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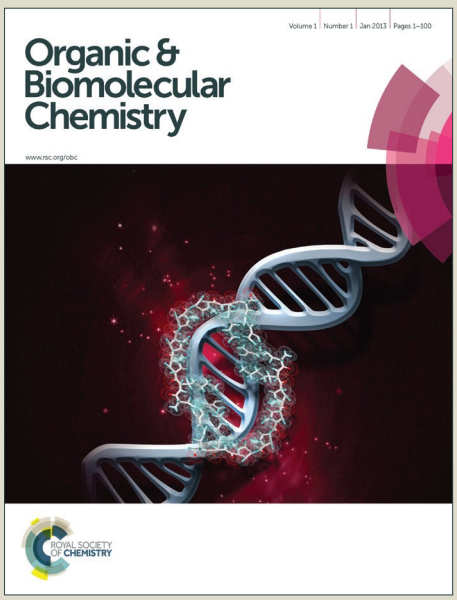

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ARTICLE TYPE

Development of an efficient route toward meiogynin A-inspired dual inhibitors of Bcl-xL and Mcl-1 anti-apoptotic proteins

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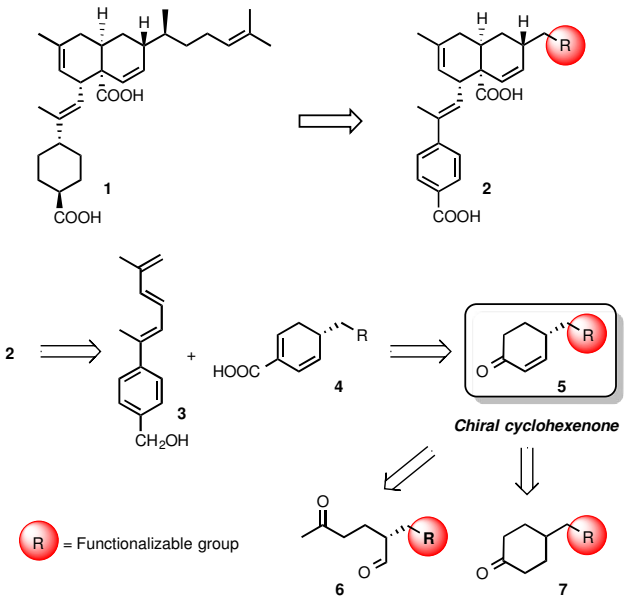
The synthesis, on a large scale, with very good yield and *er via* an efficient strategy, of a chiral 4-substituted 2-cyclohexenone intermediate, was a milestone in the synthesis of seven analogues of meiogynin A, a natural sesquiterpenoid dimer. These compounds were elaborated in ten linear steps. Their binding affinities for Bcl-xL and Mcl-1, two proteins of the Bcl-2 family, overexpressed in various types of cancers, were evaluated. This enabled to further SAR studies en route to the elaboration of potent dual inhibitors of anti-apoptotic proteins of the Bcl-2 family.

Introduction

Meiogynin A **1**[1] was isolated a few years ago from the bark of a Malaysian tree of the Annonaceae family. This compound is a natural inhibitor[2] of Mcl-1 and Bcl-xL, two antiapoptotic proteins of the Bcl-2 family, which are key players in apoptosis.[3] They are divided into anti-apoptotic members such as Bcl-2, Bcl-xL and Mcl-1 and pro-apoptotic members such as Bax, Bak and Bid. The anti-apoptotic proteins disable the pro-apoptotic ones by binding in a hydrophobic cleft through protein–protein interactions. Over the past decade, it has been shown that overexpression of the anti-apoptotic Bcl-2, Bcl-xL or Mcl-1 proteins is involved in the development of many kinds of cancers or confers resistance to apoptosis induced by standard anticancer therapies.[4] Thus, this family of proteins represents an interesting target for tumour treatment. The most promising therapeutic approach consists of disrupting protein–protein interactions between anti- and pro-apoptotic members of the Bcl-2 family, using small molecule inhibitors.[5] Some of these are currently in clinical or pre-clinical studies either as selective inhibitors of a subset of proteins[6] or as pan-inhibitors.[7]

The biological properties and unique structure of meiogynin A **1**, led us to consider its total synthesis *via* a biomimetic approach[8] and later on, to elaborate analogues to further SAR studies.[9,10] Particularly, we showed that the cyclohexane moiety of meiogynin A could be replaced by an aromatic without influencing its biological activities.[9] In this paper, we disclose the synthesis of analogues of type **2**, in which a modular chain replaced the lateral terpene chain of meiogynin A.

The main issue of this synthesis resides in the large-scale elaboration of a chiral 4-substituted 2-cyclohexenone **5**, carrying a functionalizable lateral chain that could lead to various analogues of meiogynin A **1**. In the literature, asymmetric routes to such compounds are relatively limited[11] and often require multi-steps sequences or inconvenient experimental conditions. Two strategies were envisaged: an intramolecular aldol condensation of keto aldehyde **6** and a desymmetrization/oxidation from a prochiral cylohexanone **7**.



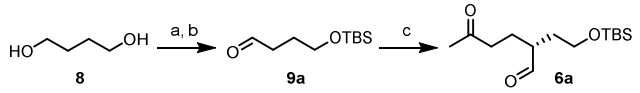
Scheme 1 Retrosynthetic approach to analogues **2** of meiogynin A **1** and key intermediates involved.

Synthesis of chiral 2-cyclohexenone 5 by intramolecular aldol condensation

First, a stepwise Robinson-type annulation employing an asymmetric Michael addition of a protected hydroxy-aldehyde to methyl vinyl ketone followed by a base-mediated ring closure was envisaged to prepare the functionnalizable cyclohexenone **5** (Scheme 1). Baran's[12] and Nicolaou's[13] groups elegantly

developed this strategy for the synthesis of dihydrojunenol and *ent*-7-epizingiberene respectively. In a similar fashion, the precursors of meiogynin A **1** and its aromatic derivatives were elaborated starting from both (*R*)- and (*S*)-citronellal.[8] The group of McQuade has recently disclosed that base mediated cyclisation of 2-monosubstituted-5-oxohexanals requires branching of the substituent to prevent partial epimerization due to the enolisation of the aldehyde intermediate.[14] These observations highlighted the potential difficulty to keep the enantiomeric *ratio* determined for compound **6** over the ring closure reaction.

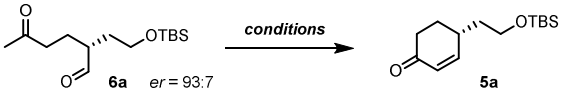
The aldehyde precursor **9a** was obtained in two steps from 1,4-butanediol **8** by a mono-protection using TBSCl[15] and oxidation with PCC.[16] Then, an asymmetric addition to methyl vinyl ketone in presence of a catalytic amount of (*R*)-2,2-diphenylprolinol methyl ether[9,13,17] and ethyl 3,4-dihydroxybenzoate as co-catalyst (that could electrophilically activate the enone via hydrogen bond donation to the carbonyl oxygen) gave the desired TBS-protected Michael adduct **6a**[14] after 6 days with 79% yield and a good asymmetric induction (*er* = 93:7).[18]

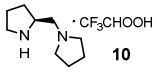


Scheme 2 Synthesis of the chiral Michael adduct **6a**. Reagents and conditions: (a) **8** (5 equiv.), TBSCl (1 equiv.), Et_3N (2 equiv.), CH_2Cl_2, rt, 18 h, 98%; (b) PCC (1.2 equiv.), CH_2Cl_2, 0 °C, 1 h, 81%; (c) Methyl vinyl ketone (1.2 equiv.), (*R*)-2,2-diphenylprolinol methyl ether (5 mol%), ethyl 3,4-dihydroxybenzoate (20 mol%), 4 °C, 6 d, 79%, *er* = 93:7.

Various conditions were investigated for the intramolecular aldol condensation of the keto-aldehyde **6a** (Table 1). A catalytic amount of LiOH in *i*-PrOH was first used to carry out this reaction (entry 1) as Baran *et al.*[19] reported that these conditions could avoid the epimerization of the chiral center. However, despite the fact that the 2-cyclohexenone **5a** could be isolated with a good yield (86%), we observed partial epimerization (*er* = 73:27). The use of K_2CO_3 in MeOH (entry 2) or a mixture of acetic acid and isopropylamine in toluene[20] (entry 3) gave even worst results with lower yields and complete erosion of optical purity. Only traces of cylohexenone **5a** were detected when the substrate was heated with PTSA under Dean-Stark conditions (entry 4). In addition, whatever the conditions tested, variable amounts (5-30%) of deprotected cyclohexenone were obtained. Finally, we used the procedure described by McQuade,[14] who developed specific conditions to perform the aldol condensation reaction of unbranched systems, using the TFA salt of a proline catalyst **10** in hexane (entry 5). Nevertheless, in our hands, these conditions were not successful as poor conversion and partial loss of optical purity were observed.

Table 1 Study of the intramolecular aldol condensation of **6a**.

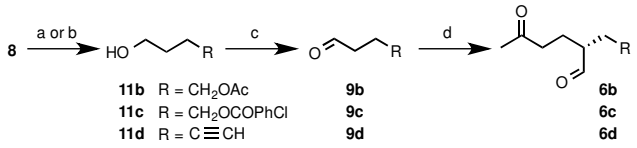


Entry	Conditions	Yield (%)[a]	*er*[b]
1	LiOH (0.1 equiv.), *i*-PrOH, rt, 48 h	86	73:27
2	K_2CO_3 (2 equiv.), MeOH, rt, 1 h	51	61:39
3	AcOH (2 equiv.), *i*-$PrNH_2$ (1 equiv.), toluene, rt, 18 h	67	50:50
4	PTSA (1.2 equiv.), toluene, Dean Stark, 120 °C, 48 h	traces	nd[c]
5	 **10** (0.2 equiv.), hexane, rt, 18 h	17	53:46

[a] Isolated yield obtained after purification on silica gel. [b] Enantiomeric ratios were determined by chiral HPLC. [c] Not determined.

These disappointing results prompted us to change the aldehyde intermediate, in case the TBS-hydroxy had a detrimental effect on the cyclisation reaction. Thus, three aldehydes possessing either a hydroxy group protected as an ester (**9b**[21] and **9c**), or a terminal alkyne (**9d**[22]) were prepared by oxidation of the corresponding alcohol **11b, 11c,**[23] **11d** with PCC (Scheme 3). The alkyne function of **9d** could be used to extend the lateral chain of the corresponding cyclohexenone, by Sonogoshira coupling.

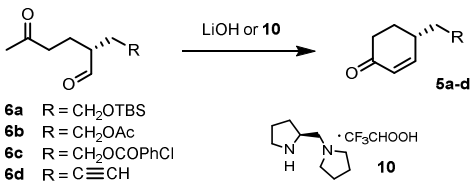
They were directly engaged in asymmetric Michael addition to methyl vinyl ketone, leading to the keto-aldehydes **6b-d** with reasonable yields. The enantiomeric *ratio* of **6b** and **6d** could not be measured on chiral HPLC (Table 2, entries 1 and 3) although several conditions were tested on different columns. However the *p*-chlorobenzoyl compound **6c** exhibited a good enantiomeric *ratio* of 80:20 (entry 2), slightly lower than the TBS-protected hydroxy one **6a** (Scheme 1).



Scheme 3 Preparation of the Michael adducts **6b-d**. Reagents and conditions: (a) **8** (5 equiv.), AcOH (1 equiv.), H_2SO_4 (0.1 equiv.), CH_2Cl_2, rt, 18 h, 98% (**11b**); (b) **8** (5 equiv.), *p*-chlorobenzoyl chloride (1 equiv.), Et_3N (2 equiv.), CH_2Cl_2, 0 °C, 4 h, 84% (**11c**); (c) PCC (1.1 equiv.), CH_2Cl_2, 0 °C, 1 h, 74% (**9b**), 89% (**9c**), 34% (**9d**); (d) Methyl vinyl ketone (1.2 equiv.), (*R*)-2,2-diphenylprolinol methyl ether (5 mol%), ethyl 3,4-dihydroxybenzoate (20 mol%), 4 °C, 6 d, 51% (**6b**), 70% (**6c**), 36% (**6d**).

The best conditions obtained for intramolecular aldol condensation of compound **6a**, *ie* 10 mol% of LiOH in *i*-PrOH, were applied on these aldehydes **6b-d**. In these conditions, the acetylated compound **6b** led to complete degradation (Table 2, entry 1). The alkyne derivative **5d** could be isolated with only 5% yield (low conversion) and with an *er* of 75:25, while the *p*-chlorobenzoyloxy derivative **6c** gave the corresponding cyclized product **5c** with 32% yield but with a loss of optical purity (*er* = 68:32). The use of McQuade's conditions (catalyst **10** in hexane) was not successful (moderate conversion and partial loss of optical purity regardless of the substrate **6b-d** (Table 2, entries 1-3). The lack of solubility of these keto-aldehydes **6b-d** could explain the low conversion rate, and therefore the partial enolization.

Table 2 Aldol condensation of various Michael adducts **6b-d**: comparison of two different bases.



Entry	Substrate	*er*[a]	LiOH (0.1 equiv.)[b] Yield (%)[d]	*er*[a]	**10** (0.2 equiv.)[c] Yield (%)[d]	*er*[a]
1	**6b**	nd[e]	–[f]	nd[c]	51	nd[c]
2	**6c**	80:20	32	68:32	67	55:45
3	**6d**	nd[c]	5	75:25	traces	68:32

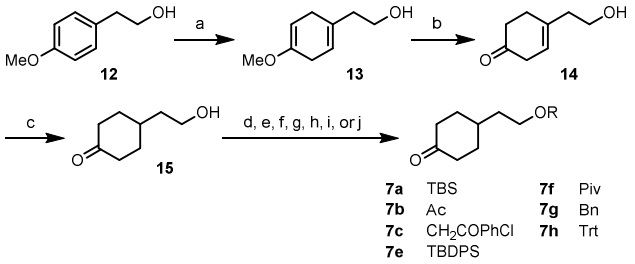
[a] Enantiomeric ratios were determined by chiral HPLC. [b] Reagents and conditions: LiOH (0.1 equiv.), *i*-PrOH, rt, 48 h. [c] Reagents and conditions: **10** (0.2 equiv.), hexane, rt, 18 h. [d] Isolated yield obtained after purification on silica gel. [e] Not determined. [f] Degradation was observed.

Indeed, only a very little racemisation was observed in the course of the synthesis of meiogynin A and its aromatic analogues that possess a branched lateral chain, whereas those unbranched keto-aldehydes **6a-d** led to almost complete racemization. The screening of all these conditions and the poor results thus obtained in term of yield and enantiomeric excess are in line with McQuade's observation and prompted us to revise our synthetic strategy for the preparation of optically active 2-cyclohexenones **5**.

Synthesis of chiral 2-cyclohexenone 5 by desymmetrization

We then turned our attention to the desymmetrization of a prochiral cyclohexanone, as an alternative method to the asymmetric synthesis of **5**. Kinetic deprotonation of prochiral cyclic ketones by chiral amide bases has been extensively studied in the early 90's.[24] In the literature, most of the examples deal with the desymmetrization of 4-*t*-butyl or 4-isopropylcyclohexanones.[25] We applied this strategy to the desymmetrization of various cyclohexanones **7a-h**, whose hydroxyethyl chain at position 4 was protected by various groups and that were prepared in 4 linear steps (Scheme 4). The *p*-methoxyphenethyl alcohol **12** was submitted to a Birch reduction followed by cleavage of the methyl enol ether in acidic conditions. The remaining double bond of the 3-cyclohexenone **14** was then reduced by hydrogenation and gave the prochiral cyclohexanone **15** in 87% over the 3 steps.[26] Different protecting groups were chosen for the alcohol in order to evaluate their influence on the desymmetrization. Silyl ethers **7a** and **7e** were obtained almost quantitatively using standard conditions. An acetyl, *p*-chlorobenzoyl, pivaloyl and trityl protecting group were also introduced with 78%, 97%, 79% and 92% yield respectively. To prepare the benzylated alcohol **7g**, silver(I) oxide was used as base because classical conditions (*ie* NaH and BnBr) led to complete degradation of the starting cyclohexanone **15**.

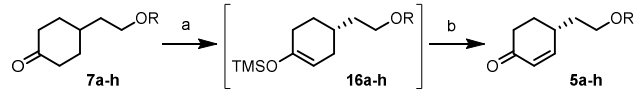
These prochiral cyclohexanones **7a-h** were converted to the corresponding cyclohexenones **5a-h** in a two-step procedure (Table 3).



Scheme 4 Preparation of the protected cyclohexanones **7a-h**. Reagents and conditions: (a) Li (6 equiv.), *t*-BuOH, NH_3, -78 °C, 5 h; (b) H_2SO_4, THF, rt, 2 h; (c) Pd/C, EtOAc, H_2 atm, rt, 18 h, 87% (3 steps); (d) TBSCl (1.05 equiv.), imidazole (2 equiv.), DMAP (0.05 equiv.), DMF, rt, 18 h, 98%; (e) Ac_2O (5 equiv.), Et_3N (2 equiv.), DMAP (5 mol%), CH_2Cl_2, rt, 2 h, 78%; (f) *p*-chlorobenzoyl chloride (1.05 equiv.), Et_3N (3 equiv.), CH_2Cl_2, 0 °C, 2 h, 97%; (g) TBDPSCl (1.05 equiv.), imidazole (2 equiv.), DMAP (5 mol%), DMF, rt, 18 h, 98%; (h) PivCl (1.05 equiv.), Et_3N (2 equiv.), CH_2Cl_2, rt, 18 h, 79%; (i) BnBr (1.1 equiv.), Ag_2O (1.5 equiv.), CH_2Cl_2, rt, 18 h, dark, 71%; (j) TrtCl (2 equiv.), pyridine, 70 °C, 2 h, 92%.

Indeed, after an enantioselective deprotonation with lithium bis((*R*)-1-phenylethyl)amide[27] and *in situ* enolate quench with trimethylsilyl chloride, chiral silyl enol ether **16a-h** intermediates could be obtained. They were immediately transformed into the expected 2-cyclohexenones **5a-h**, using Saegusa's oxidation conditions[28] under O_2 atmosphere in presence of catalytic amount of palladium(II) acetate.

Table 3 Synthesis of chiral cyclohexenones **5a-h** by asymmetric desymmetrization.



Entry	Substrate	R	Yield (%)[a,b]	*er*[c]
1	**7a**	TBS	63	91:9
2	**7b**	Ac	39	nd[d]
3	**7c**	COPhCl	92[e]	94:6
4	**7e**	TBDPS	88	92:8
5	**7f**	Piv	89	nd[d]
6	**7g**	Bn	79	92:8
7	**7h**	Trt	83	91:9

[a] Reagents and conditions: (a) bis[(*R*)-1-phenylethyl]amine (1.1 equiv.), *n*-BuLi (1.2 equiv.), THF, -78 °C, 30 min, then TMSCl (5 equiv.), **7a-h** in THF, -78 °C, 1 h; (b) $Pd(OAc)_2$ (5 mol%), DMSO, O_2 atm, rt, 18 h. [b] Isolated yield over 2 steps obtained after purification on silica gel. [c] Enantiomeric ratios were determined by chiral HPLC. [d] Not determined. [e] Optimized yield.

Whatever the protecting group, the 2-cylohexenones were generally isolated with good yields, except compound **5b** (entry 2). Moreover a very good asymmetric induction was observed during the formation of all the cylohexenones **5** (*er* between 91:9 and 94:6) except for the acetyl and pivaloyl derivatives **5b** and **5f** (entries 2 and 5) for which the *er* could not be measured. However, the partial separation obtained in chiral HPLC for these two compounds let us supposed that they should have an *er* in the same range. These results clearly emphasize that this strategy is a very convenient way to elaborate chiral 4-(2-hydroxyethyl)cyclohexan-1-one.

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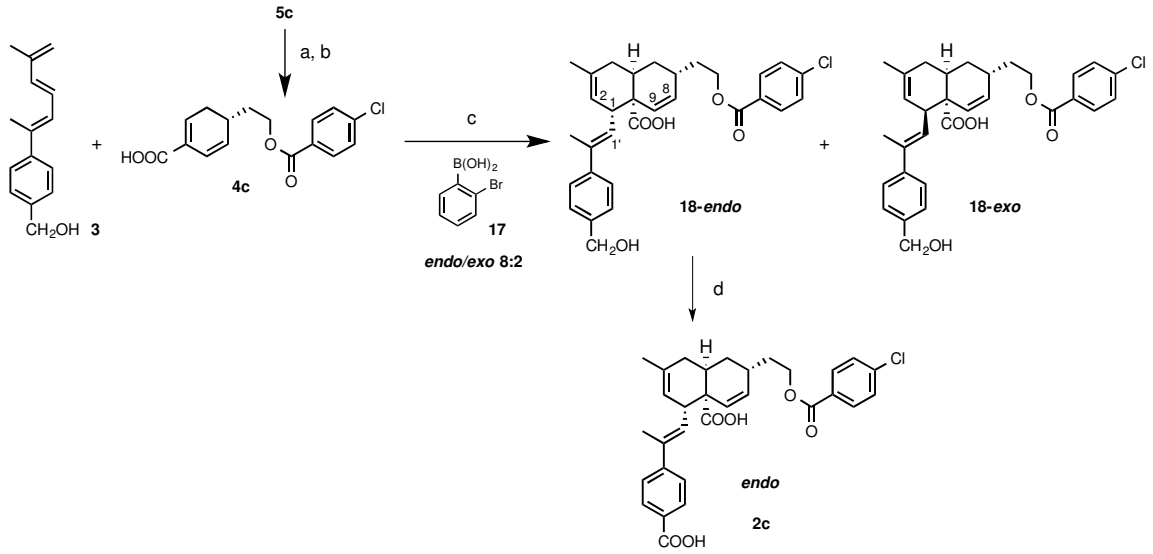


Scheme 5 Formation of the decalin **2c**. Reagents and conditions: (a) NaHMDS (2 equiv.), THF, -78 °C, 1 h, then Comins' reagent (3 equiv.), -78 °C, 3 h, 99%; (b) KOAc (4 equiv.), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), DMF, CO atm, rt, 7 h, 94%; (c) **4c** (1 equiv.), **17** (20 mol%), benzene, 60 °C, 8 d, dark, 98% (*endo/exo* 8:2), 75% (*endo*); (d) Jones reagent (2.5 equiv.), acetone, rt, 5 h, 98%.

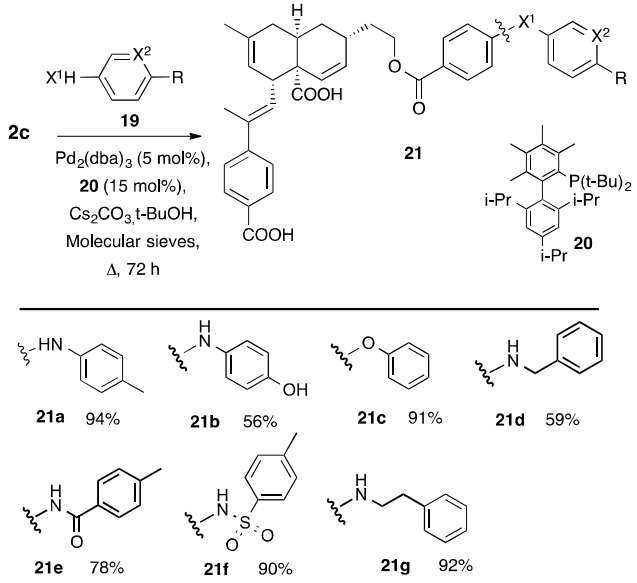
As no significant differences were observed between the protected cyclohexenones **5a-h** in terms of *er* and yield, the *p*-chlorobenzoyl derivative **5c** (entry 3) was selected to go further in the synthesis. Indeed, the chlorine atom could be used as an handle to extend the lateral chain by organometallic couplings. This robust synthetic pathway of six linear steps could be scaled up to 5 g of 4-substituted 2-cyclohexenone **5c**, which was isolated with an excellent overall yield of 78% and with a very good *er* (94:6).

Formation of the decalin core

The decalin core of analogues of meiogynin A was elaborated by a Diels-Alder cycloaddition reaction between the triene **3** and the dienophile **4c**. Compound **3** was prepared in two steps from 4-ethynylbenzyl alcohol.[9] Compound **4c** was obtained in 94% yield from the cyclohexenone **5c** by a carbonylation of its triflate intermediate.[10] The two partners were engaged in the Diels-Alder cycloaddition in presence of a substoichiometric amount of 2-bromophenylboronic acid **17**[29] in benzene (Scheme 5). A complete conversion was observed after 8 days at 60 °C and the *cis*-decalin **18** was isolated in 98% yield with very good chemo-, regio-, and facial selectivities, as only one out of the two possible dienes of **3** reacted with dienophile **4c**, *anti* to its lateral chain. In addition, the diastereoselectivity was satisfying (albeit lower than when a chlorinated triene is used[10]), as a 8:2 mixture of *endo* and *exo* products **18** was obtained. The pure *endo* compound could be isolated in 75% yield after purification on silica gel. Its structure was unambiguously assigned by comparison of its NMR spectra to those of natural meiogynin A[1] and of its aromatic analogues[9] that are very similar, particularly regarding the chemical shifts of H-1 (m, 3.31-3.38), H-2 (m, 5.18-5.22), H-1' (d, 5.51) and H-8 and H-9 (m, 5.63-5.72). Finally, the desired functionalizable meiogynin A analogue **2c** was obtained by Jones oxidation with 98% yield. It should be noted that alternative greener and/or catalytic conditions were unsuccessful, resulting either in recovery of the starting material or in degradation products.

Extension of the lateral chain and biological evaluation on Bcl-xL and Mcl-1

The lateral chain of this pre-functionalized *cis*-decalin **2c** was finally extended by Buchwald–Hartwig cross coupling with various nucleophiles (Scheme 6). In the presence of a monodentate biaryl phosphine–Pd catalyst **20**, aniline, phenol, alkylamine, amide, or sulphonamide led to the corresponding cross coupling product **21a-g** with good to excellent yields 56% to 94% (Scheme 6).



Scheme 6 Functionalization of the chlorobenzyl ester **2c** by Buchwald-Hartwig cross coupling.

The binding affinities to Bcl-xL and Mcl-1 of the final compounds **21a-g**, as well as those of their precursors **3**, **4c**, **18** and **2c** were evaluated, using a fluorescence polarization assay adapted from Qian and co-workers[30] (Table 4). The principle of this biological test is based on the competition of interaction between a small molecule inhibitor and a fluorescent pro-apoptotic peptide (BH3 domain of BAK protein or BID protein) with the antiapoptotic proteins Bcl-xL and Mcl-1. First of all, triene **3** and dienophile **4c** are poor ligands of both proteins (entries 2 and 3). Second, almost all the analogues prepared show a higher affinity for both proteins than meiogynin A **1** (entry 1). The two *p*-chlorobenzoyl derivatives **18** and **2c** exhibit a good binding affinity toward Mcl-1 (entries 4 and 5). However, a difference was observed on the Bcl-xL/Bak displacement assay since the benzoic acid **2c** seems to better bind into the Bcl-xL cleft than the benzyl alcohol **18** (K_i = 2.4 and 13.1 µM respectively). Then, all the elongated compounds **21** have a significant binding affinity for both proteins although in same range as the chlorinated precursor **2g**, except **21c** and **21e**. In fact, the *p*-cresyl ether **21c** is ten times more active on the two proteins than meiogynin A **1** (entry 8). The benzamide analogue **21e** exhibits an excellent affinity for Mcl-1 of the order of 300 nM (entry 10), *ie* almost twenty times more active than the natural reference **1**. These very good results show that an elongation of the side chain with aromatic groups can improve the affinity. Moreover, the benzoic acid seems to be crucial for the interaction with Bcl-xL contrary to Mcl-1.

Table 4 Biological evaluation of the ligands on Bcl-xL/Bak and Mcl-1/Bid displacement assays.

Entry	Ligand	Bcl-xL/Bak binding affinity[a] K_i[b] (µM)	Mcl-1/Bid binding affinity[a] K_i[b] (µM)
1	**1**	8.3 ± 1.2	5.2 ± 1.2
2	**3**	> 23	> 33
3	**4c**	> 23	> 33
4	**18**	13.1 ± 0.8	2.0 ± 0.1
5	**2c**	2.4 ± 0.1	2.2 ± 0.1
6	**21a**	1.3 ± 0.1	1.2 ± 0.1
7	**21b**	3.8 ± 0.2	2.1 ± 0.1
8	**21c**	0.7 ± 0.1	0.5 ± 0.1
9	**21d**	2.4 ± 0.1	1.5 ± 0.1
10	**21e**	1.8 ± 0.1	0.3 ± 0.1
11	**21f**	3.5 ± 0.1	1.1 ±0.2
12	**21g**	3.2 ± 0.7	1.5 ± 0.2

[a] Binding affinities were measured by fluorescence polarization after competition between the ligand and a fluorescein-labelled peptide *ie* BH3 domain of BAK protein (F-Bak) or BID protein (F-Bid) to Bcl-xL and Mcl-1. [b] K_i is the concentration of the ligand corresponding to 50% of the binding of the labelled reference compound, and corrected for experimental conditions (see experimental section).

Conclusions

Seven analogues **21a-g** of natural sesquiterpenoid dimer meiogynin A **1** were elaborated in ten linear steps. Their biological activity confirmed that replacement of the lateral terpene chain by a modular aromatic chain is beneficial for their binding affinities to Bcl-xL and Mcl-1. In addition, the key intermediate, the chiral 4-substituted 2-cyclohexenone **5c** was obtained on a large scale with very good yield and *er* using a highly selective two-step procedure from the corresponding cyclohexanone. This strategy was applied to the synthesis of a set of linear 4-substituted 2-cyclohexenones that could be useful intermediates for synthesis of natural compounds.

Experimental section

Materials and methods

All reagents and solvents were used as purchased from commercial suppliers or were purified/dried according to Armarego and Chai.[31] Purifications by column chromatography on silica gel were performed using Merck Silica Gel 60 (70-230 mesh) and purifications by preparative thin layer chromatography on silica gel using Merck Silica Gel 60 PF_{254}. ^1H and ^{13}C NMR spectra were recorded on a Bruker ARX500 instrument using $CDCl_3$, acetone-d_6, or CD_3OD with trace mono-protonated residual solvents used 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) or by Atmospheric Pressure Photo-Ionization (APPI). Melting points were measured with a Büchi Melting Point B-540 apparatus. Optical rotation, $[\alpha]_D^{20}$ values, were measured using an Anton Paar MCP 300 instrument and are expressed in $deg.cm^3.g^{-1}.dm^{-1}$ for a concentration of compound in $g.cm^{-1}$. IR spectrum of compound

2c was recorded on a Perkin Elmer Spectrum BX-FTIR spectrometer. Chiral HPLC was performed on a Waters Alliance 2695 apparatus.

1,4-Butanediol-1-acetate (11b). To a solution of 1,4-butanediol **8** (8.8 mL, 100 mmol, 1eq) in CH_2Cl_2 (100 mL) was added, at rt, AcOH (5.6 mL, 98 mmol, 1 eq) and H_2SO_4 (0.3 mL, 5 mmol, 0.05 eq). The mixture was stirred for 18 h then water was added. The product was then extracted with CH_2Cl_2 (3 times) and the combined organic phases were washed successively with a saturate solution of Na_2CO_3 and brine, dried over $MgSO_4$ and concentrated under reduced pressure to give compound **11b** as a colourless oil (13.1 g, 97 mmol, 98%) that was used without further purification. The spectroscopic data were similar to those already reported in the literature.[32]

4-Hydroxybutyl 4-chlorobenzoate (11c). To a solution of 1,4-butanediol **8** (11.1 mL, 125 mmol, 5 eq) and Et_3N (7.0 mL, 50 mmol, 2 eq) in CH_2Cl_2 (50 mL) at 0 °C was slowly added *p*-chlorobenzoyl chloride (3.2 mL, 25 mmol, 1 eq). The mixture was stirred at this temperature for 4 h and quenched with a saturated solution of NH_4Cl. The product was then extracted with MTBE (3 times) and the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using heptane/EtOAc from 8:2 to 1:1 to obtain the ester as a yellow oil (4.8 g, 21 mmol, 84%). R_f = 0.3 (heptane/EtOAc 6:4); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, J = 8.4 Hz, 2 H), 7.39 (d, J = 8.4 Hz, 2 H), 4.35 (t, J = 6.2 Hz, 2 H), 3.71 (t, J = 6.2 Hz, 2 H), 1.89-1.82 (m, 2 H), 1.75-1.67 (m, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.8, 139.3, 130.9 (2 C), 128.7, 128.6 (2 C), 65.0, 62.3, 29.1, 26.2 ppm; HRMS (ESI): *m/z* calcd. for $C_{11}H_{14}ClO_4$ $[M+H]^+$ 229.0626; found 229.0633.

4-Oxobutyl 4-chlorobenzoate (9c). To a suspension of molecular sieves 4 Å in powder (5 g) in anhydrous dichloromethane (40 mL) was added the alcohol **11c** (19.2 mmol, 1 eq). The mixture was cooled down to 0 °C and PCC (21.1 mmol, 1.1 eq) was added portionwise. After 1 h at rt, the mixture was filtered and the filtrate was concentrated under reduced pressure. The product was then purified by column chromatography on silica gel using heptane/EtOAc from 8:2 to 1:1 to give the corresponding aldehyde **9c** as colorless oil (3.9 g, 17 mmol, 89%) that was immediately engaged in the next reaction. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.78 (s, 1 H), 7.94 (d, J = 9.3 Hz, 2 H), 7.40 (d, J = 9.3 Hz, 2 H), 4.34 (t, J = 6.8 Hz, 2 H), 2.61 (t, J = 6.8 Hz, 2 H), 2.10 (q, J = 6.8 Hz, 2 H).

General procedure for the asymmetric 1,4-addition

A mixture of (*R*)-2,2-diphenylprolinol methyl ether (190 mg, 0.7 mmol, 0.05 eq), ethyl 3,4-dihydroxybenzoate (500 mg, 2.8 mmol, 0.2 eq) and the aldehyde **9a-d** (13.8 mmol, 1 eq) in methyl vinyl ketone (1.35 mL, 16.6 mmol, 1.2 eq) was stirred at 0 °C for 6 days. The product was then isolated after purification by chromatography on silica gel.

(*R*)-2-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-5-oxohexanal (6a). Obtained as a yellow oil (64% over 2 steps from **11a**); R_f = 0.25 (heptane/EtOAc 9:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.57 (d, J = 2.4 Hz, 1 H), 3.70-3.59 (m, 2 H), 2.55-2.33 (m, 3 H), 2.12 (s, 3 H), 1.96-1.84 (m, 2 H), 1.77-1.64 (m, 2 H), 0.86 (s, 9 H), 0.08 (s, 6 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.8, 204.1, 60.5, 48.6, 40.7, 32.5, 30.0, 25.8 (3 C), 22.2, 18.2, -5.5 (2 C) ppm; HRMS (ESI): *m/z* calcd. for $C_{14}H_{29}O_3Si$ $[M+H]^+$ 273.1880; found 273.1882.

(*R*)-3-Formyl-6-oxoheptyl acetate (6b). Obtained as a yellow oil (38% over 2 steps from **11b**); R_f = 0.3 (heptane/EtOAc 1:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.57 (d, J = 1.6 Hz, 1 H), 4.08 (t, J = 6.4 Hz, 2 H), 2.53-2.34 (m, 3 H), 2.11 (s, 3 H), 2.06-2.01 (m, 1 H), 2.00 (s, 3 H), 1.94-1.85 (m, 1 H), 1.80-1.71 (m, 2 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.4, 203.3, 170.7, 61.8, 48.2, 40.2, 29.9, 27.9, 22.0, 20.7 ppm; HRMS (ESI): *m/z* calcd. for $C_{10}H_{16}NaO_4$ $[M+Na]^+$ 223.0941; found 223.0949.

(*R*)-3-Formyl-6-oxoheptyl 4-chlorobenzoate (6c). Obtained as a yellow oil (57% over 2 steps from **11c**); R_f = 0.4 (heptane/EtOAc 6:4); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.65 (d, J = 1.7 Hz, 1 H), 7.93 (d, J = 7.3 Hz, 2 H), 7.42 (d, J = 7.3 Hz, 2 H), 4.37 (t, J = 6.4 Hz, 2 H), 2.55-2.46 (m, 2 H), 2.24-2.16 (m, 1 H), 2.14 (s, 3 H), 2.03-1.80 (m, 3 H) ppm; HRMS (ESI): *m/z* calcd. for $C_{15}H_{16}ClO_4$ $[M-H]^-$ 295.0743; found 295.0731.

(*R*)-5-oxo-2-(prop-2-yn-1-yl)hexanal (6d). Obtained as a yellow oil (11% from commercial **11d**); R_f = 0.3 (heptane/EtOAc 7:3); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.67 (d, J = 1.4 Hz, 1 H),2.61-2.40 (m, 5 H), 2.14 (s, 3 H), 2.09-2.00 (m, 2 H), 1.91-1.82 (m, 1 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.4, 202.4, 80.3, 70.8, 49.0, 40.0, 29.9, 21.7, 18.0 ppm; HRMS (ESI): *m/z* calcd. for $C_9H_{11}O_2$ $[M-H]^-$ 151.0765; found 151.0754.

General procedure for the aldol condensation with LiOH

To a solution of the keto-aldehyde **6a-d** (3.7 mmol, 1 eq) in *i*-PrOH (15 mL) was added $LiOH.H_2O$ (15 mg, 0.4 mmol, 0.1 eq). The mixture was stirred overnight at rt and concentrated under reduced pressure. A saturated solution of NH_4Cl was then added and the product was extracted with MTBE (3 times). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The cyclohexenone **5a-c** was obtained after purification by column chromatography on silica gel.

4-[2-(*tert*-Butyldimethylsilyloxy)ethyl]cyclohex-2-en-1-one (5a). Obtained as a colorless oil (86% from **6a**); R_f = 0.4 (heptane/EtOAc 8:2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.90 (d, J = 9.9 Hz, 1 H), 5.96 (dd, J = 9.9, 1.7 Hz, 1 H), 3.78-3.66 (m, 2 H), 2.66-2.58 (m, 1 H), 2.53-2.46 (m, 1 H), 2.41-2.31 (m, 1 H), 2.16-2.07 (m, 1 H), 1.80-1.66 (m, 2 H), 1.65-1.56 (m, 1 H), 0.89 (s, 9 H), 0.05 (s, 6 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.8, 155.2, 128.9, 60.4, 37.2, 36.8, 33.0, 28.5, 25.9 (3 C), 18.3, -5.4 (2 C) ppm; HRMS (ESI): *m/z* calcd. for $C_{14}H_{27}O_2Si$ $[M+H]^+$ 255.1775; found 255.1777.

2-(4-Oxocyclohex-2-en-1-yl)ethyl acetate (5b). Obtained as a colorless oil (51% from **6b**); R_f = 0.1 (heptane/EtOAc 8:2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.81 (d, J = 10.3 Hz, 1 H), 5.95 (dd, J = 10.3, 2.2 Hz, 1 H), 4.21-4.09 (m, 2 H), 2.56-2.42 (m, 2 H), 2.37-2.29 (m, 1 H), 2.16-2.08 (m, 1 H), 2.02 (s, 3 H), 1.88-1.79 (m, 1 H), 1.76-1.64 (m, 2 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.2, 170.8, 153.5, 129.3, 61.7, 36.6, 33.2, 33.0, 28.4, 20.8 ppm; HRMS (ESI): *m/z* calcd. for $C_{10}H_{15}O_3$ $[M+H]^+$ 183.1016; found 183.1014.

2-(4-Oxocyclohex-2-en-1-yl)ethyl 4-chlorobenzoate (5c). Obtained as a white solid (70% from **6c**); R_f = 0.2 (heptane/EtOAc 7:3); Mp = 44 ± 2 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, J = 8.3 Hz, 2 H), 7.41 (d, J = 8.3 Hz, 2 H), 6.88 (d, J = 10.0 Hz, 1 H), 6.01 (d, J = 10.0 Hz, 1 H), 4.49-4.40

(m, 2 H), 2.68-2.59 (m, 1 H), 2.56-2.48 (m, 1 H), 2.43-2.33 (m, 1 H), 2.24-2.16 (m, 1 H), 2.06-1.97 (m, 1 H), 1.93-1.85 (m, 1 H), 1.83-1.73 (m, 1 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.1, 165.5, 153.3, 139.5, 130.9 (2 C), 129.5, 128.8 (2 C), 128.4, 62.5, 36.7, 33.4, 33.2, 28.5 ppm; HRMS (ESI): *m/z* calcd. for $C_{15}H_{16}ClO_3$ $[M+H]^+$ 279.0782; found 279.0795.

4-[2-(*tert*-Butyldimethylsilyloxy)ethyl]cyclohexan-1-one (7a). To a solution of alcohol **15** (400 mg, 2.8 mmol, 1 eq) in DMF (10 mL) under Ar atm. was added imidazole (380 mg, 5.6 mmol, 2 eq), DMAP (10 mg) and *tert*-butyldimethylsilyl chloride (445 mg, 2.9 mmol, 1.05 eq). The mixture was stirred at rt overnight and quenched with a saturated solution of NH_4Cl. The product was then extracted with MTBE (3 times) and the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using heptane/EtOAc 95:5 to obtain **7a** as a colorless oil (710 mg, 2.76 mmol, 98%). R_f = 0.4 (heptane/EtOAc 8:2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.68 (t, J = 6.4 Hz, 2 H), 2.40-2.28 (m, 4 H), 2.09-2.02 (m, 2 H), 1.95-1.85 (m, 1 H), 1.53 (q, J = 6.4 Hz, 2 H), 1.40 (dq, J = 4.8, 12.2 Hz, 2 H), 0.90 (s, 9 H), 0.05 (s, 6 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.2, 61.0, 40.8 (2 C), 38.3, 32.7 (3 C), 25.9 (3 C), 18.3, -5.3 (2 C) ppm; HRMS (ESI): *m/z* calcd. for $C_{16}H_{32}NO_2Si$ $[M+MeCN+H]^+$ 298.2197; found 298.2198.

2-(4-Oxocyclohexyl)ethyl acetate (7b). To a solution of alcohol **15** (400 mg, 2.8 mmol, 1 eq) in CH_2Cl_2 (20 mL) under Ar atm. was added Et_3N (1.6 mL, 11.2 mmol, 4 eq), DMAP (10 mg) and acetic anhydride (800 µL, 8.4 mmol, 3 eq). After 2 h at rt, the reaction mixture was quenched with water. The product was then extracted with CH_2Cl_2 (3 times) and the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using heptane/EtOAc 7:3 to obtain **7b** as a colorless oil (402 mg, 2.2 mmol, 78%). R_f = 0.3 (heptane/EtOAc 7:3); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.10 (t, J = 6.7 Hz, 2 H), 2.37-2.25 (m, 4 H), 2.06-2.02 (m, 2 H), 2.01 (s, 3 H), 1.86-1.76 (m, 1 H), 1.61 (q, J = 6.7 Hz, 2 H), 1.39 (dq, J = 4.8, 12.2 Hz, 2 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.5, 171.0, 62.4, 40.6 (2 C), 34.2, 33.0, 32.5 (2 C), 21.0 ppm; HRMS (ESI): *m/z* calcd. for $C_{12}H_{20}NO_3$ $[M+MeCN+H]^+$ 226.1438; found 226.1438.

2-(4-Oxocyclohexyl)ethyl 4-chlorobenzoate (7c). To a solution of alcohol **15** (8.0 g, 56 mmol, 1 eq) in CH_2Cl_2 (100 mL) at 0 °C under Ar atm. was added Et_3N (23.5 mL, 169 mmol, 3 eq) and 4-chlorobenzoyl chloride (7.6 mL, 59 mmol, 1.05 eq). The mixture was allowed to warm to rt overnight and quenched with a saturated solution of NH_4Cl. The product was then extracted with MTBE (3 times) and the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using heptane/EtOAc 8:2 to obtain **7c** as a white solid (15.3 g, 55 mmol, 97%). R_f = 0.2 (heptane/EtOAc 8:2); Mp = 58 ± 2 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, J = 8.6 Hz, 2 H), 7.40 (d, J = 8.6 Hz, 2 H), 4.39 (t, J = 6.7 Hz, 2 H), 2.42-2.29 (m, 4 H), 2.15-2.08 (m, 2 H), 1.97-1.88 (m, 1 H), 1.79 (q, J = 6.7 Hz, 2 H), 1.48 (dq, J = 5.0, 12.3 Hz, 2 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.3, 165.6, 139.4, 130.9 (2 C), 128.7 (2 C), 128.6, 63.2, 40.6 (2 C), 34.3, 33.1, 32.5 (2 C) ppm; HRMS (ESI): *m/z* calcd. for $C_{17}H_{21}ClNO_3$ $[M+MeCN+H]^+$ 322.1204; found 322.1202.

4-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]cyclohexan-1-one (7e). To a solution of alcohol **15** (400 mg, 2.8 mmol, 1 eq) in DMF (10 mL) under Ar atm. was added imidazole (380 mg, 5.6 mmol, 2 eq), DMAP (10 mg) and *tert*-butyldiphenylsilyl chloride (770 µL, 2.9 mmol, 1.05 eq). The mixture was stirred at rt overnight and quenched with a saturated solution of NH_4Cl. The product was then extracted with MTBE (3 times) and the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using heptane/EtOAc 95:5 to obtain **7e** as a colorless oil (1.05 g, 2.76 mmol, 98%). R_f = 0.4 (heptane/EtOAc 8:2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, J = 7.3 Hz, 4 H), 7.43-7.38 (m, 6 H), 3.76 (t, J = 6.4 Hz, 2 H), 2.38-2.24 (m, 4 H), 2.03-1.88 (m, 3 H), 1.58 (q, J = 6.4 Hz, 2 H), 1.37 (dq, J = 4.8, 12.1 Hz, 2 H), 1.09 (s, 9 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.3, 135.5 (4 C), 134.8 (2 H), 127.6 (6 C), 61.8, 40.7 (2 C), 38.0, 32.6 (3 C), 26.9 (3 C), 19.2 ppm; HRMS (ESI): *m/z* calcd. for $C_{24}H_{36}NO_2Si$ $[M+NH_4]^+$ 398.2510; found 398.2514.

2-(4-Oxocyclohexyl)ethyl pivalate (7f). To a solution of alcohol **15** (400 mg, 2.8 mmol, 1 eq) in CH_2Cl_2 (10 mL) under Ar atm. was added Et_3N (780 µL, 5.6 mmol, 2 eq) and pivaloyl chloride 360 µL, 2.09 mmol, 1.05 eq). The mixture was stirred at rt overnight and quenched with a saturated solution of NH_4Cl. The product was then extracted with MTBE (3 times) and the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using heptane/EtOAc 7:3 to obtain **7f** as a light yellow oil (505 mg, 2.2 mmol, 79%). R_f = 0.2 (heptane/EtOAc 8:2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.13 (t, J = 6.7 Hz, 2 H), 2.41-2.27 (m, 4 H), 2.10-2.03 (m, 2 H), 1.89-1.79 (m, 1 H), 1.65 (q, J = 6.7 Hz, 2 H), 1.44 (dq, J = 4.7, 12.3 Hz, 2 H), 1.19 (s, 9 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.6, 178.5, 62.4, 40.7 (2 C), 38.7, 34.2, 33.3, 32.5 (2 C), 27.2 (3 C) ppm; HRMS (ESI): *m/z* calcd. for $C_{15}H_{26}NO_3$ $[M+MeCN+H]^+$ 268.1907; found 268.1913.

4-(2-Benzyloxyethyl)cyclohexan-1-one (7g). To a solution of alcohol **15** (400 mg, 2.8 mmol, 1 eq) in CH_2Cl_2 (10 mL) under Ar atm. was added benzyl bromide (370 µL, 3.1 mmol, 1.1 eq) followed by silver(I) oxide (980 mg, 4.2 mmol, 1.5 eq). The mixture was stirred in the dark at rt overnight and filtered over a Celite pad. The filtrate was then concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using heptane/EtOAc from 95:5 to 7:3 to obtain **7g** as a colorless oil (465 mg, 2.0 mmol, 71%). R_f = 0.3 (heptane/EtOAc 8:2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38-7.25 (m, 5 H), 4.52 (s, 2 H), 3.54 (t, J = 6.3 Hz, 2 H), 2.40-2.27 (m, 4 H), 2.08-2.00 (m, 2 H), 1.98-1.89 (m, 1 H) 1.63 (q, J = 6.3 Hz, 2 H), 1.40 (dq, J = 4.8, 12.2 Hz, 2 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.0, 138.4, 128.3 (2 C), 127.6 (3 C), 73.0, 68.0, 40.7 (2 C), 35.3, 32.9, 32.6 (2 C) ppm; HRMS (APPI): *m/z* calcd. for $C_{15}H_{20}O_2$ $[M]^{+\bullet}$ 232.1458; found 232.1462.

4-(2-Trityloxyethyl)cyclohexan-1-one (7h). A solution of alcohol **15** (400 mg, 2.8 mmol, 1 eq) and trityl chloride (1.57 mg, 5.6 mmol, 2 eq) in pyridine (10 mL) under Ar atm. was heated at 70 °C for 2 h. The mixture was then cooled to rt and a saturated

aqueous solution of NH_4Cl was added. The compound was extracted with MTBE (3 times) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using heptane/EtOAc 95:5 to obtain a white amorphous powder (990 mg, 2.6 mmol, 92%). R_f = 0.5 (heptane/EtOAc 7:3); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, J = 7.6 Hz 6 H), 7.34 (t, J = 7.6 Hz 6 H), 7.27 (d, J = 7.6 Hz 3 H), 3.20 (t, J = 6.4 Hz, 2 H), 2.40-2.27 (m, 4 H), 2.01-1.91 (m, 3 H), 1.67 (q, J = 6.4 Hz, 2 H), 1.37 (dq, J = 4.8, 12.2 Hz, 2 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.1, 144.3 (3 C), 128.6 (6 C), 127.7(6 C), 126.9 (3 C), 86.5, 61.4, 40.7 (2 C), 35.6, 33.0, 32.6 (2 C) ppm; HRMS (ESI): *m/z* calcd. for $C_{27}H_{28}NaO_2$ $[M+Na]^+$ 407.1982; found 407.1987.

General procedure for chiral desymmetrization followed by Saegusa oxidation

A 1.5 M solution of *n*-BuLi in hexanes (14.2 mL, 21.4 mmol, 1.2 eq) was added dropwise to a solution of bis[(*R*)-1-phenylethyl]amine (4.48 mL, 19.6 mmol, 1.1 eq) in THF (150 mL) at -78 °C under Ar atm. After 30 min, TMSCl (11 mL, 89 mmol, 5 eq) was added, followed by a solution of the cyclohexanone **7a-h** (17.8 mmol, 1 eq) in THF (30 mL) over a period of 1 h. After the addition was complete, the mixture was stirred for an additional 1 h at -78 °C and quenched with Et_3N (20 mL). A saturated solution of $NaHCO_3$ (20 mL) was then added and the reaction mixture was allowed to warm to rt. After addition of water, the mixture was extracted with MTBE (3 times) and the combined organic phases were dried over $MgSO_4$. The solvent was then partially evaporated under reduced pressure and the residue was washed with a 0.5 M citric acid solution to remove the amine. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to give the silyl enol ether **16a-h** as a yellow oil. $Pd(OAc)_2$ (200 mg, 0.89 mmol, 0.05 eq) was then added to a solution of the **16a-h** in dry DMSO (50 mL). O_2 was bubbled through for 5 min and the resulting black mixture was stirred at rt under O_2 atm. overnight. The reaction mixture was quenched with a saturated solution of NH_4Cl and the product was extracted with MTBE (3 times). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was then purified by column chromatography on silica gel to give the cyclohexenone **5a-h**.

(*R*)-4-[2-(*tert*-Butyldimethylsilyloxy)ethyl]cyclohex-2-en-1-one (5a). Obtained as a colorless oil (63% from **7a**); R_f = 0.4 (heptane/EtOAc 8:2) ; $[\alpha]_D^{20}$ = -24.4 ° (*c* 1.0, Acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.90 (d, J = 9.9 Hz, 1 H), 5.96 (dd, J = 9.9, 1.7 Hz, 1 H), 3.78-3.66 (m, 2 H), 2.66-2.58 (m, 1 H), 2.53-2.46 (m, 1 H), 2.41-2.31 (m, 1 H), 2.16-2.07 (m, 1 H), 1.80-1.66 (m, 2 H), 1.65-1.56 (m, 1 H), 0.89 (s, 9 H), 0.05 (s, 6 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.8, 155.2, 128.9, 60.4, 37.2, 36.8, 33.0, 28.5, 25.9 (3 C), 18.3, -5.4 (2 C) ppm; HRMS (ESI): *m/z* calcd. for $C_{14}H_{27}O_2Si$ $[M+H]^+$ 255.1775; found 255.1777.

(*R*)-2-(4-Oxocyclohex-2-en-1-yl)ethyl acetate (5b). Obtained as a colorless oil (39% from **7b**); R_f = 0.1 (heptane/EtOAc 8:2) ; $[\alpha]_D^{20}$ = -52.7 ° (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.81 (d, J = 10.3 Hz, 1 H), 5.95 (dd, J = 10.3, 2.2 Hz, 1 H), 4.21-4.09 (m, 2 H), 2.56-2.42 (m, 2 H), 2.37-2.29 (m, 1 H), 2.16-2.08 (m, 1 H), 2.02 (s, 3 H), 1.88-1.79 (m, 1 H), 1.76-1.64 (m, 2 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.2, 170.8, 153.5, 129.3, 61.7, 36.6, 33.2, 33.0, 28.4, 20.8 ppm; HRMS (ESI): *m/z* calcd. for $C_{10}H_{15}O_3$ $[M+H]^+$ 183.1016; found 183.1014.

(*R*)-2-(4-Oxocyclohex-2-en-1-yl)ethyl 4-chlorobenzoate (5c). Obtained as a white solid (92% from **7c**); R_f = 0.2 (heptane/EtOAc 7:3); Mp = 44 ±2 °C; $[\alpha]_D^{20}$ = -45.0 ° (*c* 2.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, J = 8.3 Hz, 2 H), 7.41 (d, J = 8.3 Hz, 2 H), 6.88 (d, J = 10.0 Hz, 1 H), 6.01 (d, J = 10.0 Hz, 1 H), 4.49-4.40 (m, 2 H), 2.68-2.59 (m, 1 H), 2.56-2.48 (m, 1 H), 2.43-2.33 (m, 1 H), 2.24-2.16 (m, 1 H), 2.06-1.97 (m, 1 H), 1.93-1.85 (m, 1 H), 1.83-1.73 (m, 1 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.1, 165.5, 153.3, 139.5, 130.9 (2 C), 129.5, 128.8 (2 C), 128.4, 62.5, 36.7, 33.4, 33.2, 28.5 ppm; HRMS (ESI): *m/z* calcd. for $C_{15}H_{16}ClO_3$ $[M+H]^+$ 279.0782; found 279.0790.

(*R*)-4-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]cyclohex-2-en-1-one (5e). Obtained as a colorless oil (88% from **7e**);. R_f = 0.5 (heptane/EtOAc 8:2); $[\alpha]_D^{20}$ = -12.9 ° (*c* 1.0, Acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, J = 6.9 Hz, 4 H), 7.47 (t, J = 6.9 Hz, 2 H), 7.42 (t, J = 6.9 Hz, 4 H), 6.87 (d, J = 9.9 Hz, 1 H), 5.98 (dd, J = 9.9, 1.8 Hz, 1 H), 3.85-3.75 (m, 2 H), 2.73-2.65 (m, 1 H), 2.51-2.44 (m, 1 H), 2.40-2.31 (m, 1 H), 2.10-2.02 (m, 1 H), 1.85-1.77 (m, 1 H), 1.73-1.62 (m, 2 H), 1.09 (s, 9 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.7, 155.1 (2 C), 135.5 (4 C), 133.6, 129.7 (2 C), 128.9, 127.7 (4 C), 61.2, 37.1, 36.8, 32.9, 28.5, 26.9 (3 C), 19.2 ppm; HRMS (ESI): *m/z* calcd. for $C_{24}H_{31}O_2Si$ $[M+H]^+$ 379.2088; found 379.2102.

(*R*)-2-(4-Oxocyclohex-2-en-1-yl)ethyl pivalate (5f). Obtained as a colorless oil (89% from **7f**); R_f = 0.2 (heptane/EtOAc 8:2); $[\alpha]_D^{20}$ = -59.2 ° (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.85 (d, J = 10.3 Hz, 1 H), 5.99 (dd, J = 10.3, 1.8 Hz, 1 H), 4.23-4.12 (m, 2 H), 2.59-2.46 (m, 2 H), 2.41-2.31 (m, 1 H), 2.19-2.11 (m, 1 H), 1.93-1.84 (m, 1 H), 1.80-1.68 (m, 2 H), 1.19 (s, 9 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.2, 178.4, 153.7, 129.4, 61.7, 38.7, 36.7, 33.4, 33.3, 28.5, 27.2 (3 C) ppm; HRMS (ESI): *m/z* calcd. for $C_{13}H_{21}O_3$ $[M+H]^+$ 225.1485; found 225.1483.

(*R*)-4-[2-(Benzyloxy)ethyl]cyclohex-2-en-1-one (5g). Obtained as a colorless oil (79% from **7g**); R_f = 0.3 (heptane/EtOAc 8:2) ; $[\alpha]_D^{20}$ = -50.9 ° (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38-7.28 (m, 5 H), 6.88 (d, J = 10.6 Hz, 1 H), 5.97 (dd, J = 10.6, 1.7 Hz, 1 H), 4.52 (s, 2 H), 3.64-3.54 (m, 2 H), 2.69-2.61 (m, 1 H), 2.53-2.45 (m, 1 H), 2.41-2.31 (m, 1 H), 2.15-2.07 (m, 1 H), 1.90-1.80 (m, 1 H), 1.75-1.63 (m, 2 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.7, 154.8, 138.2, 129.0, 128.4 (2 C), 127.7, 127.6 (2 C), 73.1, 67.4, 36.8, 34.5, 33.3, 28.6 ppm; HRMS (ESI): *m/z* calcd. for $C_{15}H_{19}O_2$ $[M+H]^+$ 231.1380; found 231.1383.

(*R*)-4-[2-(Trityloxy)ethyl]cyclohex-2-en-1-one (5h). Obtained as a white solid (83% from **7h**); R_f = 0.3 (heptane/EtOAc 8:2); Mp = 101 ±2 °C; $[\alpha]_D^{20}$ = -34.8 ° (*c* 1.0, Acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (d, J = 8.0 Hz, 6 H), 7.34 (t, J = 8.0 Hz, 6 H), 7.27 (t, J = 8.0 Hz, 3 H), 6.83 (d, J = 10.6 Hz, 1 H), 5.97 (dd, J = 10.6, 1.7 Hz, 1 H), 3.31-3.19 (m, 2 H), 2.73-2.65 (m, 1 H), 2.50-2.43 (m, 1 H), 2.39-2.30 (m, 1 H), 2.05-1.97 (m, 1 H), 1.91-1.82 (m, 1 H), 1.76-1.68 (m, 1 H), 1.67-1.57 (m, 1 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.7, 154.9, 144.1, 128.9 (3 C), 128.6 (6 C), 127.8 (6 C), 127.0 (3 C), 86.7,

60.7, 36.8, 34.7, 33.3, 28.6 ppm; HRMS (ESI): *m/z* calcd. for $C_{27}H_{27}O_2$ $[M+H]^+$ 383.2006; found 383.1998.

Compound 18. A solution of triene **3** (560 mg, 2.6 mmol, 1 eq), dienophile **4c** (805 mg, 2.6 mmol, 1 eq) and 2-bromophenylboronic acid **17** (100 mg, 0.5 mmol, 0.2 eq) in benzene (10 mL) was heated at reflux for 8 days. The reaction mixture was then concentrated under reduced pressure and purified by column chromatography on silica gel using heptane/EtOAc/AcOH from 99:0:1 to 80:19:1 to obtain the *endo* decalin **18** as a white solid (1.03 g, 2.0 mmol, 75%). R_f = 0.3 (heptane/EtOAc/AcOH 50:49:1); Mp = 150 ± 2 °C; $[\alpha]_D^{20}$ = -168.0 ° (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.2 Hz, 2 H), 7.41 (d, *J* = 8.2 Hz, 2 H), 7.23 (d, *J* = 8.2 Hz, 2 H), 7.18 (d, *J* = 8.2 Hz, 2 H), 5.72-5.63 (m, 2 H), 5.51 (d, *J* = 10.4 Hz, 1 H), 5.22-5.18 (m, 1 H), 4.61 (s, 2 H), 4.31-4.20 (m, 2 H), 3.38-3.31 (m, 1 H), 2.66-2.59 (m, 1 H), 2.50-2.41 (m, 1 H), 2.07-1.96 (m, 4 H), 1.87-1.78 (m, 2 H), 1.77-1.67 (m, 2 H), 1.63 (s, 3 H), 1.61-1.53 (m, 1 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 179.6, 165.9, 143.4, 139.4, 139.3, 135.2, 133.8, 132.5, 131.0 (2 C), 130.2, 128.7 (2 C), 128.6, 127.7, 126.8 (2 C), 126.1 (2 C), 119.4, 65.0, 63.1, 48.5, 43.8, 34.8, 31.8, 31.0, 29.0, 28.3, 23.3, 16.1 ppm; HRMS (ESI): *m/z* calcd. for $C_{31}H_{32}ClO_5$ $[M-H]^-$ 519.1914; found 519.1949.

Compound 2c. To a solution of the benzyl alcohol **18** (640 mg, 1.23 mmol, 1 eq) in acetone (10 mL) at 0 °C was added a 2 M solution of Jones reagent in water (1.3 mL, 2.60 mmol, 2.1 eq). After 3 h, a saturated solution of sodium metabisulfite was added and the compound was extracted with MTBE (3 times). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to obtain a solid. A column chromatography on silica gel using heptane/EtOAc/AcOH (80:19:1) followed by a precipitation in a mixture of EtOAc and heptane afforded **2c** as a white solid (648 mg, 1.21 mmol, 98%). R_f = 0.25 (heptane/EtOAc/AcOH 70:29:1); Mp = 211 ± 2 °C; $[\alpha]_D^{20}$ = -262.5 ° (*c* 0.5, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, *J* = 8.3 Hz, 2 H), 7.57 (d, *J* = 8.3 Hz, 2 H), 7.43 (d, *J* = 8.3 Hz, 2 H), 7.27 (d, *J* = 8.3 Hz, 2 H), 5.83-5.75 (m, 2 H), 5.71 (d, *J* = 10.2 Hz, 1 H), 5.22-5.17 (m, 1 H), 4.46-4.36 (m, 2 H), 3.47-3.40 (m, 1 H), 2.78-2.70 (m, 1 H), 2.57-2.47 (m, 1 H), 2.10 (s, 3 H), 2.00-1.85 (m, 5 H), 1.81-1.72 (m, 1 H), 1.67 (s, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 181.0, 171.1, 165.7, 147.5, 139.4, 134.4, 134.3, 133.5, 131.0 (2 C), 129.9 (2 C), 129.7, 129.0, 128.7 (2 C), 126.8, 125.2 (2 C), 118.8, 63.1, 48.8, 44.7, 34.9, 34.9, 31.3, 31.1, 29.2, 28.2, 23.4, 15.6 ppm; HRMS (ESI): *m/z* calcd. for $C_{31}H_{32}ClO_6$ $[M+H]^+$ 535.1882; found 535.1889.

General procedure for Buchwald-Hartwig coupling on 2c

A mixture of Cs_2CO_3 (55 mg, 0.17 mmol, 3 eq) and 3 Å molecular sieves in powder (300 mg) was heated for 1 h at 300 °C under *vacuum*. The flask was then cooled to rt under Ar atm. and the chlorinated compound **2c** (30 mg, 0.06 mmol, 1 eq), the nucleophile **19** (12 mg, 0.11 mmol, 2 eq), $Pd_2(dba)_3$ (3 mg, 0.003 mmol, 0.05 eq), 2-di-*tert*-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl (4 mg, 0.01 mmol, 0.15 eq), and dry *t*-BuOH (1.5 mL) were successively added. The reaction mixture was heated at reflux for 72 h and then quenched with a 2 M HCl solution (3 mL). The molecular sieves was filtered off and washed with MTBE. Water was added to the filtrate and the product was extracted with MTBE (3 times). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was then purified by column chromatography on silica gel using CH_2Cl_2/AcOH 99:1 to CH_2Cl_2/MeOH/AcOH 97:2:1.

Compound 21a. Obtained as a white solid (94%); R_f = 0.1 (CH_2Cl_2/ AcOH 99:1); Mp = 186 ± 2 °C; $[\alpha]_D^{20}$ = -205.3 ° (*c* 0.5, MeOH); ^{1}H NMR (500 MHz, acetone-d_6): *δ* 12.00-10.00 (brs, 2 H), 7.96 (d, *J* = 8.6 Hz, 2 H), 7.86 (d, *J* = 8.7 Hz, 2 H), 7.82 (brs, 1 H), 7.47 (d, *J* = 8.6 Hz, 2 H), 7.18-7.12 (m, 4 H), 7.04 (d, *J* = 8.7 Hz, 2 H), 5.79-5.67 (m, 3 H), 5.27-5.21 (m, 1 H), 4.38-4.27 (m, 2 H), 3.50-3.44 (m, 1 H), 2.75-2.67 (m, 1 H), 2.60-2.52 (m, 1 H), 2.30 (s, 3 H), 2.14 (s, 3 H), 2.11-2.06 (m, 1 H), 1.98-1.79 (m, 4 H), 1.72-1.65 (m, 1 H), 1.63 (s, 3 H) ppm; ^{13}C NMR (125 MHz, acetone-d_6): *δ* 175.6, 167.5, 166.6, 150.4, 149.4, 139.8, 134.8, 134.4, 133.0, 132.9, 132.1 (2 C), 131.7, 131.3, 130.7 (2 C), 130.4 (2 C), 129.6, 126.7 (2 C), 121.6 (2 C), 121.0, 120.1, 114.6 (2 C), 62.8, 48.9, 44.8, 36.1, 32.4, 31.8, 30.2, 29.3, 23.5, 20.8, 15.8 ppm; HRMS (ESI): *m/z* calcd. for $C_{38}H_{40}NO_6$ $[M+H]^+$ 606.2850; found 606.2830.

Compound 21b. Obtained as a white solid (56%); R_f = 0.05 (CH_2Cl_2/MeOH/AcOH 97:2:1); Mp = 187 ± 2 °C; $[\alpha]_D^{20}$ = -184.4 ° (*c* 0.5, MeOH); ^{1}H NMR (500 MHz, acetone-d_6): *δ* 12.00-10.00 (brs, 2 H), 7.96 (d, *J* = 8.4 Hz, 2 H), 7.82 (d, *J* = 8.7 Hz, 2 H), 7.47 (d, *J* = 8.4 Hz, 2 H), 7.10 (d, *J* = 8.4 Hz, 2 H), 6.90 (d, *J* = 8.7 Hz, 2 H), 7.86 (d, *J* = 8.4 Hz, 2 H), 5.78-5.67 (m, 3 H), 5.26-5.21 (m, 1 H), 4.37-4.26 (m, 2 H), 3.49-3.43 (m, 1 H), 2.74-2.67 (m, 1 H), 2.60-2.51 (m, 1 H), 2.14 (s, 3 H), 2.08-2.04 (m, 1 H), 1.98-1.78 (m, 4 H), 1.75-1.64 (m, 1 H), 1.63 (s, 3 H), 1.32-1.25 (m, 2 H) ppm; ^{13}C NMR (125 MHz, acetone-d_6): *δ* 175.6, 167.5, 156.7, 154.9, 151.8, 149.4, 134.8, 134.4, 133.9, 133.0, 132.1 (2 C), 131.7, 131.3, 130.4 (2 C), 129.6, 126.6 (2 C), 125.1 (2 C), 125.0, 120.0, 116.8 (2 C), 113.6 (2 C), 62.6, 48.9, 44.8, 36.1, 32.6, 32.4, 31.6, 30.6, 23.5, 15.8 ppm; HRMS (ESI): *m/z* calcd. for $C_{37}H_{38}NO_7$ $[M+H]^+$ 608.2643; found 608.2664.

Compound 21c. Obtained as a white solid (91%); R_f = 0.15 (CH_2Cl_2/AcOH 99:1); Mp = 228 ± 2 °C; $[\alpha]_D^{20}$ = -204.9 ° (*c* 0.2, MeOH); ^{1}H NMR (500 MHz, acetone-d_6): *δ* 8.02 (d, *J* = 9.0 Hz, 2 H), 7.95 (d, *J* = 8.4 Hz, 2 H), 7.46 (d, *J* = 8.4 Hz, 2 H), 7.27 (d, *J* = 8.4 Hz, 2 H), 7.03-6.99 (m, 4 H), 5.77-5.68 (m, 3 H), 5.25-5.21 (m, 1 H), 4.44-4.33 (m, 2 H), 3.49-3.42 (m, 1 H), 2.74-2.66 (m, 1 H), 2.60-2.53 (m, 1 H), 2.35 (s, 3 H), 2.14 (s, 3 H), 2.11-2.06 (m, 1 H), 1.97-1.80 (m, 4 H), 1.75-1.65 (m, 1 H), 1.63 (s, 3 H) ppm; ^{13}C NMR (125 MHz, acetone-d_6): *δ* 175.7, 167.8, 166.2, 163.2, 154.2, 149.2, 135.2, 134.7, 134.4, 133.8, 132.4 (2 C), 131.9, 131,5 (2 C), 131.2, 130.4 (2 C), 130.0, 126.6 (2 C), 125.5, 121.0 (2 C), 120.1, 117.7 (2 C), 63.4, 55.5, 48.9, 44.8, 35.9, 32.5, 31.8, 30.4, 23.5, 20.8, 15.9 ppm; HRMS (ESI): *m/z* calcd. for $C_{38}H_{39}O_7$ $[M+H]^+$ 625.1999; found 607.2690.

Compound 21d. Obtained as a white solid (59%); R_f = 0.1 (CH_2Cl_2/AcOH 99:1); Mp = 131 ± 2 °C; $[\alpha]_D^{20}$ = -164.8 ° (*c* 0.5, MeOH); ^{1}H NMR (500 MHz, acetone-d_6): *δ* 11.50-9.50 (brs, 2 H), 7.96 (d, *J* = 8.5 Hz, 2 H), 7.78 (d, *J* = 8.8 Hz, 2 H), 7.47 (d, *J* = 8.5 Hz, 2 H), 7.39 (d, *J* = 7.3 Hz, 2 H), 7.32 (t, *J* = 7.3 Hz, 2 H), 7.24 (t, *J* = 7.3 Hz, 1 H), 6.69 (d, *J* = 8.8 Hz, 2 H), 6.28 (brs, 1 H), 5.78-5.66 (m, 3 H), 5.25-5.21 (m, 1 H), 4.45 (s, 2 H), 4.34-4.25 (m, 2 H), 3.49-3.42 (m, 1 H), 2.74-2.66 (m, 1 H), 2.58-2.50 (m, 1 H), 2.14 (s, 3 H), 2.11-2.06 (m, 1 H), 1.95-1.76 (m,

4 H), 1.70-1.64 (m, 1 H), 1.63 (s, 3 H) ppm; ^{13}C NMR (125 MHz, acetone-d_6): δ 175.6, 167.5, 166.8, 153.6, 149.4, 140.3, 134.8, 134.4, 133.0, 132.0 (2 C), 131.7, 131.3, 130.4 (2 C), 129.6, 129.3 (2 C), 128.1 (2 C), 127.8, 126.7 (2 C), 120.1, 118.7, 112.4 (2 C), 62.5, 48.9, 47.5, 44.8, 36.1, 32.4, 31.8, 30.3, 30.1, 23.5, 15.8 ppm; HRMS (ESI): *m/z* calcd. for $C_{38}H_{40}NO_6$ $[M+H]^+$ 606.2850; found 606.2845.

Compound 21e. Obtained as a white solid (78%); R_f = 0.2 (CH_2Cl_2/MeOH/AcOH 97:2:1); Mp = 244 ± 2 °C; $[\alpha]_D^{20}$ = -211.7 ° (*c* 0.5, MeOH); ^{1}H NMR (500 MHz, acetone-d_6): δ 9.72 (s, 1 H), 8.05-7.90 (m, 8 H), 7.47 (d, *J* = 8.4 Hz, 2 H), 7.34 (d, *J* = 8.3 Hz, 2 H), 5.78-5.69 (m, 3 H), 5.26-5.22 (m, 1 H), 4.44-4.33 (m, 2 H), 3.50-3.44 (m, 1 H), 2.75-2.68 (m, 1 H), 2.62-2.55 (m, 1 H), 2.41 (s, 3 H), 2.14 (s, 3 H), 2.12-2.07 (m, 1 H), 1.99-1.82 (m, 4 H), 1.76-1.67 (m, 1 H), 1.64 (s, 3 H) ppm; ^{13}C NMR (125 MHz, acetone-d_6): δ 175.7, 167.6, 166.5, 166.4, 144.8, 143.2, 140.3, 134.8, 134.4, 133.3, 133.1, 132.9, 131.8, 131.3, 131.2 (2 C), 130.4 (2 C), 130.0 (2 C), 128.5 (2 C), 126.7, 126.2, 120.2 (2 C), 120.1 (2 C), 63.3, 49.0, 44.8, 35.9, 32.5, 31.8, 31.0, 29.1, 23.5, 21.4, 15.9 ppm; HRMS (ESI): *m/z* calcd. for $C_{39}H_{40}NO_7$ $[M+H]^+$ 634.2799; found 634.2830.

Compound 21f. Obtained as a white solid (90%); R_f = 0.3 (CH_2Cl_2/MeOH/AcOH 97:2:1); Mp = 233 ± 2 °C; $[\alpha]_D^{20}$ = -217 ° (*c* 0.5, MeOH); ^{1}H NMR (500 MHz, acetone-d_6): δ 12.00-10.00 (brs, 2 H), 9.41 (brs,1 H), 7.96 (d, *J* = 8.4 Hz, 2 H), 7.91 (d, *J* = 8.6 Hz, 2 H), 7.77 (d, *J* = 8.3 Hz, 2 H), 7.47 (d, *J* = 8.4 Hz, 2 H), 7.38-7.31 (m, 4 H), 5.78-5.67 (m, 3 H), 5.25-5.20 (m, 1 H), 4.39-4.29 (m, 2 H), 3.50-3.42 (m, 1 H), 2.73-2.65 (m, 1 H), 2.60-2.50 (m, 1 H), 2.36 (s, 3 H), 2.14 (s, 3 H), 2.09-2.01 (m, 1 H), 1.96-1.78 (m, 4 H), 1.72-1.64 (m, 1 H), 1.63 (s, 3 H) ppm; ^{13}C NMR (125 MHz, acetone-d_6): δ 175.6, 167.5, 166.1, 149.3, 144.9, 143.4, 137.8, 134.8, 134.4, 132.8, 131.8, 131.6 (2 C), 131.2, 130.6 (2 C), 130.4 (2 C), 129.6, 128.0 (2 C), 126.6 (2 C), 126.5, 120.0, 119.4 (2 C), 63.4, 48.9, 44.8, 35.8, 32.4, 31.7, 30.4, 29.3, 23.5, 21.4, 15.8 ppm; HRMS (ESI): *m/z* calcd. for $C_{38}H_{39}NNaO_8S$ $[M+Na]^+$ 692.2289; found 692.2284.

Compound 21g. Obtained as a white solid (92%); R_f = 0.2 (CH_2Cl_2/AcOH 99:1); Mp = 151 ± 2 °C; $[\alpha]_D^{20}$ = -185.4 ° (*c* 0.5, MeOH); ^{1}H NMR (500 MHz, acetone-d_6): δ 12.00-9.50 (brs, 2 H), 7.96 (d, *J* = 8.5 Hz, 2 H), 7.81 (d, *J* = 8.8 Hz, 2 H), 7.48 (d, *J* = 8.5 Hz, 2 H), 7.33-7.17 (m, 5 H), 6.68 (d, *J* = 8.8 Hz, 2 H), 5.80-5.66 (m, 3 H), 5.26-5.21 (m, 1 H), 4.37-4.24 (m, 2 H), 3.51-3.41 (m, 3 H), 2.94 (t, *J* = 7.3 Hz, 2 H), 2.77-2.67 (m, 1 H), 2.60-2.51 (m, 1 H), 2.14 (s, 3 H), 2.10-2.06 (m, 1 H), 1.99-1.77 (m, 4 H), 1.71-1.64 (m, 1 H), 1.63 (s, 3 H) ppm; ^{13}C NMR (125 MHz, acetone-d_6): δ 175.6, 167.5, 166.9, 153.6, 149.4, 140.5, 134.8, 134.4, 133.0, 132.1 (2 C), 131.7, 131.3, 130.4 (2 C), 129.6 (2 C), 129.3 (2 C), 127.1 (2 C), 126.7 (2 C), 120.1, 118.7, 112.1 (2 C), 62.5, 49.0, 45.3, 44.8, 36.1, 36.0, 32.5, 31.9, 31.2, 30.6, 23.5, 15.9 ppm; HRMS (ESI): *m/z* calcd. for $C_{39}H_{42}NO_6$ $[M+H]^+$ 620.3007; found 620.3022.

Bcl-xL and Mcl-1 Binding Affinity Assays

The binding affinities of compounds for Bcl-xL and Mcl-1 were evaluated by competition against fluorescently labelled reference compounds, Bak and Bid, respectively, as described by Qian *et al*.[30] Bak, 5-Carboxyfluorescein-Bak, Bid and 5-carboxyfluorescein-Bid peptides (synthetized by PolyPeptide Laboratories) as well as Human 45-84/ C37 Bcl-xL and mouse DN150/DC25 Mcl-1 proteins were used for this assay (for details on their sequences, see Azmi *et al.*[33]). Unlabeled peptides were dissolved in DMSO and labelled peptides were diluted in assay buffer, which contained 20 mM Na_2HPO_4 (pH 7.4), 50 mM NaCl, 2 µM EDTA, 0.05% Pluronic F-68, without pluronic acid for storage at −20 °C. Liquid handling instrument, Biomek®NX and Biomeck®3000 (Beckman Coulter, Villepinte, France), were used to add protein and fluorescein-labelled peptides. 15 nM labelled BH3 peptide, 100 nM protein, and 100 µM of unlabelled BH3 peptide or compound (first diluted in 10 mM DMSO and then buffer for final concentration from 10^{-9} to 10^{-4} M) into a final volume of 40 µL were distributed in a 96 well black polystyrene flat-bottomed microplate (VWR 734-1622). The microplate was then incubated at room temperature for 1 h and shaken before fluorescent polarization measure. Fluorescence polarization in millipolarization units was measured with a Beckman Coulter Paradigm® using FP cartridge (λex 485 nm, λem 535nm). The exposure time was 300 ms per channel. All experimental data were collected using the Biomek Software® (Beckman Coulter, Inc, Brea, CA, USA) and analysed using Microsoft Excel 2010 (Microsoft, Redmond, WA, USA). Results are expressed as binding activity, *i.e.*, percentage of inhibition of the binding of labelled reference compound, or as K_i, the concentration corresponding to 50% of such inhibition, and corrected for experimental conditions according to Kenakin rearranged equation,[34] which is adapted from Cheng and Prusoff equation.[35] Unlabeled peptides Bak and Bid were used as positives control. The performance of the assays was monitored by use of Z' factors as described by Zhang *et al*..[36] The Z' factors for these assays are 0.8 (Bcl-xL/Bak) and 0.7 (Mcl-1/Bid) indicating that they should be robust assays.

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Notes and references

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