (m, 1H) ; 2.1-2.6 (m, 8H) ; 2.1 (d, 1H, J = 2.3) ; 1.1-1.3 (m, 4H). ^{13}C NMR : 177.7, 132.9, 122.3, 85.3, 70.2, 41.6, 39.2, 36.8, 31.4, 29.7, 26.1, 24.7, 22.5.

3-(Ethynyl)-6-bromo-(E)-hexanoic acid (15b) was prepared as described for **8a** starting from desilylated **14b**. Purification by flash chromatography (PE/AcOEt : 1/1). Yield 51%. IR : 3500, 3300, 1710 cm^{-1}. ^{1}H NMR : δ 9.8 (br. s, 1H) ; 6.2 (m, 2H) ; 2.9 (m, 1H) ; 2.3-2.6 (m, 4H) ; 2.1 (d, 1H, J = 2.3). ^{13}C NMR : 177.3, 130.9, 110.5, 84.5, 70.6, 38.8, 29.6, 26.7.

2,3,3a,4-Tetrahydro-2-oxonaphtho[2,3-b]furan (10a) . The Palladium (0) complex was preformed following this general method : to a solution of Pd(OAc)$_2$ (0.05 eq) in DMSO (0.05 M) tri (2-furyl) phosphine (procedure A) or triphenylphosphine (procedure C) (0.1 eq) and heptene (0.1 eq) were added. The solution was warmed for about 15 min until a dark red solution of Pd(0) was obtained.

Procedure A : to a solution of **8a** (314 mg ; 1 mmol) in DMSO (5 ml) tBuOK (168 mg, 1.5 mmol) was added. Then the solution of Pd(0) (0.05 mol.) was added via canula. After 30 min at room temperature Et$_2$O and HCl 5% were added. The layers were separated and the aqueous layer was extracted with Et$_2$O. The combined organic extracts were dried over Na$_2$SO$_4$ and concentrated to give the crude product. Flash chromatography (PE/Et$_2$O: 7/3) yielded 145 mg (78%) of pure **10a** as a white solid.

Procedure B :As procedure A but dry KF (1.1 eq) was used as base instead of tBuOK. After work up and flash chromatography 60% of pure **10a** was obtained.

Procedure C : To a solution of **8a** (314 mg ; 1 mmol) in DMSO (5 ml), Et$_3$N (3.3 ml, 24 eq) and Et$_3$BnNCl (222 mg, 1 mmol) were added and soon the Pd(0) (0.05 mmol.) solution was canuled. After 45 min the reaction was worked up as in procedure A. Flash chromatography yielded 112 mg (60%) of pure **10a**.

Analytical data are accorded with literature [27]. IR : 1810, 1690, 1590, 1570 cm^{-1}. ^{1}H NMR : δ 7.0–7.3 (m, 4H) ; 6.1 (d, *J* = 2.4, 1H) ; 2.7-3.4 (m, 4H) ; 2.4-2.6 (dd, 1H, J = 17.4 ; 10.2). ^{13}C NMR : 174.0, 154.6, 133.7, 131.8, 127.7, 127.2, 126.5, 126.2, 101.4, 35.1, 34.6, 33.5.

2,3,3a,4-Tetrahydro-6,7-methylen-dioxy-2-oxonaphtho[2,3-b]furan (10b) was prepared starting from **8c** (procedure A, yield 50%) and **8d** (procedure B, yield 50%). Purification by flash chromatography (PE/Et$_2$O : 8/2) IR: 1810, 1690 cm^{-1}. ^{1}H NMR: δ 6.67 (s, 1H) ; 6.6 (s, 1H) ; 6.0 (d, 1H, J = 2.6) ; 5.9 (s, 2H) ; 3.2 (m, 1H) ; 3.0 (m, 1H) ; 2.75 (m, 1H) ; 2.4-2.5 (dd, 1H, J = 17.5 ; 10.3). ^{13}C NMR : 174.1, 153.3, 146.7, 145.6, 127.4, 125.3, 108.8, 107.3, 101.5, 101.1, 35.5, 34.6, 33.5.

2,3,3a,4-Tetrahydro-2-oxonaphtho[2,3-b]furan-1-trimethylsilyl derivative (10c) was prepared starting from **8f** following procedure A (yield 65 % of a 1:1 mixture with **10a**) and procedure B (yield 64 %). Purification by flash chromatography (PE/Et$_2$O : 8/2) . IR : 2180, 1810 cm^{-1}. ^{1}H NMR : δ 7.1- 7.4 (m, 4H); 2.6-3.2 (m, 4H) ; 2.4-2.55 (dd,1H, J = 17 ; 8.9) ; 0.4 (s, 9H). ^{13}C NMR : 174.3, 162.2, 137.1, 132.7, 127.8, 127.4, 126.9, 125.5, 109.6, 35.6, 34.5, 34.1, 0.9.

2,3,3a,4-Tetrahydro-1-methyl-2-oxonaphtho[2,3-b]furan derivative (10d) was prepared starting from **8e** following procedure A (yield 70 %). Purification by flash chromatography (PE/Et$_2$O : 85/15). IR : 1810, 1690cm^{-1}. ^{1}H NMR : δ 7.1- 7.4 (m,4H) ; 2.6-3.4 (m, 4H) ; 2.5 (dd, 1H, J = 17.4 ; 10.2) ; 2.1 (br. s, 3H). ^{13}C NMR : 174.4, 149.7, 135.8, 132.3, 127.5, 127.3, 126.0, 123.3, 107.3, 35.4, 35.3, 29.7, 10.8. Mass spectrum (m/e) : 200 ($M^{+\cdot}$), 129, 115.

3-(1'-Indinylidene)-butenolide (12) was prepared starting from **9** following procedure A (yield 77 %) and procedure B (yield 64 %). Purification by flash chromatography (PE/Et$_2$O : 8/2) . IR : 1810, 1690cm^{-1}. ^{1}H

NMR : δ 7.1- 7.3 (m, 4H) ; 3.2-3.1 (m, 2H) ; 2.9-3.0 (m, 2H) ; 2.6-2.8 (m, 4H). ^{13}C NMR : 179.1, 146.9, 142.3, 139.0, 127.0, 126.6, 125.3, 122.2, 119.5, 29.7, 29.3, 27.8, 24.7. Mass spectrum (m/e) : 200 ($M^{+\cdot}$), 144, 115.

2,3,3a,4-Tetrahydro-5-methoxy-2-oxonaphtho[2,3-b]furan (10e) was prepared starting from **8j** following procedure A (yield 60 %) and procedure B (yield 68 %). Purification by flash chromatography (PE/Et_2O : 85/15). IR : 1810, 1690cm^{-1}. ^1H NMR : δ 7.1- 7.3 (dd, 1H) ; 7.15 (t, 1H, J = 8.3) ; 6.7 (dd, 2H, J = 8 ; 1.8) ; 6.1 (d, 1H, J = 2.5) ; 3.82 (s, 3H) ; 3.6 (dd, 1H, J = 15.5 ; 7.1) ; 3.0-3.3 (m, 1H) ; 2.9 (dd, 1H, J = 17.4 ; 9.3) ; 2.46 (dd, 1H, J = 17.4 ; 10.5) ; 2.31 (t, 1H, J = 15.3). ^{13}C NMR : 172.8, 156.3, 154.9, 134 9, 127.8, 119.6, 119.5, 109.1, 101.2, 55.5, 34.8, 33.2, 27.3.

2,3,3a,4-Tetrahydro-5-methoxy-1-trimethylsilyl-2-oxonaphtho[2,3-b]furan (10f) was prepared starting from **8k** following procedure B (yield 73 %). Purification by flash chromatography (PE/Et_2O : 85/15). IR : 1810cm^{-1}. ^1H NMR : δ 7.15 (t, 1H, J = 8.3) ; 6.95 (d, 1H, J = 7.7) ; 6.75 (d, 1H, J = 8.1) ; 3.85 (s, 3H), 3.55 (m, 1H) ; 3.0-3.3 (m, 1H), 2.2-2.9 (m, 3H) ; 0.35 (s, 9H). Mass spectrum (m/e) : 288 ($M^{+\cdot}$), 231, 71.

3-(2-Bromo-3-4-methylendioxy-benzyl) butenolide (11a) was obtained starting from **8d** following procedure C (yield 47 %) and procedure A (yield 8%). IR : 1810, 1690cm^{-1}. ^1H NMR : δ 6.9 (s, 1H) ; 6.6 (s, 1H) ; 5.5 (s, 2H) ; 4.7 (br. s, 1H), 4.15 (br. s, 1H) ; 3.35 (m, 1H) ; 3.0 (dd, 1H, J = 13.8 ; 6.3) ; 2.5-2.8 (m, 2H) ; 2.4 (dd, 1H, J = 17.9 ; 5.6).

3-(2-Bromo-benzyl) butenolide (11b) was obtained starting from **8b** following procedure A (yield 43 %). IR : 1810, 1690cm^{-1}. ^1H NMR : δ 7.5 (d, 1H, J = 7.5) ; 7.2 (m, 3H) ; 4.8 (br. s, 1H) ; 4.2 (br. s, 1H), 3.5 (m, 1H) ; 3.2 (dd, 1H, J = 15 ; 7.5), 2.8 (dd, 2H, J = 15 ; 7.5) ; 2.7 (dd, 1H, J = 16 ; 7.5) ; 2.5 (dd, 1H, J = 16 ; 7.5). ^{13}C NMR : 173.6, 159.0, 137.2, 133.2, 131.3, 128.8, 127.5, 124.5, 89.2, 40.7, 37.6, 33.7.

3-(2-Bromo-5-methoxy-benzyl) butenolide (11f) was obtained starting from **8i** following procedure A (yield 11 % as 1:1 mixture with **10e**). ^1H NMR : δ 7.1-7.3 (m, 2H) ; 6.85 (m, 1H) ; 4.75 (br. s, 1H), 4.3 (br. s, 1H) ; 3.85 (s, 3H), 3.5 (m, 1H) ; 3.1 (m, 2H) ; 2.55 (m, 2H).

Butenolide derivative (11c) was obtained starting from **15a** following procedure A (yield 20 %) and procedure C (yield 20%). Purification by flash chromatography (PE/EE : 8/2). IR : 1810, 1670cm^{-1}. ^1H NMR : δ 4.8 (br. s, 1H) ; 4.3 (br. s, 1H), 3.35 (m, 1H), 2.3-2.8 (m, 8H) ; 1.75 (m, 4H). Mass spectrum (m/e) : 274-272 ($M^{+\cdot}$) 222, 213.

Butenolide derivative (11d) was obtained starting from **15b** following procedure A (yield 10 %). Purification by flash chromatography (PE/EE : 8/2). IR : 1810, 1670 cm^{-1}. ^1H NMR : δ 6.3 (d, 1H, J = 7.1) ; 6.1 (dd, 1H, J = 7.1 ; 14.3), 4.8 (br. s, 1H), 4.35 (br. s, 1H) ; 3.2 (m, 1H) ; 2.7-2.8 (dd, 1H, J = 9.6 ; 18) ; 2.2-2.7 (m, 3H). Mass spectrum (m/e) : 137 (100) ; 119 (46) ; 91 (42) ; 67 (43) ; 39 (44).

3-(2-Iodo-Benzyl)-4-penten-1-ol (18). To a solution of **6a** (400 mg, 1.34 mmol) in EtOH (9 ml), quinoline (52 ml, 0.4 mmol) and Pd/$BaSO_4$ (60 mg, 0.2 mmol) were added and the reaction mixture was stirred under H_2 (1 atm.) for 3 hours. The catalyst was removed by filtration through celite and washed with EtOH. Removal of the solvent and purification of the crude product by flash chromatography (PE/Et_2O : 1/1) gave 326 mg (yield 81%) of pure **18**. IR : 3350, 1645, 1570 cm^{-1}. ^1H NMR : δ 7.8 (d, 1H, J = 7.8) ; 7.3 (m, 2H), 6.95 (m, 1H), 5.7 (m, 1H) ; 5.0 (m, 2H) ; 3.7 (m, 2H) ; 2.8 (m, 2H) ; 2.6 (m, 1H) ; 1.70 (m, 2H) ; 1.5 (br. s, 1H).

3-(2-Iodo-Benzyl)-4-pentenoic-acid (19). was prepared as described for **8a** starting from (**18**). Purification by flash chromatography (PE/AcOEt 1:1) (yield 72 %). IR : 3500, 1710, 1640, 1570cm^{-1} . ^1H NMR : δ 7.8 (d, 1H, J = 7.8) ; 7.25 (m, 2H), 6.9 (m, 1H), 5.8 (m, 1H) ; 5.0 (m, 2H) ; 3.0 (m, 1H) ; 2.85 (m, 2H) ; 2.5 (m, 2H).

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