DOI: 10.1002/adsc.201300459

Copper-Catalyzed Domino Route to Natural Nostoclides and Analogues: A Total Synthesis of Nostoclides I and II

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Received: May 26, 2013; Published online: October 9, 2013

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201300459.

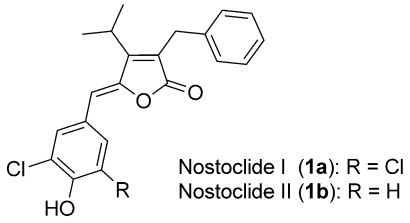
Abstract: An original and convenient domino route to natural nostoclides I and II has been developed using a two-step sequence consisting of a copper-catalyzed tandem reaction associated with Suzuki cross-coupling. The methodology employed for this total synthesis appeared to be an interesting and sufficiently flexible tool to allow the synthesis of numerous analogues of these nostoclides.

Keywords: copper catalysis; domino reactions; heterocyclic compounds; nostoclides; total synthesis

Introduction

Nostoclides are metabolites extracted from *Nostoc* sp. a blue-green cyanobacteria symbiote of the common lichen *Peltigera canina*. Their structure based on a γ-butyrolactone core has been elucidated by Yang et al.[1] The same authors reported that nostoclides I and II (Scheme 1) possess a moderate cytotoxicity towards Neuro-2aCCL and KB CCL17 cancer cells, however other works emphasize the antimicrobial,[1,2] phytogrowth and photosynthesis[3] inhibiting activities of nostoclide analogues.

Only a few papers deal with the synthesis of these structures.[4] The first total syntheses of nostoclides I and II were reported by Boukouvalas and co-workers.[4a] The route proceeds *via* the obtaining of a suitable γ-butyrolactone before the creation of the exocyclic double bond by a Mukaiyama-like condensation on the γ-position of the obtained butenolide followed by elimination. Two other papers by Rossi[4b] and Argade[4c] are present in the literature. But the described procedures differ only from the Boukouvalas route by the access to the butenolide. We report here a novel and totally different approach to access nostoclides I and II, exploiting a convenient method for the synthesis of (*Z*)-configured α,β-substituted γ-alkylidenebutenolides[5] in two steps including a copper-catalyzed tandem coupling–heteroannulation followed by palladium-catalyzed cross-coupling.

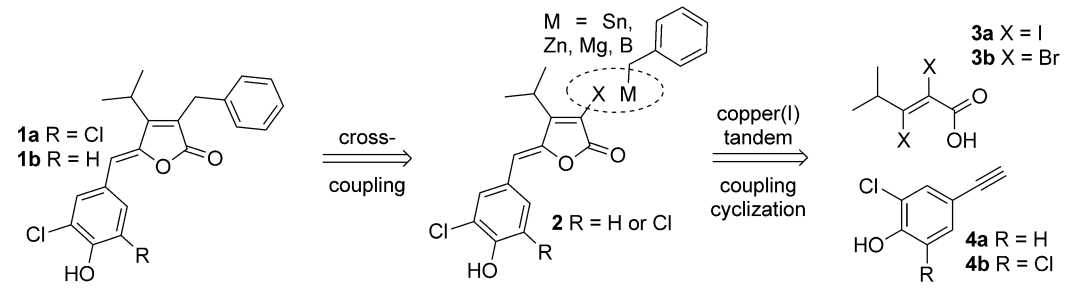


Scheme 1. Structures of nostoclide I and II.

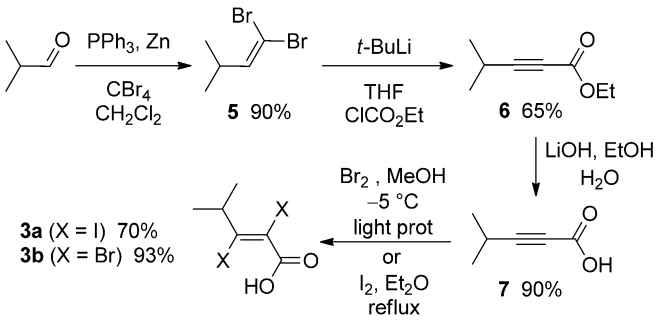
Results and Discussion

The reaction sequence we planned to follow is presented in Scheme 2. In the presence of a catalytic amount of copper iodide (CuI), terminal alkynes **4** and (*E*)-2,3-dihalo-4-methylpent-2-enoic acids **3** undergo a tandem coupling–oxacyclization reaction to selectively yield the α-brominated nostoclides precursors **2**. The latter product should be able to undergo a benzylation using the remaining α-halogen and give the desired nostoclides. The same procedure using palladium catalysts should fail at the first step, leading to the β-elimination by-product.[5]

The achievement of these total syntheses involved the efficient preparation of (*E*)-α,β-dihaloacrylic acid derivatives **3** and alkynes **4**. Acids **3** were synthesized in four steps starting from isobutyraldehyde, with the use of Corey–Fuchs[6] methodology (Scheme 3). Submitted to the action of a mixture of triphenylphos-



Scheme 2. Retrosynthetic route to nostoclides I and II.

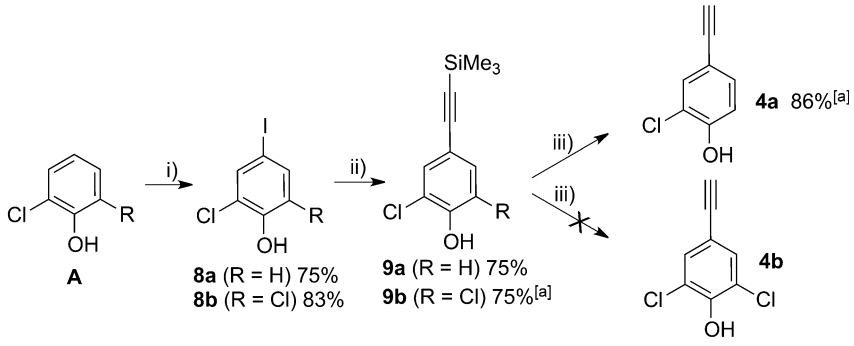


Scheme 3. Synthesis of (*E*)-α,β-dihaloacrylic acid derivatives.

phine, zinc and carbon tetrabromide in equimolar proportions, isobutyraldehyde afforded 1,1-dibromo-3-methylbut-1-ene **5** in 90% yield. A treatment of **5** with butyllithium led to the corresponding lithium acetylide trapped with ethyl chloroformate to afford ethyl 4-methylpent-2-ynoate **6** in 65% yield. The nature of the organolithium reagent was found to be an important factor in this step. Using *n*- or *s*-BuLi promoted the formation of mixtures of by-products along with the desired compound. The use of *t*-BuLi eliminated that issue. Saponification of **6** with lithium hydroxide at room temperature provided acid **7** in 90% yield. Using a previously reported[7] direct halogenation reaction of propiolic acid derivatives, acid **7** stereoselectively led to **3a** and **3b** in excellent yields.

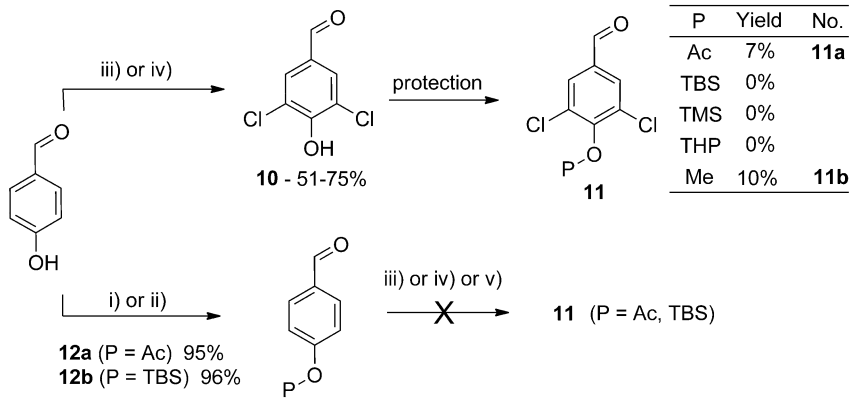
We initially planned to access alkynes **4** in three steps from *ortho*-chlorinated and dichlorinated phenols **A** (Scheme 4). The phenols **A** were firstly *para*-iodinated in good yields by the action of a methanolic mixture of sodium hydroxide, sodium iodide and sodium hypochlorite.[8] The obtained products **8** were reacted with trimethylsilylacetylene in a Sonogashira-like cross-coupling.[9] The last step consisted in the removal of the TMS protection by *n*-tetrabutylammonium fluoride to afford the terminal alkynes. Alkyne **4a** was obtained from **9a** in 86% yield after a fast chromatography because of its instability over silica gel. A lengthy exposure to silica leads to the reduction of the triple bond into the corresponding styrene derivative. The recovery of the alkyne was found to be very difficult by distillation. Precursor **9b** was obtained in 75% yield, then TMS was deprotected without further purification because of its instability over silica gel. Unfortunately the reaction led to a mixture of by-products and we were unable to isolate the minimal amount of alkyne obtained from it, probably because of the same instability. We tried to optimize the cleavage of the silane by lowering the temperature or by adding MeLi, but these changes did not provide increased yields of the alkyne.

We planned an alternative route to get **4b** from protected derivatives of **10**, itself obtained from 4-hydroxybenzaldehyde after treatment with *N*-chlorosuccinimide. We noticed difficulties to protect **10**. Actual-



[a] Yield was evaluated *via* ^{1}H NMR using an internal reference.

Scheme 4. Synthesis of alkynes **4**. i) *a* MeOH, NaI, NaOH, *b* NaOCl. ii) Trimethylsilylacetylene, Et_3N, CuI 0.1 equiv., $Pd(PPh_3)_4$ 0.05 equiv., DMF. iii) $(n\text{-}Bu)_4NF$, THF, −5 °C.



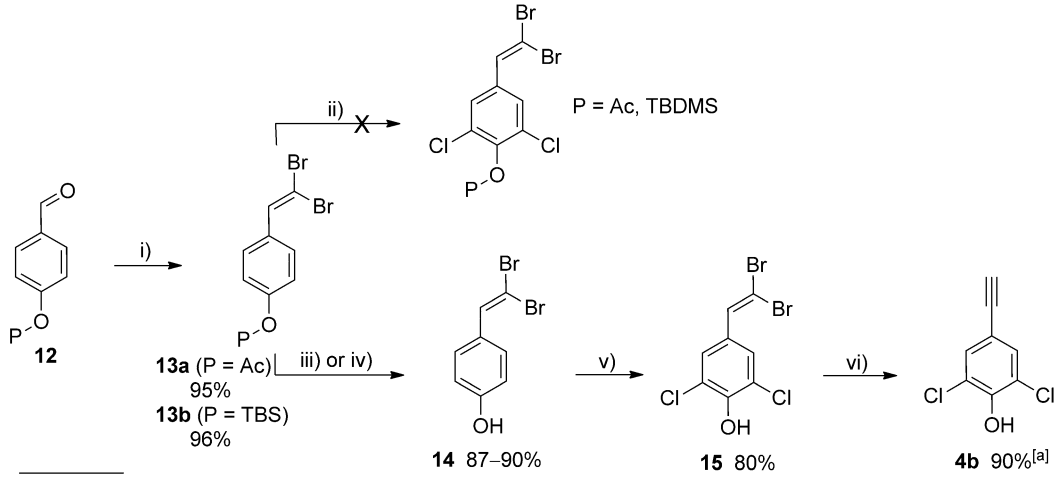
P	Yield	No.
Ac	7%	**11a**
TBS	0%	
TMS	0%	
THP	0%	
Me	10%	**11b**

Scheme 5. Attempts for the protection of dichlorophenol **10** and dichlorination of benzaldehydes **12**. i) Ac_2O 2.5 equiv., DMAP 0.05 equiv., DMF. ii) TBDMSCl 1.1 equiv., imidazole 1.1 equiv., DMF, room temperature. iii) NCS 2.5 equiv. $CHCl_3$ reflux. iv) NCS 2.5 equiv., APTS 2.5 equiv., MeCN, room temperature. v) SO_2Cl_2 2 equiv., CH_2Cl_2.

ly in the presence of *ortho*-chlorines, attempts to protect the phenol with acetyl, silyl, alkyl or THP group afforded very poor conversion yields or large amounts of by-products. On the other hand treating Ac- or TBS-protected 4-hydroxybenzaldehyde **12** with NCS or SO_2Cl_2 was useless to obtain the corresponding dichlorinated product **11**.

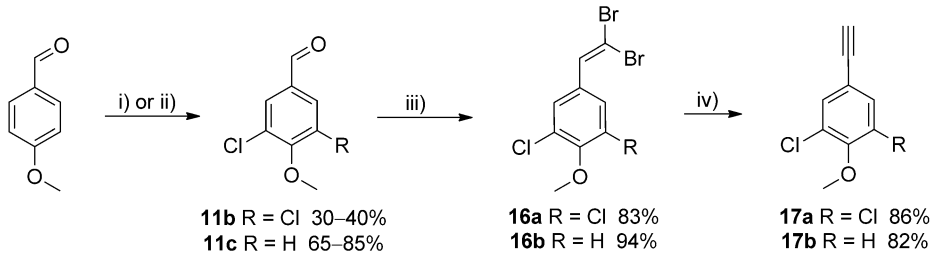
Attempts to chlorinate the *gem*-dibromo **13** (Scheme 6) obtained from **12** *via* the first step of Corey–Fuchs reaction was also a failure. Comparing the last and previous results supported the conclusion that the issue for chlorination was the Ac and TBS protecting groups. Actually, when protecting groups were removed from **13** to give **14**, chlorination with NCS in chloroform gave the expected product. It is important to note that depending on the batch of NCS, the reaction may be easy or not. Some batches were inefficient even after recrystallization. In case of difficulties with NCS, assistance of concentrated HCl or APTS should help to afford **15** (Scheme 6). A treatment with *t*-BuLi of **15** led to alkyne **4b** in good yield but unfortunately with styrene by-product in a 75/25 maximum ratio in favour of alkyne. That alkyne presented more instability than **9b** and **4a** towards silica gel and distillation also failed.

In order to synthesize some analogues, we prepared alkynes **17** in three steps from 4-methoxybenzaldehyde (Scheme 7). Even though monochlorination with NCS in $CHCl_3$ or NCS APTS in MeCN[10] was easy, dichlorination was very slow and led to an average yield of **11b**. Intermediates **16** were easily obtained by a $CBr_4/Zn/PPh_3$ treatment. Curiously, **16a** was also obtained in good yield by a treatment of **15** with dimethyl sulfate, while the carbonyl version was unable to properly undergo this transformation (Scheme 5). Alkynes **17** were obtained after the treatment of **16** with



[a] Yields of **4b** were evaluated *via* ^1H NMR using an internal reference.

Scheme 6. Alternative synthesis of dichloroalkyne **4b**. i) CBr_4 2 equiv., PPh_3 2 equiv. ii) Zn 2 equiv., CH_2Cl_2. iii) for **13a** KOH 1.5 equiv., EtOH, H_2O. iv) for **13b** Cs_2CO_3 1.3 equiv., DMF, H_2O. v) NCS 2.5 equiv., $CHCl_3$. vi) *a)* *t*-BuLi 3.1 equiv., THF; *b)* H_2SO_4.

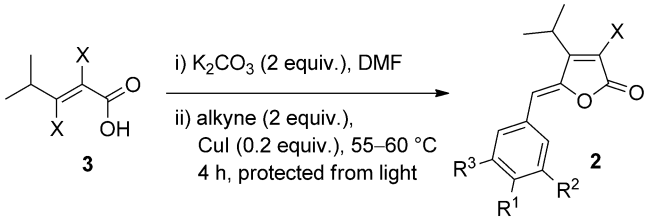


Scheme 7. Synthesis of methoxy-protected alkynes. 1) R = H: NCS 1 equiv., R = Cl: NCS 2.5 equiv., $CHCl_3$ reflux. ii) R = H: NCS 1 equiv., APTS 1 equiv., R = Cl: NCS 2 equiv., APTS 2 equiv., MeCN, room temperature. iii) CBr_4 2 equiv., PPh_3 2 equiv., Zn 2 equiv., CH_2Cl_2. iv) *a)* *t*-BuLi 2.1 equiv., THF, *b)* H_2SO_4. Yields of **17** were evaluated *via* ^1H NMR using an internal reference.

t-BuLi. The reaction yielded a mixture of alkynes and styrenes in a 93/7 maximum ratio in favour of alkyne and showed the same purification issues as the unprotected ones.

Because of issues regarding purification of alkynes prepared from styrene derivatives which were present in all cases, we found it preferable to use the crude product directly; according to our experience the mentioned impurities do not affect the behaviour of the further step. We used then 2 equiv. of alkynes **4** and **17**, and 4-hydroxyphenylacetylene for 1 equiv. of acid **3** in the presence of 0.2 equiv. of CuI, according to the conditions described in an earlier report on the copper-catalyzed orthogonal reactivity of α,β-dihaloalkenoic acid.[3] Four hours of reaction time were needed to obtain original α-halonostoclides precursors **2** (Table 1) with a total stereoselectivity in favour of the *Z*-isomer and in satisfactory isolated yields considering the purification issues. Actually methoxy-protected analogues are more stable than free hydroxylated and chlorinated moieties over silica gel. From that point of view it seemed very attractive to reach the nostoclides precursors by using methoxy-protected alkyne introducing then a deprotection sequence. But our efforts to demethylate the aromatic ether from **2f–i** with BBr_3 or HBr in acetic acid were unsuccessful. Studies are ongoing to find a suitable and easy to cleave protecting group.

Table 1. Synthesis of nostoclides precursors.



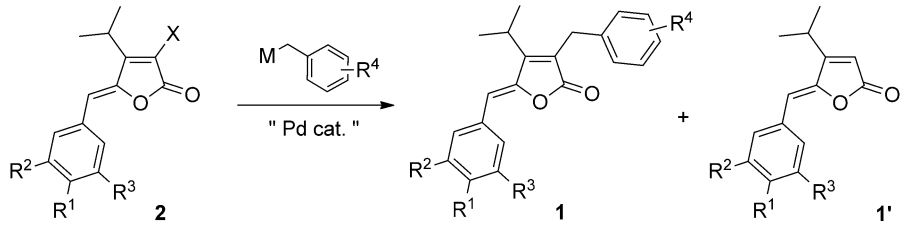
Entry	X	R^1	R^2	R^3	Product	Yield [%][a]
1	Br	H	H	H	**2a**	65
2	I	OH	H	H	2b	45
3	Br	OH	H	H	**2c**	38
4	Br	OH	H	Cl	**2d**	28
5	Br	OH	Cl	Cl	**2e**	25
6	Br	OMe	H	Cl	**2f**	65
7	I	OMe	H	Cl	**2g**	48
8	Br	OMe	Cl	Cl	**2h**	68
9	I	OMe	Cl	Cl	**2i**	45

[a] Isolated yields.

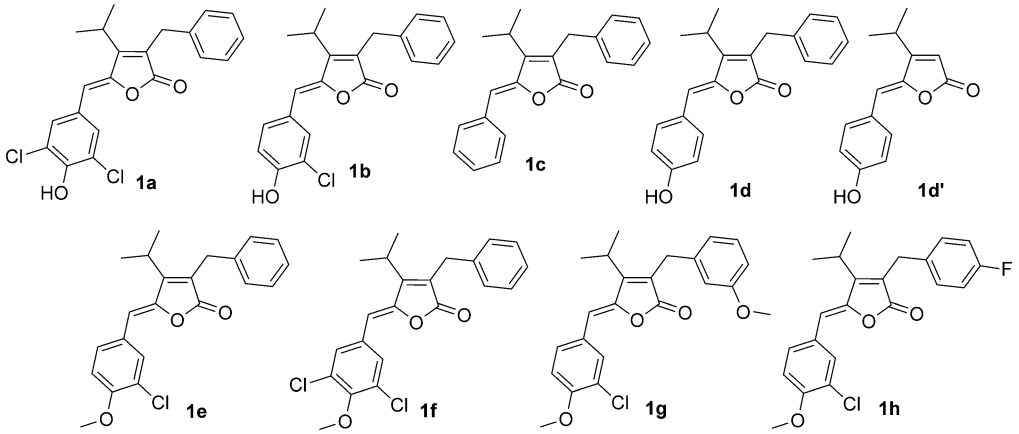
The last step to nostoclides and analogues was achieved by benzylation of the position 3 of the obtained butenolides. We tried several Pd-catalyzed cross-coupling methodologies. While Kumada and Stille coupling led to recovery of the starting material, Negishi coupling led to mixtures of needed product, α-dehalogenated parent product and starting material (Table 2, line 1). Suzuki methodology permitted us to hit our goal, even if we noticed issues. It appeared in the preliminary tests that iodinated precursors are unsuitable for benzylation with a Suzuki-like procedure. We obtained principally α-dehalogenation of the starting material (Table 2, lines 3–4). With the brominated butenolides, the reaction is more stable but seemed to stop regardless of the source of palladium used, its amount or the nature of the boronated reactant. Actually when the reaction ran with 0.05 equiv. of palladium catalyst, we obtained only 45 to 55% of conversion into the desired product even with a doubled palladium load (10%) or over 24 h of reaction (Table 2, lines 5–8).

The problem was successfully solved by a second addition of 0.05 equiv. of palladium catalyst along with 1 equiv. of boronated reagent 1 hour after the first addition. The reactions gave the needed products both on methoxylated and unprotected precursors. Slightly better yields were obtained while using the more stable and easy to handle potassium benzyltrifluoroboronates[11] instead of benzylboronic acids (Table 2, lines 10 and 11). We obtained natural nostoclides I and II, and several analogues in very good yields in the last step. Considering the principal reaction sequence presented in this report, these results make the overall yields average, allowing then to place this methodology as a serious alternative for the synthesis of nostoclides I and II, and derivatives. The

Table 2. Benzylation step of the nostoclides synthesis.



No.	Substrate	X	M	Catalyst	Temperature [°C]	Products obtained	Ratio[f]	Yield [%]
1	**2b**	I	ZnBr	$PdCl_2(MeCN)_2$[a]	r.t.	**1d/1d′/2b**	40/20/40	63
2	**2d**	Br	$B(OH)_2$	$Pd(PPh_3)_4$[b]	70	**1b/2d**	45/55	53
3	**2b**	I	$B(OH)_2$	$Pd(PPh_3)_4$[b]	70	**1d/1d′**	5/95	41
4	**2b**	I	$B(OH)_2$	$PdCl_2(MeCN)_2$	70	**1d/1d′**	10/90	59
5	**2c**	Br	$B(OH)_2$	$Pd(PPh_3)_4$[b]	70	**1d/2c**	53/47	52
6	**2c**	Br	$B(OH)_2$	$PdCl_2(MeCN)_2$[c]	70	**1d/2c**	55/45	73
7	**2c**	Br	BF_3K	$PdCl_2(dppf)$	80	**1d/2c**	53/47	78
8	**2a**	Br	BF_3K	$PdCl_2(dppf)$	80	**1c/2a**	51/49	84
9	**2a**	Br	BF_3K	$PdCl_2(dppf)$[d,e]	80	**1c**	–	82
10	**2c**	Br	BF_3K	$PdCl_2(dppf)$[d,e]	80	**1d**	–	73
11	**2c**	Br	$B(OH)_2$	$Pd(PPh_3)_4$[b,e]	70	**1d**	–	65
12	**2d**	Br	BF_3K	$PdCl_2(dppf)$[d,e]	80	**1b**	–	68
13	**2e**	Br	BF_3K	$PdCl_2(dppf)$[d,e]	80	**1a**	–	43
14	**2f**	Br	BF_3K	$PdCl_2(dppf)$[d,e]	80	**1e**	–	74
15	**2f**	Br	BF_3K	$PdCl_2(dppf)$[d,e]	80	**1g**	–	85
16	**2f**	Br	BF_3K	$PdCl_2(dppf)$[d,e]	80	**1h**	–	50
17	**2h**	Br	BF_3K	$PdCl_2(dppf)$[d,e]	80	**1f**	–	61



[a] BnZnBr 1.5 equiv., $PdCl_2(MeCN)_2$ 0.05 equiv., DMF/THF.
[b] $BnB(OH)_2$ 1.5 equiv., $Pd(PPh_3)_4$ 0.05 equiv., Na_2CO_3 2 equiv., toluene, EtOH.
[c] $BnB(OH)_2$ 1.5 equiv., $PdCl_2(MeCN)_2$ 0.05 equiv., Na_2CO_3 2 equiv., toluene, EtOH.
[d] $BnBF_3K$ 1.5 equiv., $PdCl_2(dppf)$ 0.05 equiv., Na_2CO_3 2 equiv., toluene, H_2O.
[e] A second addition of 0.05 equiv. of palladium and 1 equiv. of boron compound was made after 1 hour.
[f] Ratios were measured *via* ^1H NMR using an internal reference.

real advantage of this methodology comes from its three component configuration. It is actually possible to envisage a rapid synthesis of numerous members of the nostoclides I and II playing with the substituents of the alkyne, the acid and the boronated reactant.

Conclusions

In summary we have described an original approach to nostoclides I and II which illustrates a two-step route for the construction of butenolide structures. This three component methodology permits us to vary positions 3, 4 and exocyclic substituents of the butenolides. The transformation is sufficiently versa-

tile to allow the synthesis of several analogues of nostoclides I and II for QSAR purposes as an example. Efforts are ongoing to properly isolate the alkynes used and improve the recovery of nostoclides obtained with our methodology.

Experimental Section

General Procedure for the Synthesis of Nostoclides Precursors 2

A dry Schlenk tube protected from light by an aluminium foil and equipped with a magnetic stirrer was charged with 10.2 mmol (2 equiv.) of K_2CO_3, 5.0 mmol (1 equiv.) of **3** and 20 mL of DMF. The suspension was stirred for 15 min, then the flask was evacuated cold for 10 min and backfilled with argon. After reaching room temperature, 2 equiv. of selected alkyne and 0.2 equiv. of CuI were added. The Schlenk tube was placed in an oil bath pre-heated at 65 °C and the content stirred for 4 h. The reaction mixture was then allowed to reach room temperature and was hydrolyzed with a saturated aqueous solution of NH_4Cl (20 mL). Ethyl acetate (50 mL) was added in the Schlenk tube and the mixture was filtered over a Celite pad. The pad was washed with additional ethyl acetate (30 mL). The aqueous phase was removed and the organic layer was washed several times with water (10 × 15 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The raw material obtained was purified by flash chromatography on silica gel to give the desired α-halo-γ-alkylidenebutenolides **2**.

General Procedure for the Synthesis of Nostoclides 1

A dry Schlenk tube equipped with a magnetic stirrer and containing H_2O (2 mL) and toluene (6 mL), was charged with 0.3 mmol of **2**, 2 equiv. of potassium benzyltrifluoroboronate, 0.1 equiv. of $PdCl_2$(dppf) and 3 equiv. of Cs_2CO_3. The mixture was stirred at 80 °C. After 1 h, additional 1 equiv. of boronate and 0.05 equiv. of palladium were inserted and the medium was left under stirring at 80 °C for 4 h. The mixture was taken up with ethyl acetate (25 mL) and filtered through a Celite pad. The pad was washed with additional ethyl acetate (10 mL). The filtrate was poured in a separatory funnel and the organic layer was isolated, washed with brine (2 × 5 mL) and water (2 × 5 mL). The organic phase was dried over $MgSO_4$ and evaporated under vacuum. The crude product was purified by flash chromatography on silica gel with a suitable eluent to give the desired nostoclide derivative **1**.

The same results were obtained in the case of **2c** with the use of benzylboronic acid, $Pd(PPh_3)_4$ and aqueous Na_2CO_3 as the base at 70 °C in toluene/EtOH as solvent instead of the corresponding reactants. Suzuki-like conditions with benzyl boron derivatives were found unsuitable for iodinated nostoclides precursors. The conditions used promoted the α-dehalogenation of the starting material **2b** into **1d′**.

Acknowledgements

We thank the Département d'Analyse Chimique Biologique et Médicale for mass analyses. Special thanks to Jean-Philippe Christidès (IRBI, UMR CNRS 7261) for his great help on early nostoclides mass analyses. Johnson Matthey Company is thanked for generous gift of palladium metal salts.

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