Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: D. BROSSARD, P. Retailleau, V. Dumontet, P. Breton, S. Desrat and F. Roussi, *Org. Biomol. Chem.*, 2017, DOI: 10.1039/C7OB01236E.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/C7OB01236E

Journal Name

ARTICLE

Fast & easy preparation of 3D scaffolds from methyl benzoate by a diversity oriented synthesis strategy based on Diels-Alder and ene-reactions

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Dominique Petit,[a] Pascal Retailleau,[a] Vincent Dumontet,[a] Philippe Breton,[b] Sandy Desrat*[a] and Fanny Roussi*[a]

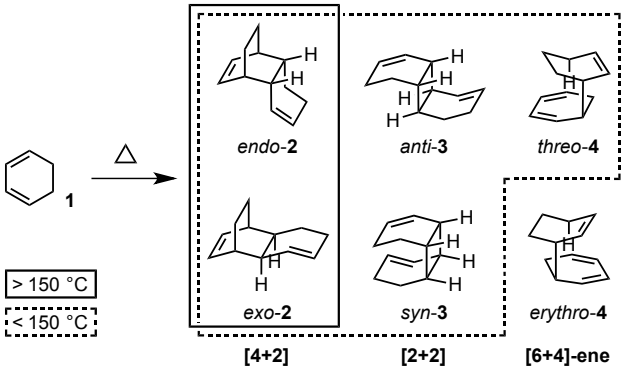
Thermic dimerization of methyl 1,3-cyclohexadiene 2-carboxylate gave original 3D-shape compounds by Diels-Alder cycloaddition and original [6+4]-ene reaction. Further selective modifications on *endo* [4+2] cycloadduct *via* a diversity oriented synthesis (DOS) strategy quickly led to the preparation of a small library of original 3D scaffolds, providing access to a larger and unexplored chemical space for drug discovery processes.

Introduction

One of the main challenges for medicinal chemists is to deal with new classes of therapeutic targets and to develop suitable new drugs from hits often discovered by screening of massive collections of compounds. Nevertheless, a tricky limitation in these libraries is the intrinsic nature of the molecules, as most of them are planar compounds (2D), built on sp^2-rich aromatic or heteroaromatic cores.[1] This is mainly due to the adaptation of methods for sp^2-sp^2 couplings to high-throughput synthesis.[2] The consequence is that these libraries only cover a tiny part of the chemical space, a concept that has recently emerged and encompasses all possible small organic molecules.[3] A few years ago, Lipkus *et al.* have shown that only 143 framework shapes can describe half of the compounds of the organic subset of the CAS Registry, which means that the exploration of the chemical space concentrates on relatively small numbers of structural scaffolds.[4] This lack of structural diversity has thus a dramatic impact on the drug discovery process. Indeed, compounds centred on a narrow chemical space are potent for a defined range of biological activities and targets[5] (mainly GPCR, kinases and proteases) but fail for many other highly important ones. These latter (antibiotics[6] or PPIs[7] for example) may be regarded as "undruggable targets" *ie* targets that lack of small molecules starting points in the traditional property space.[8]

To overcome this issue, one of the strategies is to elaborate new generations of chemical libraries as it was demonstrated that more complex molecules, *ie* with higher Fractional sp^3 character (Fsp^3: number of sp^3 hybridized carbon atoms/total carbon atoms) correlated with their three dimensional (3D) shape, access greater chemical space[9] and thus, potentiate the drug discovery process.

Diversity oriented synthesis (DOS) is a highly valuable tool to generate such a molecular diversity in an efficient manner.[1,10] DOS corresponds to the simultaneous synthesis of multiple target compounds starting from a single reagent. This allows fast and efficient generation of small collections of compounds with high degree of structural diversity and wide coverage of bioactive chemical space. In the cornucopia of available organic reactions, the thermal dimerization of 1,3-cyclohexadiene may be regarded as a particular example of DOS strategy as it provides a set of molecules with different skeletons. Hammond *et al.* showed that, at 200 °C, a mixture of *endo*-**2** and *exo*-**2** compounds (4:1) is formed by classical [4+2] Diels-Alder cycloaddition (Scheme 1).[11] Nevertheless, below 150 °C, not only *endo*-**2** and *exo*-**2** compounds but also [2+2]-cycloadducts *syn*-**3** and *anti*-**3** and an original [6+4]-ene product *threo*-**4** could be isolated (*ratio* 74:11:4:3:8 at 110 °C).[12]



Scheme 1 Cycloaddition and ene reaction products resulting from the dimerization of 1,3-cyclohexadiene **1**.

[a] *Institut de Chimie des Substances Naturelles, CNRS UPR 2301, Université Paris-Saclay, 1 avenue de la terrasse, 91198 Gif-sur-Yvette, France.*
[b] *Institut de Recherche Servier, 125 chemin de Ronde, 78290 Croissy-sur-Seine, France.*

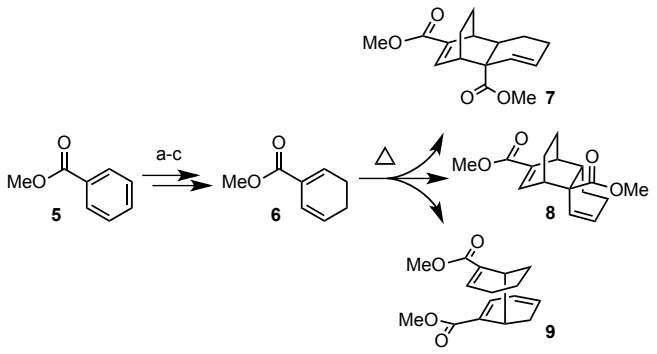
Electronic Supplementary Information (ESI) available: experimental procedures, NMR and crystallographic data. See DOI: 10.1039/x0xx00000x

Threo-**4** resulted from an unprecedented 10-electron ene reaction involving two 4-electron π-systems and a C-H σ-bond. This dimerization reaction, rationalized by calculation,[13] shows how one substrate as simple as 1,3-cyclohexadiene **1** can lead to a set of different scaffolds. Despite its potential, this dimerization has been little studied[14] and the molecular diversity that may be generated is still underexploited although Quideau *et al.* have elegantly synthesized natural (+)-aquaticol by the [4+2] cyclodimerization of cyclohexa-2,4-dienone.[15]

We wondered if properly functionalized 1,3-cyclohexadiene derivatives could generate, under thermic conditions, unprecedented sets of original compounds occupying a new chemical space. We thus have studied the thermic dimerization of methyl 1,3-cyclohexadiene 2-carboxylate **6** as it was shown to behave either as a diene[16] or as a dienophile[17] in [4+2] cycloadditions depending on the experimental conditions. This promising compound could be prepared in three steps from methyl benzoate **5** (Scheme 2), a cheap commercial source.[16]

Results and discussion

We first studied the dimerization of methyl 1,3-cyclohexadiene 2-carboxylate **6** under thermic conditions. Whatever the reaction conditions, a mixture of 5 separable compounds was obtained, including remaining starting material **6**, aromatization product **5**, *endo* and *exo* [4+2] cycloadducts **7** and **8**, as well as an original *threo* [6+4]-ene product **9** (Table 1). The reaction performed in refluxing toluene for 4 days without hydroquinone and under air mainly led to the aromatization of the starting diene **6** into methyl benzoate **5** (entry 1). In these conditions, the observed *ratio* of targeted compounds **7**-**9** by ^{1}H NMR analysis reached 38% in the crude reaction mixture. By performing the reaction in degassed toluene under inert atmosphere and after addition of 10% of hydroquinone, the amount of aromatized compound **5** could be reduced to 36% and 26% (entries 2 and 3).

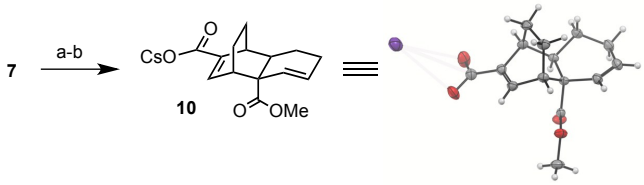


Scheme 2 From methyl benzoate **5** towards dimerization compounds **7**-**9**: a) Na, NH_3, EtOH, -78 °C, 3 h; b) 10% KOH in H_2O, hydroquinone (10 mol%), 100 °C, 4 h; c) $(COCl)_2$, THF, r.t., 12 h then MeOH, Py, r.t., 1 h, 75% (3 steps).

Table 1 Optimisation of the methyl cyclohexa-1,5-diene-1-carboxylate **6** dimerization.[a]

Entry	Conditions (solvent)	Relative ratios (%)[e]		
		5	**6**	**7+8+9**[f]
1	Toluene[b],[c]	48	15	38
2	Toluene[c]	36	8	56
3	Toluene	26	16	58
4	Neat	12	40	48
5	Methanol	43	5	52
6	Water	12	33	56
7	1,2-Dichloroethane	16	0	84
8	1,2-Dichloroethane[d]	12	4	84

[a] Reaction conditions: hydroquinone (10 mol%), under Ar atm., 120 °C, sealed tube, 4 days. [b] Performed under air. [c] Performed without hydroquinone. [d] Performed in 2 days. [e] Measured by comparative integration of ^{1}H NMR signals. [f] Compounds **7**, **8** and **9** were formed in a *ratio* of 4:1:3 respectively.

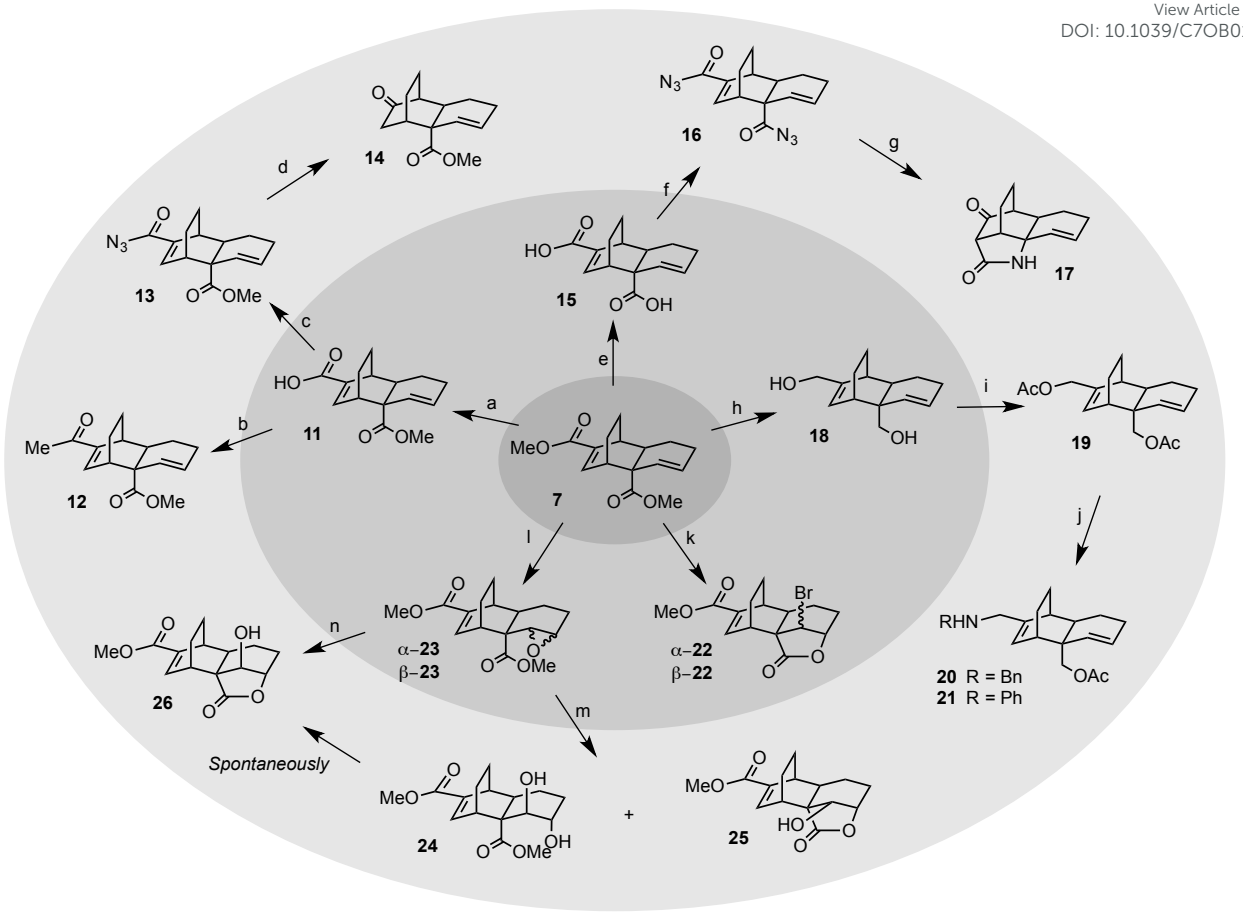


Scheme 3 ORTEP view and synthesis of compound **10**: a) LiOH.H_2O (1 eq), THF/H_2O, r.t., 2 h then 1 M HCl; b) Cs_2CO_3, methanol/water 9:1, r.t., 99% (2 steps).

A lower conversion was observed for the neat dimerization of compound **6** although the aromatization could be almost completely avoided (entry 4). Contrary to the use of methanol or water (entries 5 and 6), significant improvements were noted when 1,2-dichloromethane was employed instead of toluene (entries 7 and 8). These conditions prevented the aromatization up to 12% only and 84% of the desired compounds were observed in proton NMR. Finally, after 2 days in degassed DCE at 120 °C (sealed tube) in the presence of 10% of hydroquinone, compounds of interest **7**-**9** could be obtained with a *ratio* of 4:1:3 respectively in 64% combined yield. Interestingly, whatever the reaction conditions, no [2+2]-cycloadducts could be detected in the crude mixture, contrary to the results described by Hammond *et al*.. Each compound **7**-**9** was isolated and the structure of *endo*-**7** was confirmed by X-ray diffraction of crystal of the mono-cesium carboxylate salt **10** (Scheme 3).

As their alkene and ester functions are differently positioned in space, these 3D scaffolds **7**-**9** were promising starting points to design, by a DOS approach, original building blocks useful in medicinal chemistry for example. We chose to illustrate the versatility of these compounds by modifying the pure *endo* [4+2] cycloadduct **7** in order to prepare a library of original 3D-shape compounds (Scheme 4). Thanks to their difference of reactivity, the less hindered ester function of **7** could be selectively saponified by treatment with one equivalent of LiOH.H_2O at room temperature in a THF/water mixture. Among the organic reactions that could be performed on the mono-carboxylic acid **11**, two were selected.

View Article Online
DOI: 10.1039/C7OB01236E



Scheme 4 Functionalizations of *endo* [4+2] cycloadduct **7**: a) LiOH.H_2O (1 eq), THF/H_2O, r.t., 48 h, 100%; b) $SOCl_2$ (5.4 eq), 50 °C, 3 h, then MeCu.LiI (1.1 eq), THF, -78 °C, 15 min, 85%; c) DPPA (1.1 eq), Et_3N (1.5 eq), benzene, r.t., 2 h, 90%; d) Tol., 120 °C, 1 h then HCl 1 M in dioxane, r.t., 2 h, 60%; e) NaOH (4 eq), THF/H_2O, 80 °C, 2 h, 99%; f) DPPA (2.2 eq), Et_3N (3 eq), benzene, r.t., 2 h, 62%; g) Tol., 120 °C, 1 h then HCl 1 M in dioxane, r.t., 2 h, 58%; h) DIBAL (2 eq), Tol., 0 °C, 1 h, 79%; i) Ac_2O (3 eq), DMAP (0.4 eq), CH_2Cl_2, r.t., 1 h, 98%; j) RNH_2 (4 eq), n-BuLi (4 eq), THF, -78 °C, 3 h, 56% for **20**, 35% for **21**; k) NBS (2.2 eq), succinimide (0.2 eq), piperidine (0.2 eq), $CHCl_3$, 60 °C, sealed tube, 17 h, 36%; l) DMDO (1 eq), acetone, r.t., 3 h, 64%, α–**23**/β–**23** (8:2); m) from α–**23**: $AlCl_3$ (4 eq), THF, 60 °C, 48 h, 44% for **24**, 57% for **25**; n) from β–**23**: $AlCl_3$ (4 eq), THF, 60 °C,12 h, 40%.

On one hand, the preparation of methylketone **12** was achieved by addition of methylcuprate on intermediate acyl chloride in 85% yield. On the other hand, keto-ester **14** was prepared via an original 2-step procedure in good yield. After classical formation of the α,β-unsaturated carbonyl azide ester **13**, a simple reflux in toluene followed by acidic work-up led to the ketone **14**. This formal reduction of a methylene unit results from the hydrolysis of the imminiumobtained after formation of the transient conjugated isocyanate by Curtius rearrangement.[18] The dicarboxylic acid **15** could be obtained quantitatively from starting ester **7** when the saponification was performed with an excess of sodium hydroxide at 80 °C.

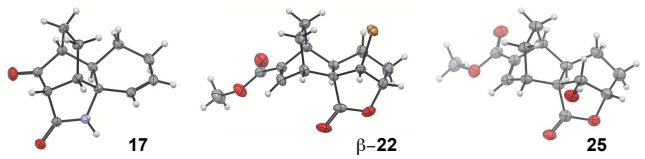


Figure 1 ORTEP view of compounds **17**, β–**24**, **25**.

Using the previous two-step strategy developed for the synthesis of keto-ester **14**, an original keto-lactame **17**, which structure was confirmed by X-ray diffraction analysis (Figure 1), was isolated after obtention of the unstable dicarbonyl azide ester intermediate **16**. Its formation can be explained by the intramolecular trapping of the isocyanate in ring junction position by the transient enamine generated on the external position.[19] The diester **7** could also be reduced to the corresponding diol **18** in the presence of DIBAL in 79% yield. After double acetylation, the resulting compound **19** was transformed into two new compounds **20** and **21** by selective functionalization of the allylic acetal by a Tsuji-Trost reactionwith benzylamine and aniline respectively. After selective modifications of the ester functions, the reactivity of the non-conjugated double bond was investigated. First, a halolactonization with NBS led to the formation of the bromolactones α– and β–**22** in a *ratio* of 1:1, which X-ray diffraction analysis (Figure 1) confirmed no modification on the conjugated double bond. Then, treatment of **7** with DMDO gave a 8:2 mixture of separable epoxide isomers α– and β–**23** in 64% yield. The major one, α–**23**, arises from epoxidation on the less hindered lower face. This compound could be opened in the presence of $AlCl_3$ at 60 °C in THF, thus yielding to diol **24** and lactone **25**. Its formation is probably due to the addition of

View Article Online
DOI: 10.1039/C7OB01236E

water during the work-up on the less hindered face of the chelated intermediate (upper face). The latter diol **24** spontaneously cyclized in few hours to lactone **26** that could, besides, be obtained directly from epoxyde β–**23** with $AlCl_3$.

Conclusions

Starting from simple methyl benzoate **5**, compounds with an increased complexity and chemical diversity were easily elaborated in few steps, providing new original stereochemically rich chiral scaffolds with readily functionalizable handles. Thus, in thermic conditions, three separable compounds could be obtained by cyclodimerization of **5**, among which an original *threo* [6+4]-ene product **9.** Furthermore, selective chemical modifications could be performed on cycloadduct **7**, taking advantage of the difference in reactivity of the two ester functions. This work led to 18 new original 3D-shape building blocks **11-26**, which are only a flavor of what can be done on such structures *via* DOS strategy. All of these new compounds possess a chiral quaternary center and have a more globular shape than most of the compounds in traditional medicinal chemistry libraries, thanks to their higher Fsp^3 character. Consequently, it allows access to a larger and unexplored chemical space for drug discovery processes.

Experimental sections

General experimental details

All reagents and solvents were used as purchased from commercial suppliers or were purified/dried according to Armarego and Chai.[20] Purifications by column chromatography on silica gel were performed using Merck Silica Gel 60 (70-230 mesh). ^1H and ^{13}C NMR spectra were recorded on Bruker ARX300 and ARX500 instruments using $CDCl_3$ or DMSO-d_6 as internal references. Chemical shifts (δ values) are given in parts per million (ppm), and multiplicity of signals are reported as follows: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet. HRMS analyses were obtained using a Waters LCT Premier instrument by ElectroSpray Ionization (ESI). IR spectra were recorded on a Perkin Elmer Spectrum BX-FTIR spectrometer. X-ray single diffraction data were recorded either on a Nonius-Enraf kappaCCD diffractometer with graphite-monochromated MoKα radiation at room temperature (for **10**, **17**, and β-**22**) or on a Rigaku mm007HF copper rotating anode equipped with CMF mirrors and Rapid2 IP detector at low temperature for **25**.

Dimerization of methyl 1,3-cyclohexadiene 2-carboxylate 6. Compound **6** (15.9 g, 115.2 mmol) and hydroquinone (1.27 g, 11.5 mmol, 0.1 eq) were dissolved in 1,2-dichloroethane (20 mL) and refluxed in a sealed tube for 48 h before concentration under reduced pressure. The residue was purified by column chromatography on silica gel using heptane/EtOAc 10:0 to 8:2 to obtain ***endo*-7** (5.48 g, 35%) as colorless oil, ***exo*-8** (0.66 g, 6%) as white solid and ***threo*-9** (3.10 g, 21%) as colourless oil.

***Endo*-7**. ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.23 (d, J = 6.5 Hz, 1H), 6.19-6.15 (m, 1H), 5.55 (dd, J = 10.0, 1.5 Hz, 1H), 3.73 (s, 3H), 3.60 (s, 3H), 3.14-3.06 (m, 1H), 3.05-3.00 (m, 1H), 2.44 (t, J = 9.5 Hz, 1H), 2.09-2.05 (m, 2H), 1.85-1.79 (m, 2H), 1.69-1.65 (m, 1H), 1.38-1.33 (m, 1H), 1.17-1.11 (m, 1H), 1.00-0.94 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) : δ 176.2, 165.2, 143.5, 139.9, 134.6, 129.4, 52.3, 51.5, 50.6, 39.2, 36.4, 35.1, 25.4, 23.7, 19.8, 18.5; HRMS (ESI): *m/z* calcd. for $C_{16}H_{24}NO_4$ $[M+NH4]^+$: 294.1705; found: 294.1699.

***Exo*-8**. ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.14 (dd, J = 7.0, 1.5 Hz, 1H), 5.86-5.81 (m, 1H), 5.54 (d, J = 10 Hz, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 3.15-3.11 (m, 1H), 3.03 (s, 1H), 2.84 (t, J = 6.0 Hz, 1H), 1.84-1.78 (m, 2H), 1.71-1.65 (m, 2H), 1.58-1.54 (m, 1H), 1.31-1.15 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 175.4, 165.8, 143.2, 137.4, 131.7, 129.5, 52.4, 52.3, 51.6, 40.1, 39.9, 36.9, 27.1, 25.9, 21.9, 21.3; HRMS (ESI): *m/z* calcd. for $C_{16}H_{24}NO_4$ $[M+NH_4]^+$: 294.1705; found: 294.1699.

***Threo*-9**.^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.05 (d, J = 5.0 Hz, 1H,), 6.90 (t, J = 3.5 Hz, 1H), 6.04-5.98 (m, 2H), 3.71 (s, 3H), 3.66 (s, 3H), 3.12-3.08 (m, 1H), 2.98-2.94 (m, 1H), 2.37-2.34 (m, 2H), 2.21-2.08 (m, 2H), 1.70-1.66 (m, 2H), 1.53-1.45 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 168.4, 167.8, 141.0, 134.4, 132.5, 132.3, 128.6, 123.5, 51.5, 51.3, 34.2, 32.0, 26.1, 25.8, 23.8, 18.4; HRMS (ESI): *m/z* calcd. for $C_{16}H_{24}NO_4$ $[M+NH_4]^+$: 294.1705; found: 294.1699.

Cesium salt 10. Monoacid **11** (20 mg, 7.2 mmol) was dissolved in a 9:1 mixture of methanol/water (300 µL). A 20% aqueous solution of cesium carbonate was added dropwise until the pH reached 7. The solvent was removed under vacuum and the residue was carefully dried by addition of acetonitrile (3 x 1 mL) to form an azeotrope. The residue was solubilized in hot $CHCl_3$ to slowly recrystalized.

Monoacid 11. Compound **7** (200 mg, 0.72 mmol) was stirred with $LiOH.H_2O$ (30 mg, 0.72 mmol, 1 eq) at r.t. for 2 h in a 1:1 mixture of THF/water (4 mL). The reaction mixture was cooled down and a 1M HCl solution (1 mL) was added. The product was extracted with CH_2Cl_2 (3 times). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure to give compound **11** (201 mg, 100% yield), as colourless oil that was used without further purification. ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.39 (dd, J = 6.6, 1.8 Hz, 1H), 6.20-6.14 (m, 1H), 5.54 (dd, J = 10.2, 2.1 Hz, 1H), 3.60 (s, 3H), 3.16-3.11 (m, 1H), 3.04-2.99 (m, 1H), 2.48-2.41 (m, 1H), 2.09-2.04 (m, 2H), 1.88-1.81 (m, 2H), 1.74-1.64 (m, 1H), 1.40-1.31 (m, 1H), 1.20-1.10 (m, 1H), 1.04-0.94 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 176.1, 169.6, 146.5, 139.4, 134.7, 129.2, 52.4, 50.6, 39.5, 36.4, 34.8, 25.3, 23.7, 19.8, 18.4; HRMS (ESI): *m/z* calcd. for $C_{15}H_{19}O_4$ $[M+H]^+$: 263.1268; found: 263.1281.

Methyl ketone 12. Compound **11** (334 mg, 1.3 mmol) was stirred at 50 °C for 3 h in thionyl chloride (500 mL, 6.9 mmol, 5.4 eq) under Ar atm, then the solvent was concentrated under reduced pressure. In parallel, a 1.37 M solution of MeLi in Et_2O (1.3 mL, 1.4 mmol, 1.1 eq) was added dropwise under Ar atm. to a suspension of CuI (267 mg, 1.4 mmol, 1.1 eq) in

View Article Online DOI: 10.1039/C7OB01365F

THF (15 mL) at 0 °C. The mixture was stirred for 10 min at 0 °C before the dropwise addition, at -78 °C, of the acid chloride issued from **11**, dissolved in THF (1 mL). The mixture was stirred for 15 min then MeOH (3 mL) was added and the reaction was warmed to r.t. After addition of a saturated solution of NH_4Cl, the product was extracted with CH_2Cl_2 (3 times) and the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was filtrated on a pad of silica (CH_2Cl_2) to give the expected compound as colourless oil (283 mg, 85%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.20 (dd, *J* = 6.6, 1.8 Hz, 1H), 6.20-6.15 (m, 1H), 5.53 (dd, *J* = 9.9, 2.1 Hz, 1H), 3.59 (s, 3H), 3.22-3.18 (m, 1H), 3.15-3.09 (m, 1H), 2.35-2.31 (m, 1H), 2.26 (s, 3H), 2.11-2.05 (m, 2H), 1.87-1.80 (m, 2H), 1.76-1.70 (m, 1H), 1.44-1.33 (m, 1H), 1.22-1.14 (m, 1H), 0.95-0.82 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 195.2, 175.8, 148.8 , 144.3, 134.7, 129.2, 52.3, 50.9, 39.4, 36.3, 32.9, 25.3, 24.7, 23.7, 19.6, 18.8; HRMS (ESI): *m/z* calcd. for $C_{16}H_{21}O_3$ $[M+H]^+$: 261,1491; found: 261.1482.

Carbonyl azide 13. Diphenylphosphorylazide (92 mL, 0.43 mmol, 1.1 eq) and Et_3N (81 mL, 0.58, 1.5 eq) were added to compound **11** (102 mg, 0.39 mmol) dissolved in benzene (10 mL). The reaction mixture was stirred at r.t. for 2 h before concentration under reduced pressure. The residue was purified by column chromatography on silica gel using heptane/EtOAc 10:0 to 95:5 to obtain the azide **13** as colourless oil (100 mg, 90%). As this compound was unstable, it was immediately engaged in the next step. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.37 (dd, *J* = 6.5, 1.5 Hz, 1H), 6.21-6.15 (m, 1H), 5.53 (dd, *J* = 9.8, 2.0 Hz, 1H), 3.60 (s, 3H), 3.15-3.07 (m, 2H), 2.43-2.37 (m, 1H), 2.13-2.02 (m, 2H), 1.89-1.80 (m, 2H), 1.74-1.66 (m, 1H), 1.40-1.31 (m, 1H), 1.19-1.11 (m, 1H), 1.00-0.91 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 176.0, 169.8, 147.0, 141.3, 134.8, 129.0, 52.4, 39.6, 36.4, 34.6, 25.2, 23.7, 20.4, 19.7, 18.4; IR (neat): ν 2168 cm^{-1} (N_3), 1725 cm^{-1} (CO), 1683 cm^{-1} (C=C).

Ketoester 14. Monoazide **13** (20 mg, 0.07 mmol) was refluxed in dry toluene for 1 h before concentration under reduced pressure. The crude mixture was dissolved in dioxane and a drop of a 1 M HCl solution was added. The reaction was stirred at r.t. for 2 h before concentration under reduced pressure. The residue was purified by column chromatography on silica gel using heptane/EtOAc 10:0 to 5:5 to obtain the ketone **14** as colourless oil (10 mg, 63%). ^{1}H NMR ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 6.14-6.09 (m, 1H), 5.65 (d, *J* = 10.0 Hz, 1H), 3.68 (s, 3H), 2.97-2.92 (m, 1H), 2.54-2.50 (m, 1H), 2.25-2.20 (m, 3H), 2.08-2.00 (m, 2H), 1.96-1.90 (m, 2H), 1.86-1.80 (m, 2H), 1.56-1.49 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 215.2, 175.4, 132.5, 129.4, 52.5, 48.6, 48.5, 41.4, 36.4, 32.6, 24.7, 22.5, 20.3, 17.5; HRMS (ESI): *m/z* calcd. for $C_{14}H_{22}NO_3$ $[M+NH_4]^+$: 252.1600; found: 252.1609.

Diacid 15. Sodium hydroxide (116 mg, 2.89 mmol, 4 eq) was added to a solution of compound **7** (200 mg, 0.72 mmol) in a 1:1 mixture of THF/water (8 mL) and the reaction mixture was refluxed for 2 h. The reaction mixture was cooled down and a 1M HCl solution (2 mL) was added. The product was extracted with CH_2Cl_2 (3 times). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure to give compound **15** (200 mg, 100% yield) as colourless oil that was used without furher purification. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.50 (dd, *J* = 6.3, 1.2 Hz, 1H), 6.29-6.21 (m, 1H), 5.53 (d, *J* = 9.6 Hz, 1H), 3.10-3.04 (m, 1H), 3.00 (s, 1H), 2.37-2.29 (m, 1H), 2.16-2.09 (m, 2H), 1.89-1.81 (m, 1H), 1.71-1.61 (m, 2H), 1.39-1.27 (m, 1H), 1.22-1.13 (m, 1H), 1.04-0.95 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 183.0, 170.5, 148.0, 138.5, 135.8, 128.8, 51.5, 38.8, 37.6, 34.6, 25.0, 23.8, 19.7, 18.1; HRMS (ESI): *m/z* calcd. for $C_{14}H_{15}O_4$ $[M-H]^-$: 247.0970; found: 247.0966.

Dicarbonyl azide 16. Diphenylphosphorylazide (345 mL, 1.28 mmol, 2.2 eq) and Et_3N (300 mL, 0.73 mmol, 3 eq) were added to compound **15** (180 mg, 0.72 mmol) dissolved in benzene (20 mL). The reaction mixture was stirred at r.t. for 2 h before concentration under reduced pressure. The residue was purified by column chromatography on silica gel using heptane/EtOAc 10:0 to 95:5 to obtain the azide **16** as colourless oil (135 mg, 62%). As this compound was unstable, it was immediately engaged in the next step. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.39 (dd, *J* = 6.6, 1.5 Hz, 1H), 6.31-6.24 (m, 1H), 5.50 (dd, *J* = 9.6, 2.4 Hz, 1H), 3.13-3.11 (m, 1H), 3.10-3.06 (m, 1H), 2.41-2.37 (m, 1H), 2.15-2.09 (m, 2H), 1.89-1.83 (m, 2H), 1.76-1.63 (m, 1H), 1.42-1.29 (m, 1H), 1.27-1.18 (m, 1H), 1.03-0.93 (m, 1H); IR (neat): ν 2167 cm^{-1} (N_3).

Keto-lactame 17. Diazide **16** (135 mg, 0.45 mmol) was refluxed in dry toluene (20 mL) for 1 h before concentration under reduced pressure. The crude mixture was dissolved in dioxane and 0.5 mL of 1M HCl solution was added. After addition of a solution of NaOH 10%, the product was extracted with CH_2Cl_2 (3 times). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using heptane/EtOAc 10:0 to 7:3 + 1% Et_3N) to obtain compound **17** as a white amorphous solid (57 mg, 58%). This compound was then crystallized in hot ethyl acetate. ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C): δ 8.03-7.97 (brs, 1H), 6.23-6.18 (m, 1H), 5.43 (dd, *J* = 9.9, 2.7 Hz, 1H), 2.90 (d, *J* = 4.2 Hz, 1H), 2.57-2.53 (m, 1H), 2.40-2.37 (m, 1H), 2.20-2.06 (m, 3H), 1.99-1.90 (m, 1H), 1.70 1.48 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6, 25 °C): δ 206.8, 169.4, 134.7, 127.7, 59.0, 58.4, 48.8, 46.1, 44.0, 25.4, 23.0, 19.9, 14.3; IR (neat): ν 1740 cm^{-1} (*CO*), 1700 (*CO*NH) ; HRMS (ESI): *m/z* calcd. for $C_{13}H_{16}NO_2$ $[M+H]^+$: 218.1176; found: 218.1177.

Diol 18. At 0 °C, under Ar atm., DIBAL (3.6 mL, 3.6 mmol, 5 eq) was added dropwise to a solution of compound **7** (200 mg, 0.72 mmol) in dry toluene (10 mL). The mixture was stirred at the same temperature for 1 h. After addition of CH_2Cl_2, the organic phase was washed with an aqueous saturated solution of $NaHCO_3$, dried over $MgSO_4$ and concentrated under reduced pressure. The pure diol **18** (126 mg, 79%) was obtained as colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 6.23-6.16 (m, 1H), 6.04 (dd, *J* = 6.6, 1.5 Hz, 1H), 5.52 (dd, *J* = 10.0, 2.1 Hz, 1H), 4.20 (d, *J* = 1.5 Hz, 2H), 3.16 (d, *J* = 2.4 Hz, 2H), 2.36-2.30 (m, 2H,), 2.14-2.05 (m, 1H), 1.97-1.77 (m, 3H), 1.73-1.62 (m, 2H), 1.51-1.39 (m, 3H), 1.18-1.08 (m, 1H), 1.05-0.96 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 147.4, 133.3, 132.6, 125.1,

72.0, 63.9, 44.9, 38.4, 37.3, 37.0, 26.0, 23.7, 21.4, 20.2; HRMS (ESI): *m/z* calcd. for $C_{16}H_{23}NO_2$ $[M+CH_3CN]^+$: 261.1128; found: 261.1117.

Diacetate 19. Compound **18** (96 mg, 0.44 mmol) and DMAP (21 mg, 0.17 mmol, 0.4 eq) were dissolved in CH_2Cl_2 (5 mL) under Ar atm.. Acetic anhydride (124 mL, 1.30 mmol, 3 eq) was added dropwise and the reaction mixture was stirred at r.t. for 1 h before the addition of a saturated solution of $NaHCO_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The pure diacetate **19** (130 mg, 98%) was obtained as colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 6.10 (dd, *J* = 6.3, 1.2 Hz, 1H), 6.07-6.01 (m, 1H), 5.56 (dd, *J* = 10.2, 1.5 Hz, 1H), 4.62 (s, 2H), 3.76 (d, *J* = 10.2 Hz, 1H), 3.53 (d, *J* = 10.2 Hz, 1H), 2.47-2.41 (m, 1H), 2.33-2.29 (m, 1H), 2.14-2.09 (m, 1H), 2.08 (s, 3H), 2.02 (s, 3H), 1.97-1.91 (m, 1H), 1.84-1.77 (m, 1H), 1.75-1.65 (m, 2H), 1.48-1.40 (m, 1H), 1.35-1.31 (m, 1H), 1.15-1.08 (m, 1H), 1.05-0.99 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 171.1, 170.9, 142.4, 133.0, 130.7, 128.5, 72.7, 64.9, 41.3, 38.4, 37.0, 36.9, 25.6, 23.4, 20.9 (2 C), 19.9; HRMS (ESI): *m/z* calcd. for $C_{18}H_{28}NO_4$ $[M+NH_4]^+$:322.2018; found: 322.2004.

Compound 20. Under Ar atm., diacetate **19** (50 mg, 0.16 mmol) was dissolved in dry THF (3 mL). Tetrakis(triphenylphosphine)palladium (19 mg, 0.016 mmol, 0.1 eq) and freshly distilled benzylamine (54 mL, 0.49 mmol, 3 eq) were added. After 24 h at reflux, the crude mixture was filtered through a pad of Celite® and the solvent was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using heptane/EtOAc 10:0 to 8:2 to obtain compound **20** as colourless oil (33 mg, 56%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.32 (d, *J* = 4.5 Hz, 4H), 7.28-7.20 (m, 1H), 6.07-5.99 (m, 1H), 5.95 (dd, *J* = 6.3, 1.5 Hz, 1H), 5.57 (dd, *J* = 10.2, 1.8 Hz, 1H), 3.83-3,75 (m, 3H), 3.56 (d, *J* = 10.2 Hz, 1H), 3.31 (d, *J* = 1.5 Hz, 2H), 2.42-2.35 (m, 1H), 2.34-2.28 (m, 1H), 2.15-2.06 (m, 1H), 2.01 (s, 3H), 1.89-1.82 (m, 1H), 1.86-1.61 (m, 4H), 1.51-1.38 (m, 1H), 1.35-1.27 (m, 1H), 1.19-0.94 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 171.2, 146.3, 140.3, 133.3, 130.5, 128.3 (2C), 128.2 (2 C), 126.9, 125.4, 73.0, 53.4, 51.8, 41.5, 39.6, 37.2, 36.9, 25.8, 23.5, 21.4, 21.0, 20.0; HRMS (ESI): *m/z* calcd. for $C_{23}H_{30}NO_2$ $[M+H]^+$: 352.2277; found: 352.2271.

Compound 21. Under Ar atm., diacetate **19** (128 mg, 0.42 mmol) was dissolved in dry THF (5 mL). Tetrakis (triphenylphosphine)palladium (49 mg, 0.04 mmol, 0.1 eq) and freshly distilled aniline (57 mL, 1.02 mmol, 1.5 eq) were added and the mixture was refluxed for 12 h. The crude mixture was filtered through a pad of Celite® and the solvent was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using heptane/EtOAc 10:0 to 9:1 to obtain compound **21** as colourless oil (50 mg, 35%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.18 (t, *J* = 7.5 Hz, 2H), 6.73 (t, *J* = 7.5 Hz, 1H), 6.68 (d, *J* = 7.5 Hz, 2H), 6.04-6.01 (m, 2H), 5.56 (dd, *J* = 10.0, 1.5 Hz, 1H), 3.85 (dd, *J* = 10.0, 1.8 Hz, 2H), 3.75 (d, *J* = 0.2 Hz, 1H), 3.57 (d, *J* = 10.2 Hz, 1H), 2.42-2.39 (m, 1H), 2.35-2.34 (m, 1H), 2.09-2.05 (m, 2H), 2.02 (s, 3H), 1.82-1.78 (m, 1H), 1.74-1.66 (m, 2H), 1.34-1.27 (m, 2H), 1.16-1.00 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 171.2, 147.8, 144.8, 133.2, 130.6, 129.2 (2C), 126.2, 117.8, 113.4 (2C), 72.9, 47.0, 41.6, 39.3, 37.2, 37.0, 25.8, 23.4, 21.3, 21.0, 20.1; HRMS (ESI): *m/z* calcd. for $C_{22}H_{28}NO_2$ $[M+H]^+$: 338.2053; found: 338.2093.

Bromolactones α– and β–22. NBS (28 mg, 0.16 mmol, 2.2 eq), succinimide (1 mg, 0.01 mmol, 0.2 eq) and piperidine (2 mL, 0.01 mmol, 0.2 eq) were added to compound **7** (20 mg, 0.07 mmol) dissolved in $CHCl_3$ (300 mL). The mixture was stirred for 17 h at 60 °C, then the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel using heptane/EtOAc 10:0 to 9:1 to obtain the lactones **β–22** (4 mg, 18%) and **α–22** (4 mg, 18%) as colourless oils. Compound **β–22** could be crystallized in hot EtOAc.

Compound α–22. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.51 (dd, *J* = 6.9, 1.5 Hz, 1H), 4.78 (d, *J* = 6.0 Hz, 1H), 4.61 (s, 1H), 3.76 (s, 3H), 3.10-3.06 (m, 1H), 3.04-3.00 (m, 1H), 2.26-2.11 (m, 1H), 2.12-2.05 (m, 1H), 1.92-1.63 (m, 5H), 1.28-1.15 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 191.0, 171.2, 147.8, 143.9, 82.6, 54.5, 51.7, 44.9, 34.3, 33.2, 29.7, 28.6, 21.2, 19.5, 16.5; HRMS (ESI): *m/z* calcd. for $C_{15}H_{21}BrNO_4$ $[M+NH_4]^+$: 358.0654; found: 358.0638.

Compound β–22. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.47 (dd, *J* = 6.9, 1.8 Hz, 1H), 4.66 (t, *J* = 5.5 Hz, 1H), 4.35 (d, *J* = 5.5 Hz, 1H), 3.68 (s, 3H), 2.95-2.93 (m, 1H), 2.81-2.77 (m, 1H), 2.60-2.47 (m, 1H), 2.28-2.18 (m, 1H), 2.04-1.97 (m, 1H), 1.96-1.86 (m, 1H), 1.81-1.75 (m, 2H), 1.57-1.50 (m, 2H), 1.30-1.20 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 168.6, 166.5, 145.7, 131.3, 78.3, 51.8, 51.7, 45.7, 43.3, 35.1, 33.6, 29.7, 25.6, 21.6, 18.5, 16.9; HRMS (ESI): *m/z* calcd. for $C_{15}H_{21}BrNO_4$ $[M+NH_4]^+$: 358.0654; found: 358.0668.

Epoxydes α–23 and β–23. Under Ar atm., freshly prepared dimethyldioxirane (10 mL, 0.72 mmol, 1 eq) in acetone was added to a solution of ester **7** (200 mg, 0.72 mmol) in acetone (5 mL). The reaction mixture was stirred at r.t. for 3 h before concentration under reduced pressure (cold bath) to give a mixture 2 isomers **α–23/β–23** (8:2) which were separated by column chromatography on silica gel using heptane/EtOAc 10:0 to 8:2 to obtain pure compound **α–23** (95 mg, 50%) and compound **β–23** (34 mg, 16% containing 20% of an inseparable impurity) as colourless oils.

Compound α–23. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.04 (dd, *J* = 11.0, 2.5 Hz, 1H), 3.66 (s, 3H), 3.65 (s, 3H), 3.33-3.32 (m, 1H), 3.21 (d, *J* = 6.5 Hz, 1H), 3.18-3.15 (m, 1H), 2.97-2.96 (m, 1H), 2.11-2.09 (m, 1H), 2.00-1.98 (m, 1H), 1.97-1.95 (m, 1H), 1.81-1.79 (m, 1H), 1.43-1.37 (m, 2H), 1.19-1.05 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 174.8, 164.6, 141.6, 141.1, 56.1, 52.6, 51.5, 46.2, 39.0, 37.9, 31.6, 21.7, 21.7, 20.2, 20.0, 19.6; HRMS (ESI): *m/z* calcd. for $C_{16}H_{21}O_5$ $[M+H]^+$: 293.1389; found: 293.1379.

Compound β–23. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.25 (dd, *J* = 10.5, 2.5 Hz, 1H), 3.70 (s, 3H), 3.65 (s, 3H), 3.27-3.23 (m, 1H), 3.18-3.13 (m, 1H), 3.11-3.08 (m, 1H), 2.85-2.83 (m, 1H), 2.25-2.15 (m, 1H), 2.05-2.02 (m, 1H), 1.98-1.97 (m, 1H), 1.94-1.93 (m, 1H), 1.76-1.70 (m, 1H), 1.42-1.37 (m, 1H), 1.17-1.09 (m, 1H), 1.05-1.00 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 175.4, 165.1, 144.1, 139.3, 56.0, 52.5, 51.4, 50.8, 49.3,

38.9, 36.5, 34.2, 22.2, 19.8, 18.9, 18.2; HRMS (ESI): *m/z* calcd. for $C_{16}H_{21}O_5$ $[M+H]^+$: 293.1389; found: 293.1379.

Diol 24 and lactone 25. $AlCl_3$ (182 mg, 1.37 mmol, 4 eq) was added, under Ar atm., to a solution of compound **α−23** (100 mg, 0.34 mmol) in anhydrous THF (10 mL) and the mixture was stirred for 48 h at 60 °C. Water was then added and the product was extracted with CH_2Cl_2 (3 times). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using heptane/EtOAc 8:2 to 0:10 to obtain, as colourless oils, pure lactone **25** (54 mg, 57%) and diol **24** (47 mg, 44%) that spontaneously lactonized in few hours in lactone **26**. Lactone **25** was recrystallized in hot EtOAc.

Diol 24. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.29 (dd, *J* = 6.6, 1.5 Hz, 1H), 4.07 (t, *J* = 10.0 Hz, 1H), 3.93 (d, *J* = 10.0 Hz, 1H), 3.73 (s, 3H), 3.66 (s, 3H), 3.44-3.32 (m, 2H), 2.97 (brs, 1H), 2.66 (brs, 2 OH), 2.44-2.32 (m, 1H), 2.19-2.06 (m, 2H), 1.95-1.71 (m, 2H), 1.64-1.57 (m, 2H), 1.49-1.39 (m, 1H), 1.22-1.08 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 175.7, 165.1, 144.7, 138.5, 74.9, 63.5, 52.5, 51.6, 42.1, 35.0, 33.7, 32.6, 26.4, 20.4, 19.5, 17.6; HRMS (ESI): *m/z* calcd. $C_{16}H_{23}O_6$ $[M+H]^+$: 311,1489; found: 311.1499.

Lactone 25. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.53 (dd, *J* = 6.9, 1.5 Hz, 1H), 4.55 (d, *J* = 6.0 Hz, 1H), 4.38 (s, 1H), 3.75 (s, 3H), 3.06-3.00 (m, 1H), 2.99-2.96 (m, 1H), 2.25-2.15 (m, 1H), 2.04-1.92 (m, 1H), 1.83-1.72 (m, 3H), 1.66-1.57 (m, 2H), 1.30-1.21 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 17. 90, 165.1, 144.5, 137.9, 82.3, 73.4, 51.6, 51.0, 43.7, 33.8, 30.1, 27.6, 22.1, 19.5, 16.8; HRMS (ESI): *m/z* calcd. for $C_{15}H_{22}NO_5$ $[M+NH_4]^+$: 296.1498; found: 296.1496.

Lactone 26. $AlCl_3$ (159 mg, 1.19 mmol, 4 eq) was added, under Ar atm., to a solution of compound **β−23** (87 mg, 0.30 mmol) in anhydrous THF (10 mL) and the mixture was stirred for 12 h at 60 °C. Water was then added and the product was extracted with CH_2Cl_2 (3 times). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using heptane/EtOAc 10:0 to 5:5 to obtain pure lactone **26** (34 mg, 40%) as colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.53 (dd, *J* = 6.9, 1.5 Hz, 1H), 4.55 (t, *J* = 5.4 Hz, 1H), 4.45 (d, *J* = 5.4 Hz, 1H), 3.74 (s, 3H), 3.00-2.75 (m, 3H), 2.38-2.26 (m, 1H), 2.24-2.06 (m, 2H), 1.97-1.84 (m, 2H), 1.76-1.50 (m, 2H), 1.28-1.01 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 177.9, 165.5, 145.8, 137.8, 77.3, 73.6, 51.6, 48.1, 42.9, 35.0, 34.1, 25.5, 21.8, 20.1, 17.0; HRMS (ESI): *m/z* calcd. for $C_{15}H_{22}NO_5$ $[M+NH_4]^+$: 296.1498; found: 296.1509.

Notes and references

1 W. R. J. D. Galloway, A. Isidro-Llobet, D. R. Spring, *Nat. Commun.,* 2010, **1:80**, 1-13.
2 W. P. Walters, J. Green, J. R. Weiss, M. A. Murcko, *J. Med. Chem.*, 2011, **54**, 6405-6416.
3 J.-L. Reymond, *Acc. Chem. Res.*, 2015, **48**, 722-730.
4 A. H. Lipkus, Q. Yuan, K. A. Lucas, S. A. Funk, W. F. Bartelt III, R. J. Schenck, A. J. Trippe, *J. Org. Chem.*, 2008, **73**, 4443-4451.
5 C. Lipinski, A. Hopkins, *Nature*, 2004, **432**, 855-861.
6 D. J. Payne, M. N. Gwynn, D. J. Holmes, D. L. Pompliano, *Nat. Rev. Drug Discov.*, 2007, **6**, 29-40.
7 X. Zhang, S. Betzi, X. Morelli, P. Roche, *Future Med. Chem.*, 2014, **6**, 1291-1307.
8 S. Dandapani, L. A. Marcaurelle, *Nat. Chem. Biol.*, 2010, **6**, 861-863.
9 *(a)* F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752-6756; *(b)* W. H. B. Sauer, M. K. Schwarz, *J. Chem. Inf. Comput. Sci.*, 2003, **43**, 987-1003.
10 *(a)* S. L. Schreiber, *Science*, 2000, **287**, 1964-1969; *(b)* D. R. Spring, *Org. Biomol. Chem.*, 2003, **1**, 3867-3870; *(c)* M. K. Dow, M. Fisher, T. James, F. Marchetti, A. Nelson, *Org. Biomol. Chem.*, 2012, **10**, 17-28; *(d)* A. W. Hung, A. Ramek, Y. Wang, T. Kaya, J. A. Wilson, P. A. Clemons, D. W. Young, *Proc. Natl. Acad. Sci.*, 2011, **108**, 6799-6804; *(e)* M. C. McLeod, G. Singh, J. N. Plampin III, D. Rane, J. L. Wang, V. W. Day, J. Aubé, *Nat. Chem.*, 2014, **6**, 133-140; *(f)* R. G. Doveston, P. Tosatti, M. Dow, D. J. Foley, H. Y. Li, A. J. Campbell, D. House, I. Churcher, S. P. Marsden, A. Nelson, *Org. Biomol. Chem.*, 2015, **13**, 859-865; *(g)* J. D. Firth, P. G. E. Craven, M. Lilburn, A. Pahl, S. P. Marsden, A. Nelson, *Chem. Commun.*, 2016, **52**, 9837-9840.
11 *(a)* K. Alder and G. Stein, *Justus Liebigs Ann. Chem.*, 1932, **496**, 197-203; *(b)* D. Valentine, N. J. Turro Jr., G. S. Hammond, *J. Am. Chem. Soc.*, 1964, **86**, 5202-5208.
12 F.-G. Klärner, B. M. J. Dogan, O. Ermer, W. von E. Doering, M. P. Cohen, *Angew. Chem. Int. Ed.*, 1986, **25**, 108-110.
13 D. H. Ess, A. E. Hayden, F. -G. Klärner, K. N. Houk, *J. Org. Chem.*, 2008, **73**, 7586-7592.
14 *(a)* D. Valentine, N. J. Turro Jr., G. S. Hammond, *J. Am. Chem. Soc.*, 1964, **86**, 5202-5208; *(b)* D. J. Bellville, D. D. Wirth, N. L. Baud, *ibid*, 1981, **103**, 718-720; *(c)* S. E. Nigenda, D. M. Schleich, S. C. Narang, T. Keumi, *J. Electrochem. Soc: Electrochem. Sci. Tech.*, 1987, **134**, 2465-2470.
15 *(a)* J. Gagnepain, R. Méreau, D. Dejugnac, J. -M. Léger, F. Castet, D. Deffieux, L. Pouységu, S. Quideau, *Tetrahedron*, 2007, **63**, 6493-6505; *(b)* J. Gagnepain, F. Castet, S. Quideau, *Angew. Chem. Int. Ed.*, 2007, **46**, 1533-1535.
16 D. L. Boger, M. Patel, F. Takusagawa, *J. Org. Chem.*, 1985, **50**, 1911-1916.
17 J. Dardenne, S. Desrat, F. Guéritte, F. Roussi, *Eur. J. Org. Chem.*, 2013, 2116-2122.
18 H. D. Zook, M. Ream, E. W. Delchamps, *J. Am. Chem. Soc.*, 1953, **75**, 5590-5591.
19 For some examples of addition of enamines to isocyantes see: *(a)* J. H. Rigby, N. Balasubramanian, *J. Org. Chem.*, 1989, **54**, 224-228; *(b)* F. Palacios, D. Aparicio, J. Garcia, *Tetrahedron*, 1997, **53**, 2931-2940; *(c)* F. Palacios, A. M. Ochoa de Retana, J. Oyarzabal, *Tetrahedron*, 1999, **55**, 5947-5964.
20 W. L. F. Amarego, C. L. L. Chai in *Purification of Laboratory Chemicals*, 7th Ed., Butterworth-Heinemann, Elsevier, Oxford, **2013**.