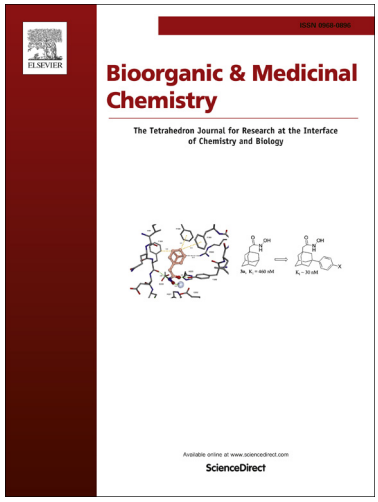


Polymer Supported Synthesis of a Natural Product-Inspired Oxepane Library

Sudipta Basu, Herbert Waldmann

PII: S0968-0896(14)00388-5
DOI: http://dx.doi.org/10.1016/j.bmc.2014.05.039
Reference: BMC 11600

To appear in: *Bioorganic & Medicinal Chemistry*

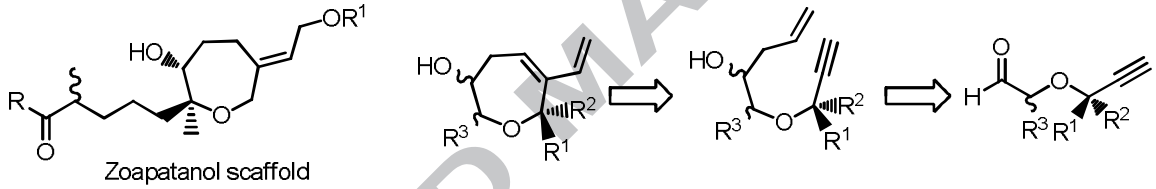
Received Date: 25 March 2014
Revised Date: 14 May 2014
Accepted Date: 16 May 2014

Please cite this article as: Basu, S., Waldmann, H., Polymer Supported Synthesis of a Natural Product-Inspired Oxepane Library, *Bioorganic & Medicinal Chemistry* (2014), doi: http://dx.doi.org/10.1016/j.bmc.2014.05.039

Polymer Supported Synthesis of a Natural Product-Inspired Oxepane Library

Sudipta Basu and Herbert Waldmann*

* Prof. Dr. H. Waldmann, Dr. Sudipta Basu
Max-Planck-Institut für molekulare Physiologie,
Otto-Hahn Strasse 11, 44227 Dortmund (Germany) and
Technische Universität Dortmund, Fachbereich Chemische Biologie,
Otto-Hahn-Str. 6, 44227 Dortmund, Germany
Fax: (+49) 321-133-2499
E-mail: herbert.waldmann@mpi-dortmund.mpg.de



Abstract

Natural product inspired compound collections are prevalidated due to the evolutionary selection of the natural product scaffolds. Their synthesis requires the development of novel strategies amenable to formats suitable for library build-up. We describe a method for the synthesis of an oxepane library inspired by the core structure of oxepane natural products endowed with multiple bioactivities. Core aspects of the strategy are the establishment of a one-pot method employing different immobilized scavengers, the employment of an enyne ring closing reaction and diversification by means of different transformations, e. g. cycloadditions and cross-metathesis reactions. In total, a collection of 115 oxepanes was obtained in 5-6-step reaction sequences.

Introduction

Biologically active natural products are a source of inspiration for the development of compound libraries based on prevalidated scaffolds.[1,2] In this context, the canonical solution synthesis of compound libraries using solid supported reagents and scavengers is a powerful technique for chemical biology and medicinal chemistry research. [2]

The oxepane scaffold occurs widely in natural products with a broad range of interesting biological activities (Figure 1). For instance, the Heliannual family contains benzoxepane systems having allelopathic and phytotoxic activities,[3] the sodwanone family, isolated from marine organisms, contains dimeric keto oxepane scaffolds and shows activity against human tumor cell lines.[4] The halogenated marine toxins regioloxepane A and isolaurepinnacin are representative memberes of the *Laurencia*-derived C15 acetogenins containing α, α'-disubstituted oxepane rings.[5] (+)-Zoapatanol is one of the numerous diterpenoid oxepanes isolated from leaves of the Mexican plant *Montanoa tomentosa*.[6] Tea prepared from extracts of the leaves has long been used as a contraceptive in ancient time and recent studies indicate that zoapatanol metabolites might be responsible for the antifertility activity.[7] Due to the manifold biological activities of these compounds, their underlying structural architectures may be regarded as biologically pre-validated and as promising guiding scaffolds for natural product inspired compound library development. In developing the concept of Biology Oriented Synthesis (BIOS)[8], we have devised synthesis methods that give efficient access to natural product inspired compound collections.[9] Among these, the oxepane scaffold had attracted our attention as well.[9e]

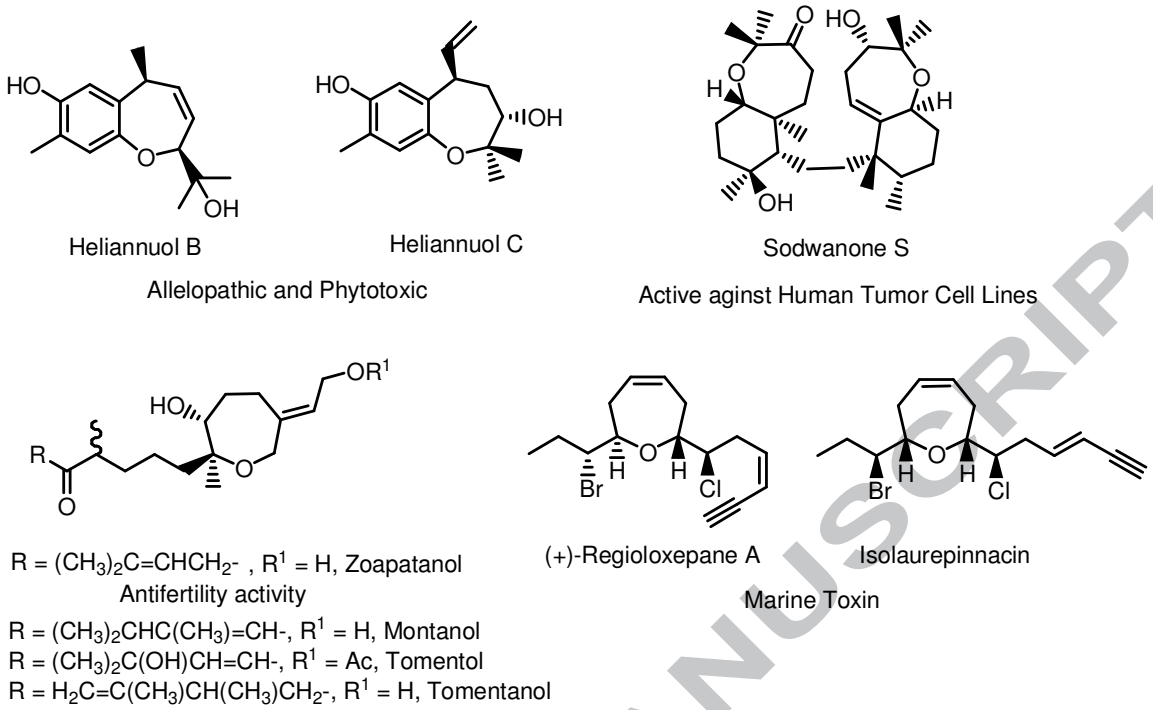
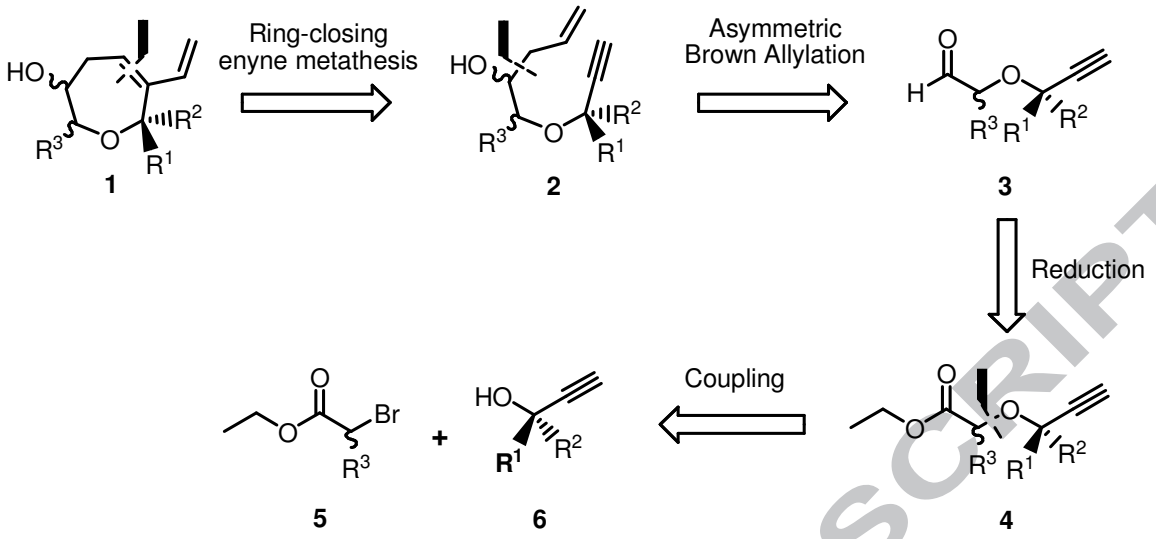


Figure 1: Natural products having different biological activities containing oxepane scaffold.

Here we report in full detail the development of a practical and efficient polymer-supported solution phase parallel synthetic route to a compound library focused on the highly substituted oxepane scaffold. The key step of the method includes a ring-closing enyne metathesis reaction.[10]

Results and discussion

The retrosynthetic analysis of the oxepane library **1** is shown in the Scheme 1. It was planned to access the oxepane core **1** by ring-closing enyne metathesis from the open chain precursors **2** as key transformation. The open chain enyne precursors **2**, homoallyl alcohols, can be obtained from the aldehydes **3**, in diastereomerically pure form using the asymmetric Brown allylation. Aldehydes **3** could be generated from the esters **4** by controlled reduction. Intermediates **4** can be synthesized from the easily available building blocks **5** and **6**, which are the starting points of the synthetic route.



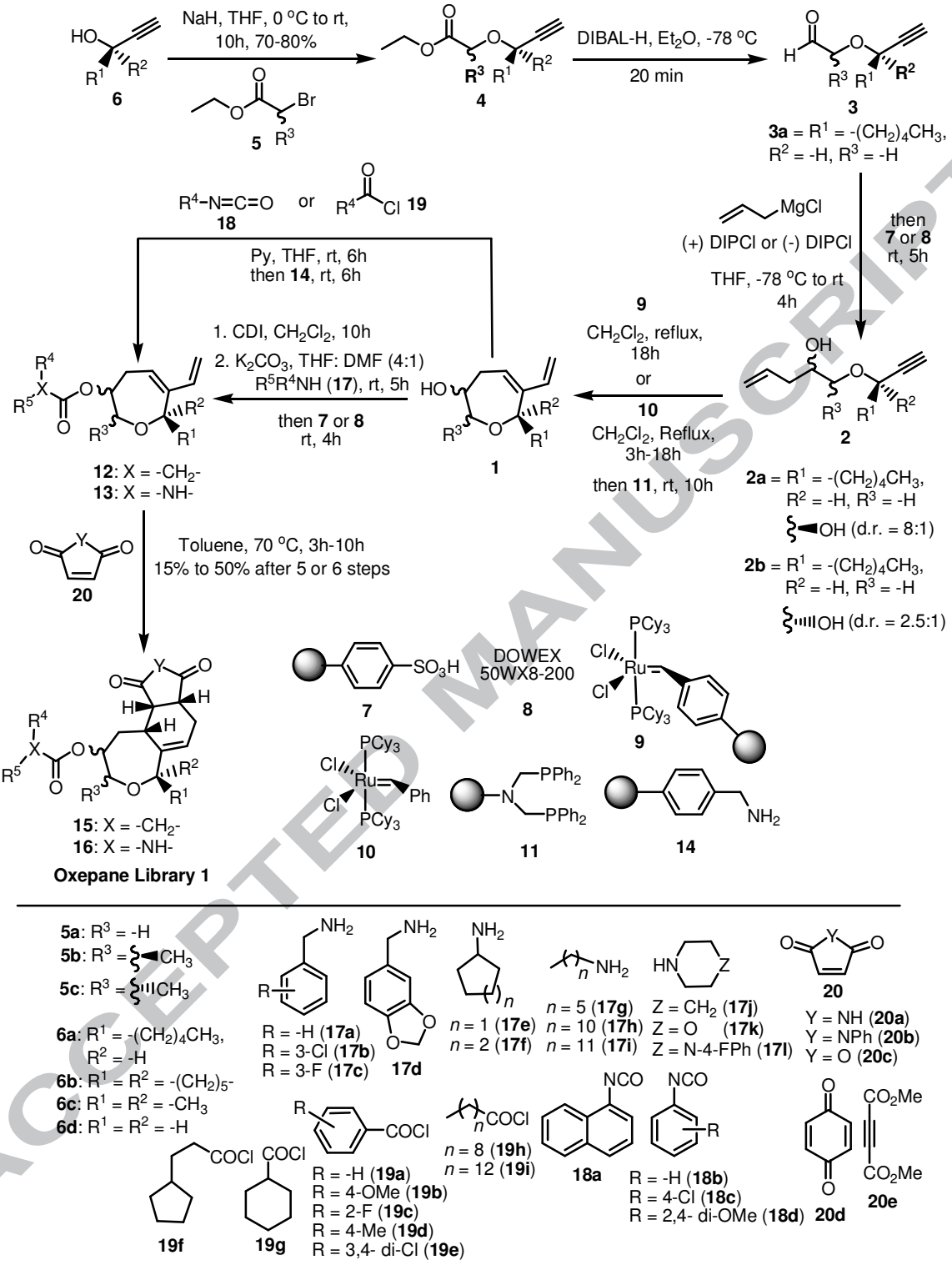
Scheme 1: Retrosynthetic analysis of focused oxepane core **1**.

Strategy for the synthesis of oxepane library 1

Keeping the retro-synthetic blue print in mind, the synthesis commenced by coupling of the substituted propargyl alcohols **6** and the substituted α-bromo ethyl acetates **5** (Scheme 2). When the alcohols **6** were deprotonated using sodium hydride as base in THF at 0 ^{o}C and coupled with **5**, the ethers **4** were formed in 70-80 % yield depending on the building blocks **5** and **6** used.[11] The ethers **4** were purified by means of silica gel chromatography. The ethyl ester in **4** was reduced in a controlled manner using diisobutyl aluminiumhydride (DIBAL-H) in diethyl ether at -78 ^{o}C for 20 minutes to afford the aldehydes **3**. Application of THF or CH_2Cl_2 for this reduction proved to be unsuitable because in those solvents a 1:1 mixture of the desired aldehydes **3** and over reduced alcohols were formed. The over reduced alcohols were removed by chromatography. All attempts to oxidize the alcohols to the desired aldehydes **3** were unsuccessful due to decomposition. The aldehydes **3** were then allylated using Brown's asymmetric allylation procedure.[12] The chiral allyl borane reagent was prepared *in situ* by treating either (+)- or (-)- *B*-chlorodiisopinocampheylborane (DIPCl) and allyl magnesium chloride at -78 ^{o}C to room temperature. When either of (+)- or (-)- diisopinocampheylallyl borane (Ipc_2B-allyl) reagents was treated with aldehydes **3** in THF at -78 ^{o}C, the homoallyl alcohols **2** were formed stereoselectively. As soon as the reaction was complete (determined by

TLC), the excess allylmagnesium chloride was scavenged using polystyrene supported sulfonic acid resin **7** or the cation exchange sulfonic acid resin DOWEX® 50WX8-200 (**8**).[13] The resin was filtered and the crude products **2** were obtained after evaporating the solvent. The diastereomeric excess was determined by means of ^{1}H NMR spectroscopy of the crude products. With aldehyde **3a** (R^1 = *n*-pentyl, R^2 = H, R^3 = H) and using (+)-DIPCl, the expected homoallyl alcohol **2a** was obtained in 8:1 diastereomeric ratio (*syn*:*anti* = 8:1). Under the same conditions (-) –DIPCl yielded the other diastereomer in only 2.5:1 diastereomeric ratio (*anti*:*syn* = 2.5:1). It was assumed at this point that the Brown asymmetric allylation proceeded with the expected stereoselectivity as predicted by Brown et al[12] and confirmed later by the nOe measurements of a particular member of the oxepane library (Figure 2). Thus, use of the chiral allylborane formed from (+) -DIPCl is a "matched" case and from (-)-DIPCl is a "mismatched" case for aldehyde **3a**.

It was also observed that the polymer bound sulfonic acid resin **7** gave better results than the DOWEX® 50WX8-200 cation exchange resin **8**. Impurities in the commercially available resin **8** contaminated the product mixture and had to be removed by chromatography before proceeding to the next reactions. But in the case of polymer bound sulfonic acid resin **7**, the impurities were negligible and the product was sufficiently pure to proceed for the next reactions. The following reactions were carried out using the isomeric mixtures of the homoallyl alcohols without any further purification.



Scheme 2. Synthesis of Oxepane Library 1.

The crude enyne precursors **2** were then subjected to the decisive enyne metathesis reaction. When intermediates **2** were treated with polymer supported 1st generation Grubbs catalyst **9**[14] (loading = 0.11 mmol/g, 2 x 40 mol%) in refluxing CH_2Cl_2, the oxepanes **1** were formed. After the reaction was complete (monitored by TLC), the resin was filtered and the solvent was evaporated to obtain the colorless crude products **1**. In this reaction the catalyst loading is too low (0.11 mmol/g) for the synthesis of an entire library. So an alternative method was implemented to scavenge the ruthenium. Precursors **2** were treated with 1st generation Grubbs catalyst **10** (20 mol%) in refluxing CH_2Cl_2. As soon as the reaction was complete (monitored by TLC), the resin **11**[15] (20 equiv. relative to the metal catalyst used) was added to scavenge the ruthenium. After filtration through a silica gel pad the solvent was evaporated to furnish the colorless crude products **1**. The strategy to scavenge ruthenium from the metathesis reaction developed by Breinbauer et. al.[15] turned out to be efficient and inexpensive for library generation. The oxepanes **1** were formed in the same diastereomeric ratio already displayed the precursors **2** which indicates that the configuration of the enyne precursor **2** was translated into the cyclic product **1** after the ring-closing enyne metathesis. The diastereomeric excess was determined by means of ^{1}H NMR spectroscopy of the crude products.

At this point, the oxepane scaffold was ready for diversification to generate a fully functionalized oxepane library 1. The free alcohol in **1** was functionalized as ester and carbamate. Hence oxepane **1** was treated with different commercially available carboxylic acids (3 equiv. relative to the alcohol **1**) in CH_2Cl_2 using either dicyclohexyl-carbodiimide (DCC) or its solid supported analogue, *N*-cyclohexyl-carbodiimide, *N'*-methyl polystyrene, dimethylamino pyridine (DMAP) as catalyst,[16] but esters **12** were not formed. As more reactive coupling partners, acid chlorides were then chosen. When alcohol **1** was treated with commercially available acid chlorides **19** (3 equiv relative to the alcohol **1**) in THF in the presence of pyridine as base, the esters **12** were formed. The same reaction conditions were used to synthesize the carbamates **13** from alcohol **1** using different commercially available isocyanates **18** (3 equiv relative to the alcohol).[17] In both cases excess acid chlorides and isocyanates were scavenged from the reaction mixture using aminomethylated polystyrene scavenger **14** (6 equiv. relative to the acid chlorides and 3 equiv relative to the isocyanate). Esters or carbamates were not formed in

the presence of polymer-supported pyridine as base. Excellent reactivity was observed using aromatic isocyanates (e.g. naphthyl **18a** and phenyl isocyanate **18b**), but a sluggish reaction was experienced in case of 2,4-dimethoxy phenyl isocyanate **18d**. Tertiary-butyl isocyanate and tertiary-butyl isothiocyanate were unreactive under these reaction conditions. In case of ester formation, aliphatic acid chlorides (**19f-i**) are more reactive than the aromatic acid chlorides (**19a-e**). Among the aromatic acid chlorides, the *ortho*-substituted acid chloride **19c** showed lower reactivity due to steric hindrence. Electron donating substituents on the aromatic ring (**19b** and **19d**) reduced reactivity whereas electron withdrawing substituents (**19e**) led to higher reactivity.

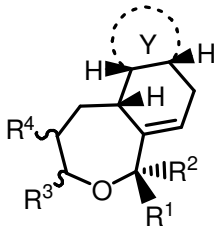
To introduce higher diversity in the oxepane library a two step carbamate synthesis protocol was implemented. To this end, alcohol **1** was treated with 1,1'-carbonyldiimidazole (CDI) in CH_2Cl_2 to obtain a imidazolyl carbamate intermediate which was immediately heated in a sealed tube at 40 ^oC with commercially available primary amines in CH_2Cl_2, using triethylamine and catalytic amounts of DMAP. The carbamates **13** were formed after 48h.[18] As this reaction appeared to be sluggish, a stronger base (K_2CO_3) was used with different primary and secondary amines **17** in THF:DMF (4:1) at room temperature for 5h (determined by TLC). The excess potassium carbonate and amines were scavenged by polymer-supported sulfonic acid resin **7** or **8**. After filtration of the resin and evaporation of the solvent the crude carbamates **13** were obtained. In this scavenging technique again the sulfonic acid resin **7** was preferable over **8** because of the described impurity problem. This two step protocol appeared to be suitable because a wide range of primary and secondary amines can be used. All primary and secondary amines showed similar reactivity in this reaction. It was noted that the secondary amines (**17j-l**) are slightly less reactive than the primary amines (**17a-i**) because of steric hindrance.

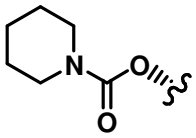
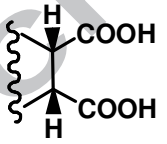
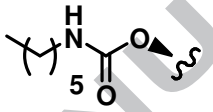
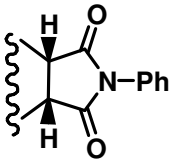
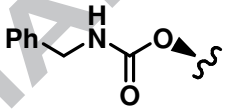
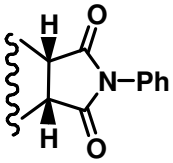
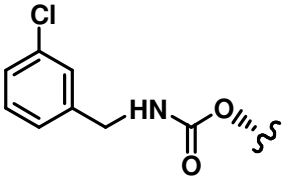
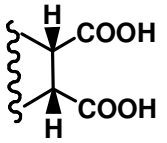
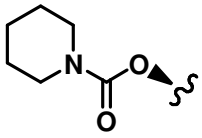
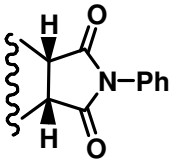
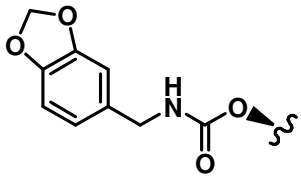
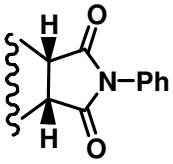
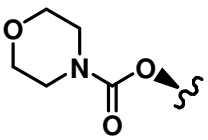
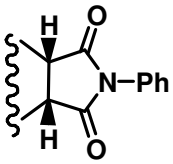
For diversification of the crude diene esters **12** and carbamates **13** were treated separately with different dienophiles **20** in toluene at 70 ^oC to afford the fully substituted oxepanes **15** and **16** respectively in 15-50% overall yield after 5 steps (for **15**) or 6 steps (for **16**). The products were isolated by column chromatography as single isomers (entries 11-14, 21-30, 32, 34, 35, 39, 40, 42, 44-46, 49-51, 56-58, 62-64, 66, 67, 74-76 in Table 1) as well as the inseparable mixtures of two isomers (entries 1-10, 15-20, 31, 33, 36-38, 41,

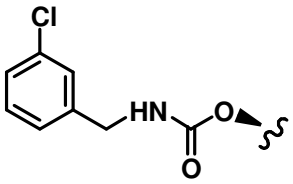
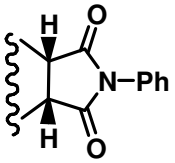
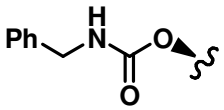
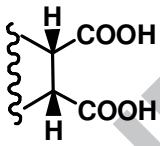
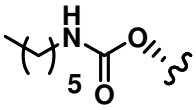
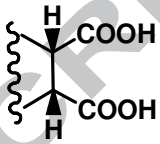
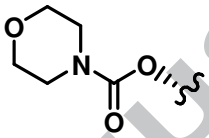
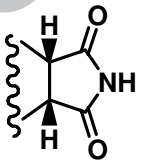
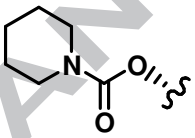
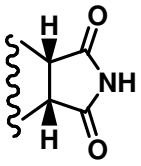
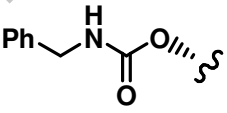
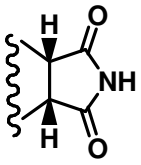
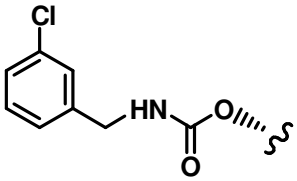
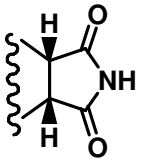
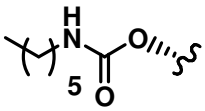
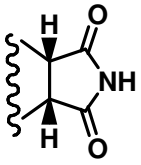
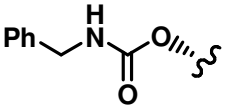
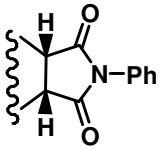
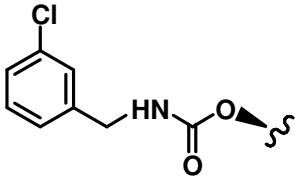
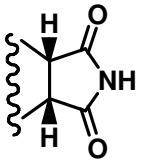
43, 47, 48, 52-55, 59-61, 65, 68-73 in Table 1) . The isomeric ratios of the oxepanes were determined by means of ^{1}H NMR spectroscopy (see the Supporting Information). All oxepanes prepared as shown in Scheme 2 are given in Table 1.

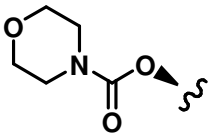
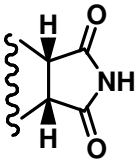
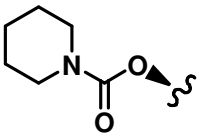
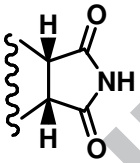
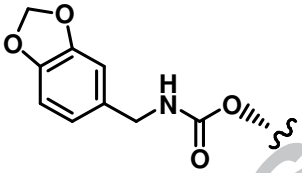
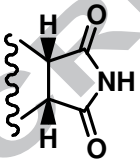
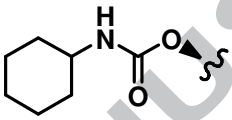
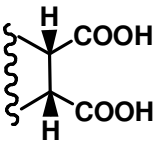
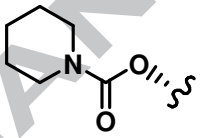
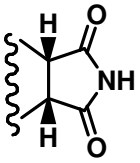
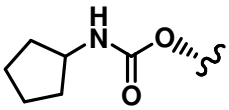
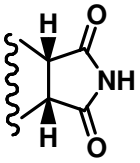
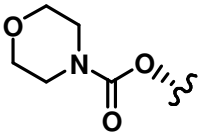
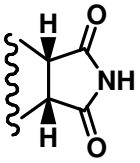
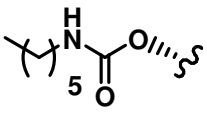
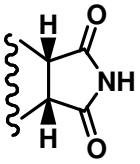
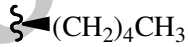
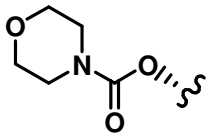
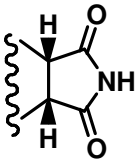
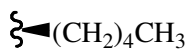
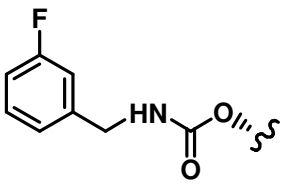
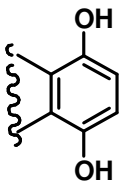
Among the different commercially available dienophiles used, the maleimide (**20a**), *N*-phenyl maleimide (**20b**) and maleic anhydride (**20c**) reacted very fast and the reactions were complete within 3h of heating in toluene. But in the case of *p*-benzoquinone (**20d**) and dimethyl acetylene dicarboxylate (**20e**), the reactions were sluggish (complete after 10h of heating). Using *p*-benzoquinone (**20d**) as dienophile, the hydroquinone product was obtained after purification, which suggests that the initial Diels-Alder adduct was aromatized in the reaction condition.

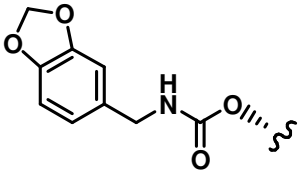
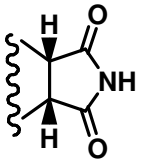
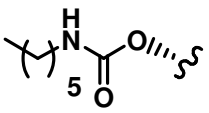
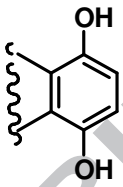
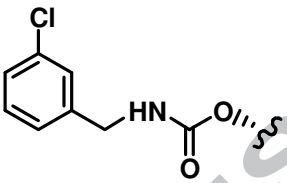
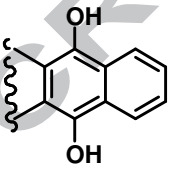
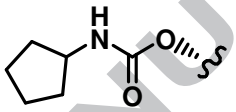
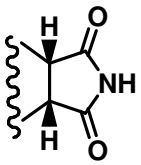
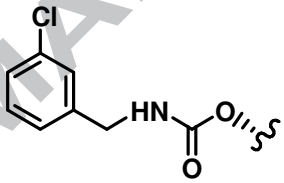
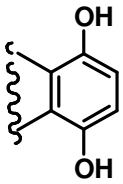
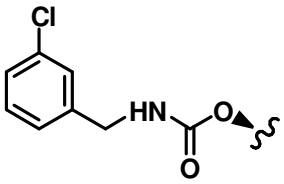
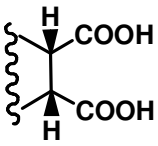
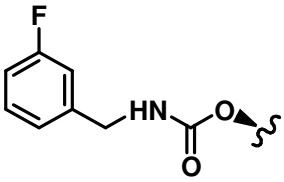
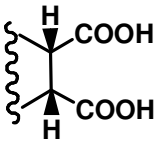
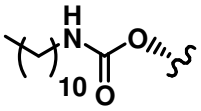
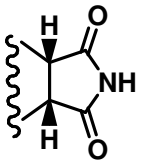
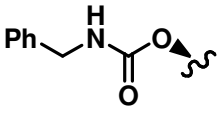
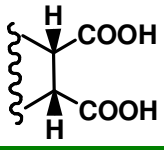
Table 1. Oxepane Library 1.

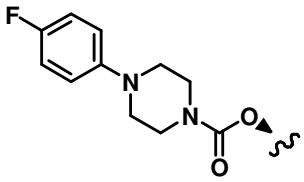
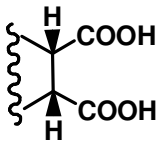
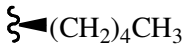
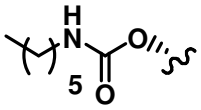
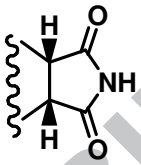
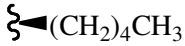
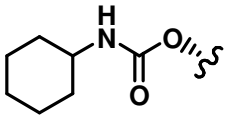
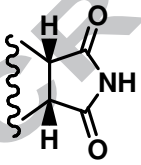
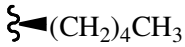
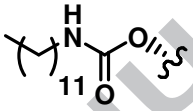
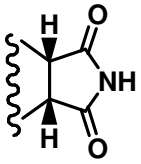
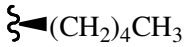
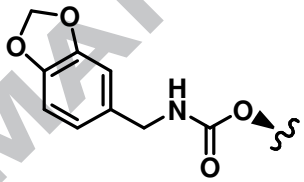
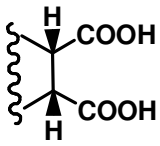
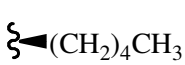
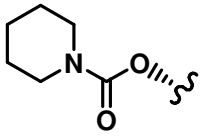
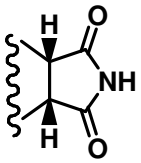
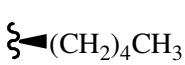
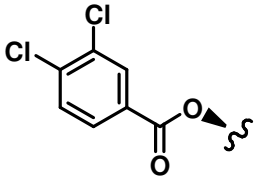
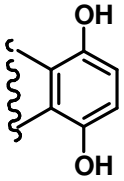
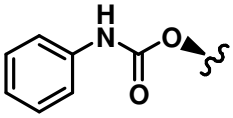
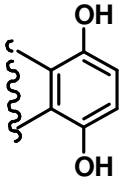
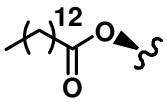
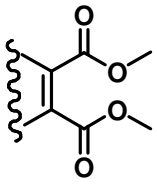


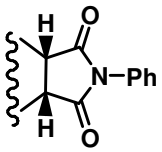
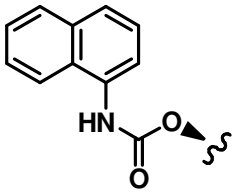
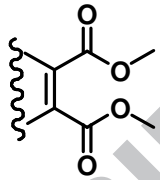
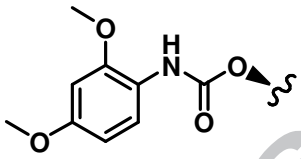
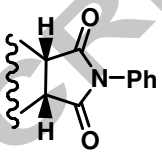
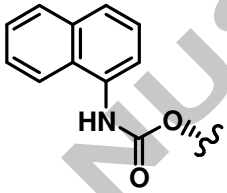
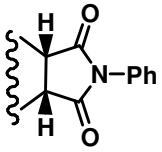
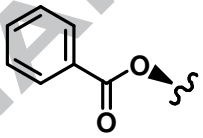
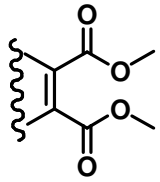
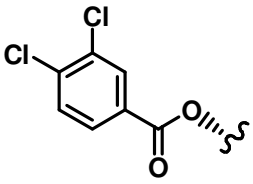
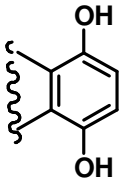
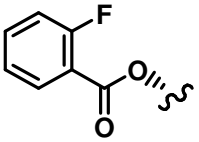
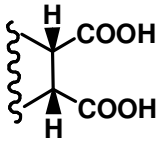
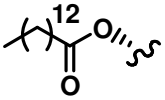
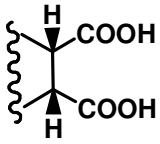
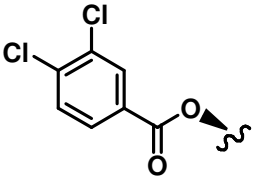
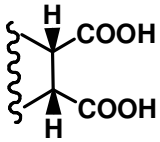
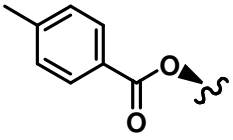
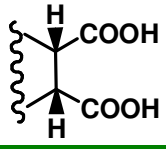
Entry	R^1	R^2	R^3	R^4	Y	Yield[a]
1.	-$(CH_2)_5$-	-$(CH_2)_5$-	-H			34 % (after 6 steps) d.r. = 4:1
2.	-$(CH_2)_5$-	-$(CH_2)_5$-	-H			32% (after 6 steps) d.r. = 8:1
3.	-$(CH_2)_5$-	-$(CH_2)_5$-	-H			40% (after 6 steps) d.r. = 7.5:1
4.	-$(CH_2)_5$-	-$(CH_2)_5$-	-H			15% (after 6 steps) d.r. = 5:1
5.	-$(CH_2)_5$-	-$(CH_2)_5$-	-H			32% (after 6 steps) d.r. = 8:1
6.	-$(CH_2)_5$-	-$(CH_2)_5$-	-H			32% (after 6 steps) d.r. = 8:1
7.	-$(CH_2)_5$-	-$(CH_2)_5$-	-H			34% (after 6 steps) d.r. = 8:1

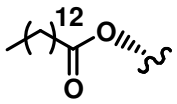
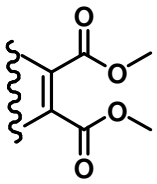
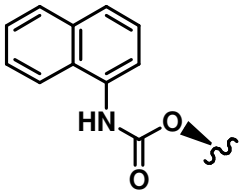
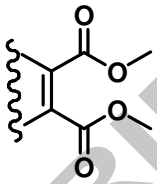
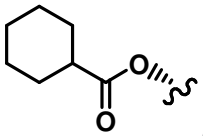
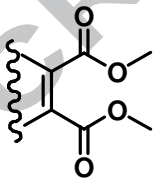
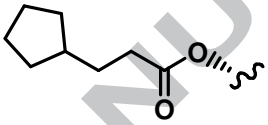
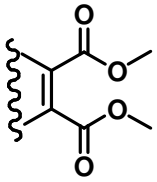
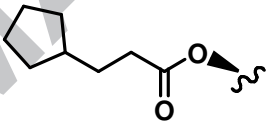
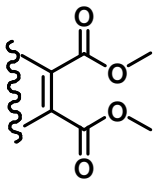
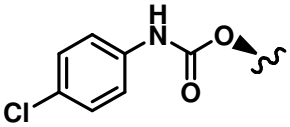
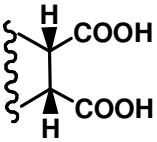
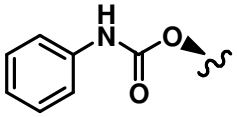
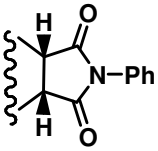
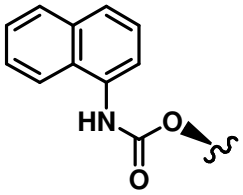
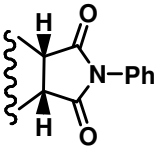
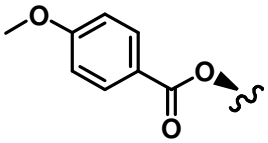
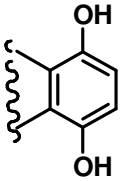
8.	$-(CH_2)_5-$	$-(CH_2)_5-$	-H			32% (after 6 steps) d.r. = 6:1
9.	$-(CH_2)_5-$	$-(CH_2)_5-$	-H			20% (after 6 steps) d.r. = 4:1
10.	$-(CH_2)_5-$	$-(CH_2)_5-$	-H			15% (after 6 steps) d.r. = 7:1
11.	$-CH_3$	$-CH_3$	-H			30% (after 6 steps)
12.	$-CH_3$	$-CH_3$	-H			22% (after 6 steps)
13.	$-CH_3$	$-CH_3$	-H			20% (after 6 steps)
14.	$-CH_3$	$-CH_3$	-H			16% (after 6 steps)
15.	$-CH_3$	$-CH_3$	-H			31% (after 6 steps) d.r. = 3:1
16.	$-(CH_2)_5-$	$-(CH_2)_5-$	-H			29% (after 6 steps) d.r. = 3:1
17.	$-CH_3$	$-CH_3$	-H			22% (after 6 steps) d.r. = 4:1

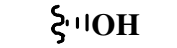
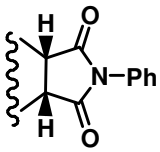
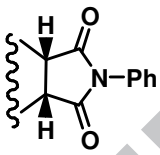
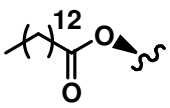
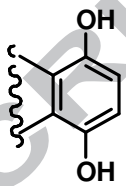
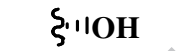
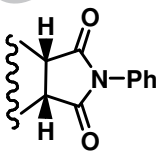
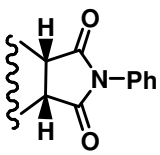
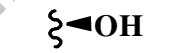
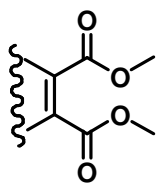
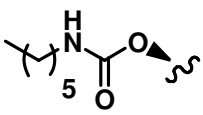
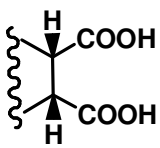
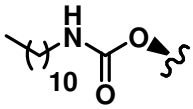
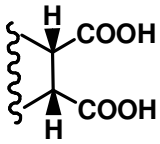
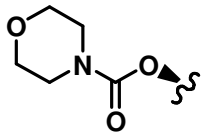
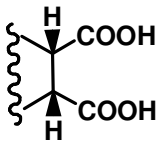
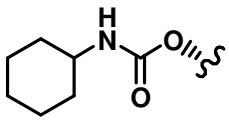
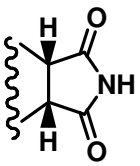
18.	$-CH_3$	$-CH_3$	-H			15% (after 6 steps) d.r. = 3:2
19.	$-CH_3$	$-CH_3$	-H			15% (after 6 steps) d.r. = 3.8:1
20.	$-CH_3$	$-CH_3$	-H			30% (after 6 steps) d.r. = 3:1
21.	$-CH_3$	$-CH_3$	-H			16% (after 6 steps)
22.	-H	-H	-H			20% (after 6 steps)
23.	-H	-H	-H			26% (after 6 steps)
24.	-H	-H	-H			30% (after 6 steps)
25.	-H	-H	-H			20% (after 6 steps)
26.		-H	-H			16% (after 6 steps)
27.		-H	-H			15% (after 6 steps)

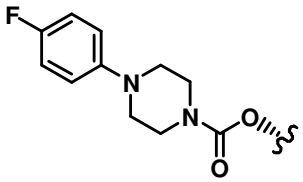
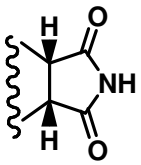
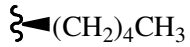
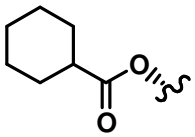
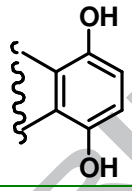
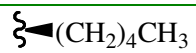
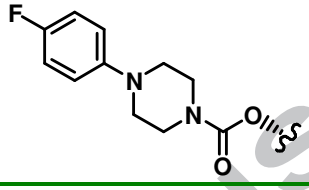
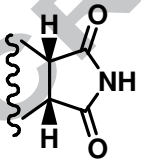
28.		-H	-H			16% (after 6 steps)
29.		-H	-H			15% (after 6 steps)
30.		-H	-H			15% (after 6 steps)
31.		-H	-H			16% (after 6 steps) d.r. = 25:1
32.		-H	-H			20% (after 6 steps)
33.		-H	-H			15% (after 6 steps) d.r. = 3:2
34.		-H	-H			20% (after 6 steps)
35.		-H	-H			23% (after 6 steps)
36.		-H	-H			41% (after 6 steps) d.r. = 3:2

37.	$-CH_3$	$-CH_3$	-H			25% (after 6 steps) d.r. = 6:1
38.		-H	-H			29% (after 6 steps) d.r. = 2.6:1
39.		-H	-H			31% (after 6 steps)
40.		-H	-H			24% (after 6 steps)
41.		-H	-H			15% (after 6 steps) d.r. = 4:1
42.		-H	-H			20% (after 6 steps)
43.		-H	-H			30% (after 5 steps) d.r. = 4:1
44.		-H	-H			20% (after 5 steps)
45.		-H	-H			44% (after 5 steps)

46.	$(CH_2)_4CH_3$	-H	CH_3	OH		70% (after 5 steps)
47.	$(CH_2)_4CH_3$	-H	CH_3			32% (after 5 steps) d.r. = 8:1
48.	$(CH_2)_4CH_3$	-H	CH_3			50% (after 5 steps) d.r. = 8:1
49.	$(CH_2)_4CH_3$	-H	CH_3			60% (after 5 steps)
50.	$(CH_2)_4CH_3$	-H	CH_3			26% (after 5 steps)
51.	$(CH_2)_4CH_3$	-H	-H			60% (after 5 steps)
52.	$(CH_2)_4CH_3$	-H	-H			21% (after 6 steps) d.r. = 8:1
53.	$(CH_2)_4CH_3$	-H	-H			25% (after 6 steps) d.r. = 9:1
54.	$(CH_2)_4CH_3$	-H	-H			24% (after 6 steps) d.r. = 6.5:1
55.	$(CH_2)_4CH_3$	-H	-H			20% (after 6 steps) d.r. = 6:1

56.	$(CH_2)_4CH_3$	-H	-H			28% (after 5 steps)
57.	$(CH_2)_4CH_3$	-H	-H			16% (after 5 steps)
58.	$(CH_2)_4CH_3$	-H	-H			32% (after 5 steps)
59.	$(CH_2)_4CH_3$	-H	-H			25% (after 5 steps) d.r. = 4:1
60.	$(CH_2)_4CH_3$	-H	-H			25% (after 5 steps) d.r. = 8:1
61.	$(CH_2)_4CH_3$	-H	-H			26% (after 6 steps) d.r. = 6:1
62.	$(CH_2)_4CH_3$	-H	-H			32% (after 5 steps)
63.	$(CH_2)_4CH_3$	-H	-H			30% (after 5 steps)
64.	$(CH_2)_4CH_3$	-H	-H			17% (after 5 steps)

65.		-H				60% (after 4 steps) d.r. = 8:1
66.		-H				70% (after 4 steps)
67.		-H	-H			23% (after 5 steps)
68.		-H	-H			65% (after 4 steps) d.r. = 20:1
69.		-H				50% (after 4 steps)
70.		-H				55% (after 4 steps) d.r. = 2.8:1
71.		-H	-H			27% (after 6 steps) d.r. = 4:1
72.	$-CH_3$	$-CH_3$	-H			20% (after 6 steps) d.r. = 6:1
73.	$-(CH_2)_5-$	$-(CH_2)_5-$	-H			10% (after 6 steps) d.r. = 4:1
74.	-H	-H	-H			25% (after 6 steps)

75.	-H	-H	-H			28% (after 6 steps)
76.		-H	-H			20% (after 5 steps)
77.		-H	-H			22% (after 6 steps)

[a]Isolated yield after column chromatography, d.r. = diastereomeric ratio.

The Diels-Alder adduct with electron withdrawing dienophiles **20** was formed with *endo*-selectivity. The relative stereochemistry of one of the library members was determined by nOe experiments as shown in Figure 2.

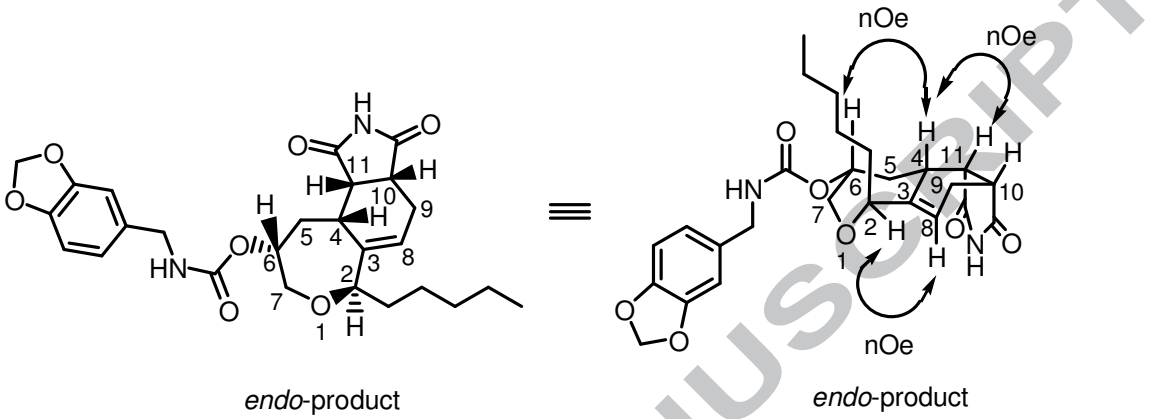


Figure 2. nOe study of a oxepane library member.

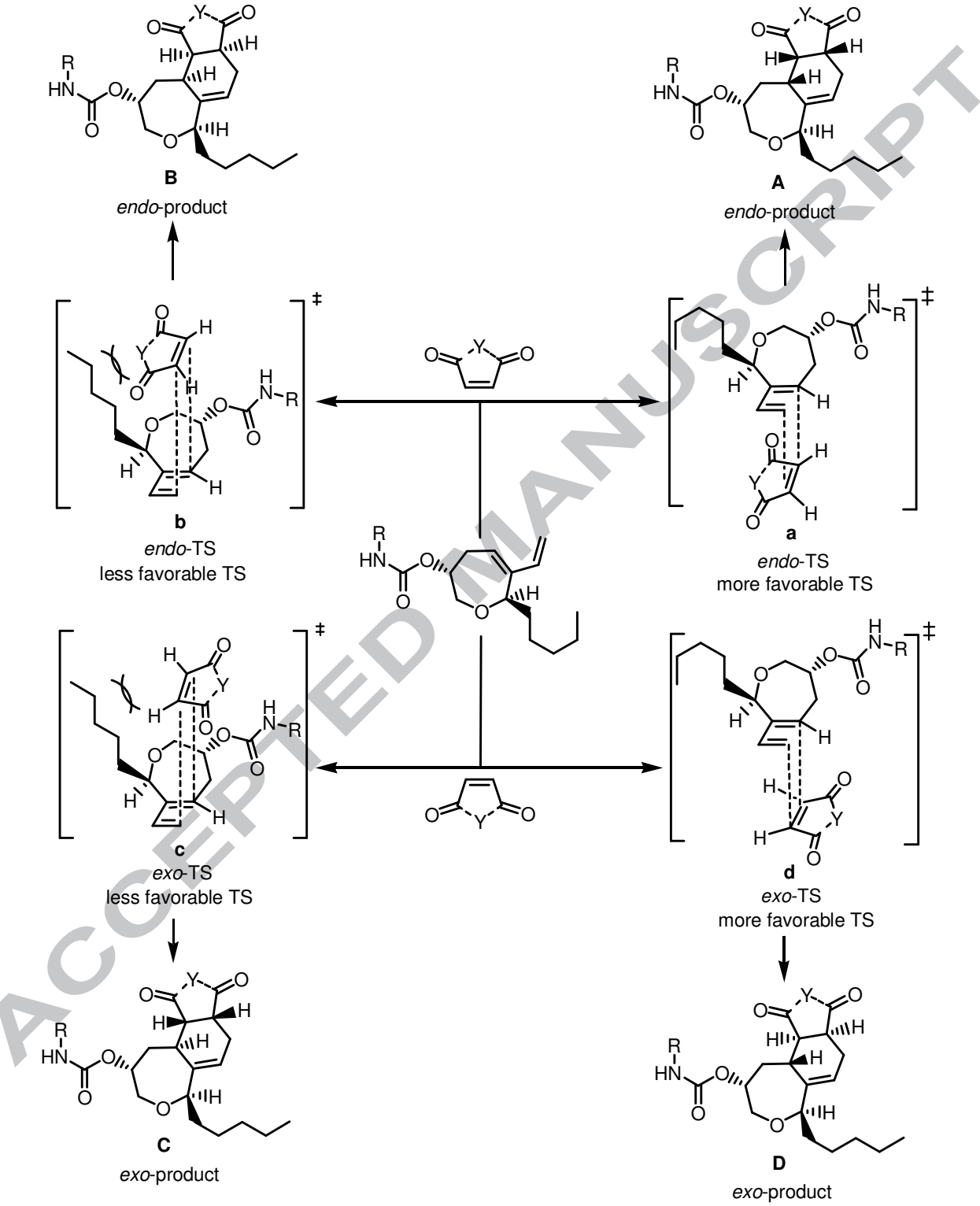
In this nOe experiment protons H^2, H^4 and H^6 were irradiated in their resonance frequency and the signal enhancements observed are shown in Table 2.

Table 2. nOe irradiation and intensity of the protons.

Irradiation at	**Signal enhancements of protons**
H^6	H^4 (5.0%), H^5 (3.0 %)
H^4	H^6 (6.0%), H^{11} (3.0%), H^5 (3.0%)
H^2	H^8 (4.0%), H^7 (2.0%)

From the nOe experiment it was evident that the Brown asymmetric allylation proceeded with the expected stereochemistry. The Diels-Alder reaction also proceeded with *endo*-selectivity. Based on this experiment the configuration of the other library members was assigned by analogy. In the Diels-Alder reaction the diene can react through four possible transition states (**a**, **b**, **c**, **d**, Scheme 3) with the dienophile. When the Diels-Alder reaction proceeds through *exo*-transition state **d**, the dienophile approaches from the less sterically hindered and more favorable face of the diene, giving rise to the *exo*-adduct **D**. When the

dienophile approaches from the face occupied by the bulky *n*-pentyl group, steric hindrance renders the *exo*-transition state **c** less favorable.

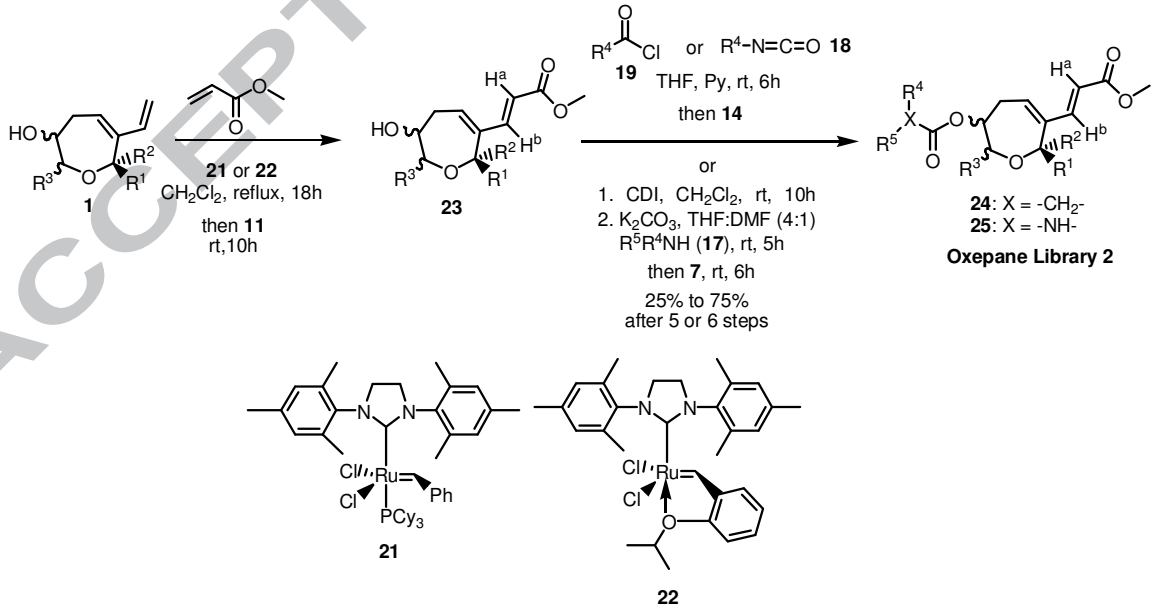


Scheme 3. *Endo*-transition state for the Diels-Alder reaction.

In transition state **b** the dienophile approaches from the side occupied by the bulky pentyl group, encountering a steric hindrance and hence making **b** a less favorable transition state. In transition state **a**, the dienophile approaches from the face opposite to the bulky *n*-pentyl group. Thus, transition state **a** is less sterically hindered and more favorable giving rise to the desired product **A**. The nOe study described above rules out the possibility of the *exo*-transition states (**c** and **d**) and also the more sterically hindered transition state **b**. Hence the only product **A** was obtained from this Diels-Alder reaction through the more favorable *endo*-transition state **a**. Interestingly, we did not detect any thermodynamically stable *exo*-product (**D**) through transition state **d**. We anticipate that kinetically controlled *endo*-product (**A**) formation was more favorable as the oxepane diene is not electronically rich leading to slow reaction kinetics even at 70 ^{o}C for 10h.[19]

Synthesis of oxepane library 2 by cross metathesis

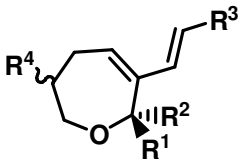
Further diversification was achieved by cross metathesis including the diene group embedded in **1**(Scheme 4). Diene **1** was refluxed in CH_2Cl_2 with methyl acrylate in the presence of either 2nd generation Grubbs catalyst **21**[20a] (15 mol%) or 2nd generation Hoveyda-Grubbs catalyst **22**[20b] (20 mol%) for 18 h. When the reaction was complete (determined by TLC), the ruthenium scavenger resin **11** was added.

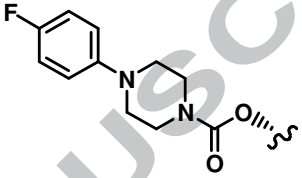
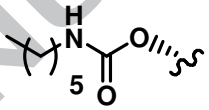
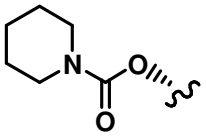
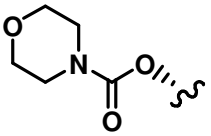
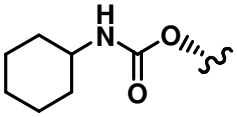
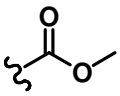
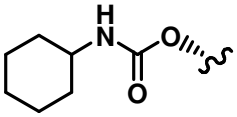
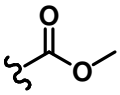
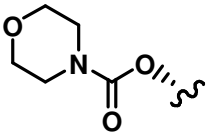
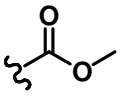
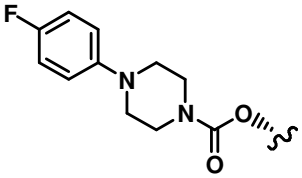
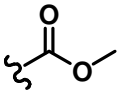
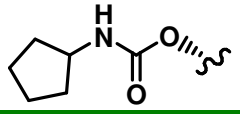


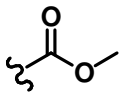
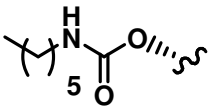
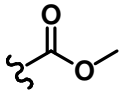
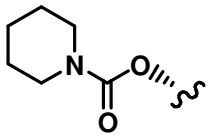
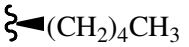
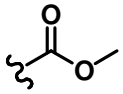
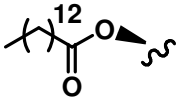
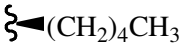
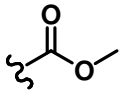
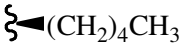
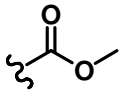
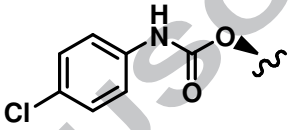
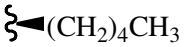
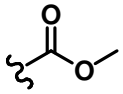
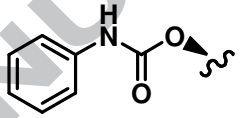
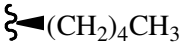
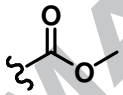
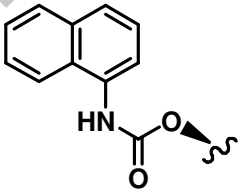
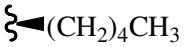
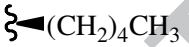
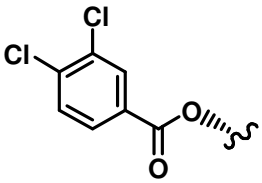
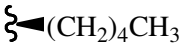
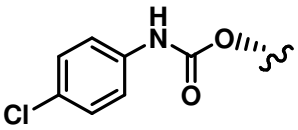
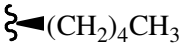
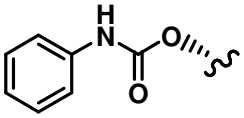
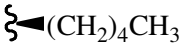
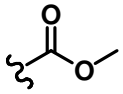
Scheme 4. Synthesis of the oxepane library 2.

In this cross metathesis strategy it was realized that the 2nd generation Grubbs catalyst **21** showed higher reactivity than the 2nd generation Hoveyda-Grubbs catalyst **22**. The free alcohol was functionalized to give esters **24** and carbamates **25** in 47%-57% (after 5 steps) and 25%-75% (after 5 or 6 steps) isolated overall yield respectively. In the products **24** and **25**, the newly formed olefin after the cross metathesis reaction was *E*-configured exclusively as was evident from the coupling constant ($J_{Ha\text{-}Hb}$ = 16.0 Hz, (see also the Supporting Information) between H^a and H^b in the ^{1}H NMR spectrum. The oxepanes synthesized by means of this procedure are shown in Table 3.

Table 3. Oxepane library 2.



Entry	R^1	R^2	R^3	R^4	Yield[a]
1.	$-CH_3$	$-CH_3$	-H		40% (after 5 steps)
2.	$-CH_3$	$-CH_3$	-H		25% (after 5 steps)
3.	$-CH_3$	$-CH_3$	-H		29% (after 5 steps)
4.	$-CH_3$	$-CH_3$	-H		40% (after 5 steps)
5.	$-CH_3$	$-CH_3$	-H		45% (after 5 steps)
6.	$-CH_3$	$-CH_3$			35% (after 6 steps)
7.	$-CH_3$	$-CH_3$			36% (after 6 steps)
8.	$-CH_3$	$-CH_3$			38% (after 6 steps)
9.	$-CH_3$	$-CH_3$			35% (after 6 steps)

10.	$-CH_3$	$-CH_3$			35% (after 6 steps)
11.	$-CH_3$	$-CH_3$			30% (after 6 steps)
12.		-H			47% (after 5 steps)
13.		-H			30% (after 5 steps)
14.		-H			75% (after 5 steps)
15.		-H			47% (after 5 steps)
16.		-H			40% (after 5 steps)
17.		-H	-H		60% (after 3 steps) d.r. = 8:1
18.		-H	-H		60% (after 3 steps) d.r. = 2.5:1
19.		-H	-H		57% (after 4 steps) d.r. = 8:1
20.		-H	-H		65% (after 4 steps) d.r. = 8:1
21.		-H	-H		40% (after 4 steps) d.r. = 8:1
22.		-H			45% (after 4 steps)

[a]Isolated yield after column chromatography, d.r. = diastereomeric ratio.

Synthesis of keto oxepanes

The Sodwanones are a family of marine natural products displaying activity against different human cancer cell lines (Figure 3).[5]

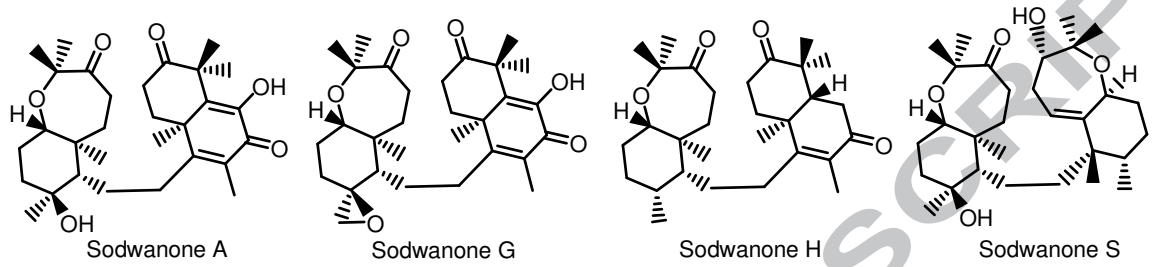
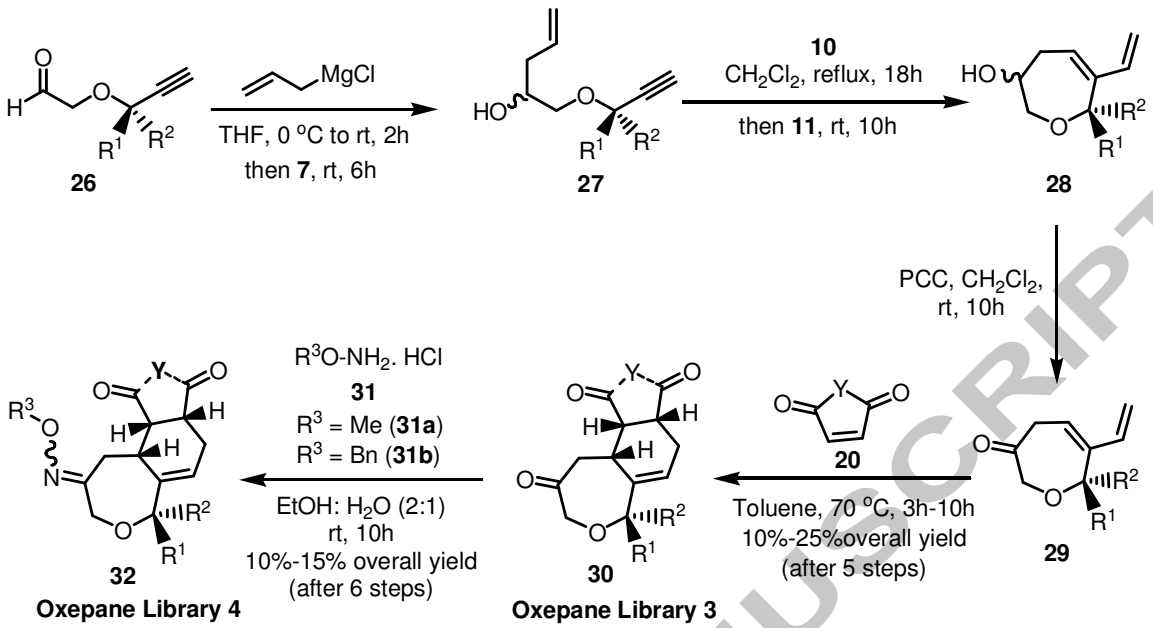


Figure 3. Few representatives of Sodwanone family natural products

The Sodwanone family contains the keto oxepane scaffold. Inspired by this marine natural product family and its anti cancer activity, a small keto oxepane collection was synthesized.

Aldehydes **26** were treated with allylmagnesium chloride in THF at 0 ^{o}C to room temperature for 2h to obtain the enyne metathesis precursors **27** as a 1:1 mixture of two inseparable isomers after scavenging the excess allylmagnesium chloride with the polymer supported sulfonic acid resin **7** (Scheme 5). These crude enyne metathesis precursors were treated with 1st generation Grubbs catalyst **10** in refluxing CH_2Cl_2 for 18h. When the reaction was complete (monitored by TLC), the ruthenium metal was scavenged using the metal chelating resin **11**. After filtering the resin and removal of solvent, a 1:1 mixture of colorless crude oxepanes **28** was obtained. The crude alcohols **28** were then oxidized to the ketones **29** using pyridinium chlorochromate (PCC) in CH_2Cl_2 at room temperature for 10h. After total consumption of the starting alcohols **28** (monitored by TLC), the reaction mixtures were filtered through a Celite pad to remove the chromium metal from the reaction mixture.

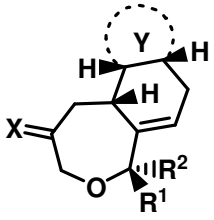


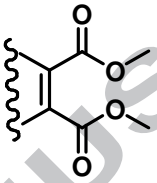
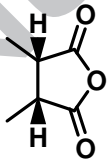
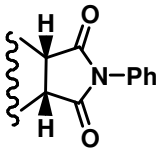
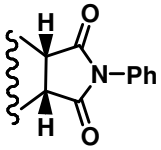
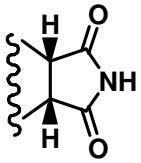
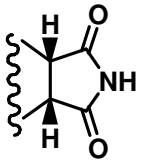
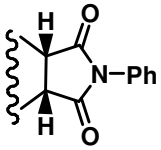
Scheme 5. Synthesis of keto-oxepane library **3** and oxime library **4**.

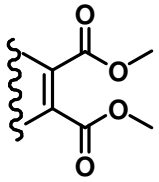
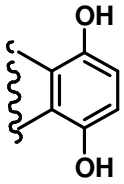
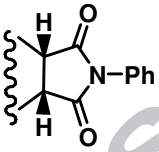
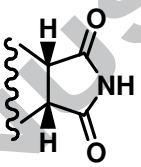
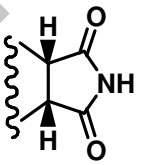
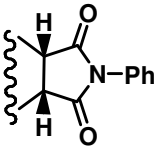
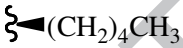
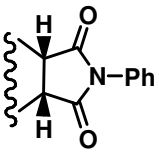
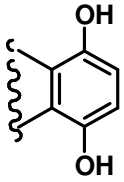
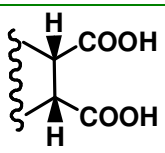
After the keto oxepane scaffold was formed the diene moiety of **29** was functionalized by means of Diels-Alder reactions. When crude **29** was treated with different commercially available dienenophiles **20** in the minimum volume of toluene necessary at 70 °C for 3h to 10h (depending on the dienophile used) the crude adducts **30** were formed. The crude products **30** were purified by silica gel chromatography to obtain pure keto oxepanes in 10% to 25% overall yield after 5 steps for the major isomer. In this case also, it was assumed that the *endo*-adduct had been formed based on the nOe study described above. The isomeric ratios of the individual keto oxepanes were determined by means of ^{1}H NMR spectroscopy and are shown in the Supporting Information and Table 4.

Crude **30** were further treated with either *O*-methyl hydroxylamine hydrochloride salt (**31a**) or *O*-benzyl hydroxylamine hydrochloride salt (**31b**) in ethanol:water (2:1) mixture at room temperature for 10h.[21] After the reaction was complete (monitored by TLC) the solvent was evaporated and the crude **32** were purified by preparative thin layer chromatography (PTLC) to afford the pure oximes in 10% to 15% overall yield after 6 steps. *O*-Benzylhydroxyl amine (**31b**) gave better yields than *O*-methylhydroxyl amine (**31a**). The structures, yields and isomeric ratios of the oximes are shown in Table 4.

Table 4. Oxepane libraries with keto-/and oxime functional groups.



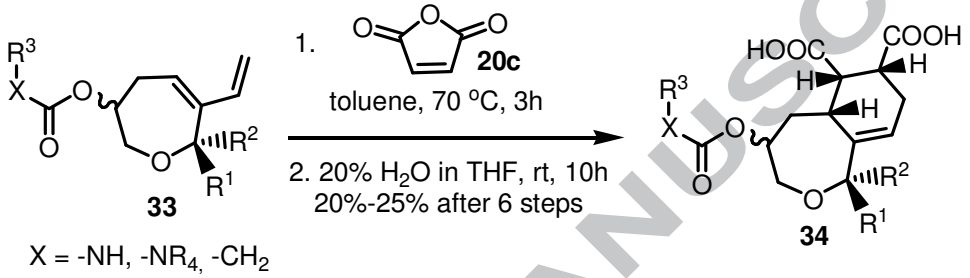
Entry	R^1	R^2	X	Y	Yield
1.	~$(CH_2)_4CH_3$	-H	O		30%[a] (after 5 steps)
2.	~$(CH_2)_4CH_3$	-H	O		25%[a] (after 5 steps)
3.	~$(CH_2)_4CH_3$	-H	O		25%[a] (after 5 steps)
4.	$-(CH_2)_5-$	$-(CH_2)_5-$	OBn N		10%[b] (after 6 steps)
5.	$-(CH_2)_5-$	$-(CH_2)_5-$	OBn N		12%[b] (after 6 steps)
6.	$-(CH_2)_5-$	$-(CH_2)_5-$	O		15%[a] (after 5 steps)
7.	$-(CH_2)_5-$	$-(CH_2)_5-$	O		10%[a] (after 5 steps)

8.	-$(CH_2)_5$-	-$(CH_2)_5$-	O		15%[a] (after 5 steps)
9.	-$(CH_2)_5$-	-$(CH_2)_5$-			10%[b] (after 6 steps) d.r. = 8:1
10.	-CH_3	-CH_3	O		12%[a] (after 5 steps)
11.	-CH_3	-CH_3	O		15%[a] (after 5 steps)
12.	-CH_3	-CH_3			15%[b] (after 6 steps)
13.	-CH_3	-CH_3			13%[b] (after 6 steps) d.r. = 4.3:1
14.		-H			10%[b] (after 6 steps) d.r. = 20:1
15.		-H	O		14%[a] (after 5 steps)
16.	-$(CH_2)_5$-	-$(CH_2)_5$-			10%[b] (after 6 steps) d.r. = 6:1

[a]Isolated yield after column chromatography, [b]Isolated yield after preparative thin layer chromatography (PTLC), d.r. = diastereomeric ratio

Synthesis of diacids

Further diversification on the oxepane scaffold was achieved after the Diels-Alder reaction with maleic anhydride (**20c**) and hydrolysis of the formed anhydride to diacids **34** (Scheme 6). The dienes **33** were treated with maleic anhydride (**20c**) in toluene at 70 ^{o}C for 3h. As soon as the dienes **33** were totally consumed (monitored by TLC), the solvent was evaporated and the crude products were dissolved in a solution of 20% water in THF and stirred at room temperature for 10h.



Scheme 6: Synthesis of diacid.

The solvent was evaporated by coevaporation with excess ethanol and purified by silica gel chromatography to obtain the diacids **34** in 20% to 25% yield after 6 steps.[22] The diacids were formed as inseparable mixtures of two isomers determined by means of ^{1}H NMR spectroscopy. The structures, yields and diastereomeric ratios of the diacids are shown in Table 1 and in the Supporting Information.

Summary and Conclusion

A collection of 77 fully functionalized oxepanes (library 1) has been synthesized by means of the synthetic strategy shown in Scheme 2. The ring-closing enyne metathesis reaction was used as the key step to synthesize the oxepane scaffold **1**. Diversity on the oxepane scaffold was generated by reacting isocyanates **18** and acid chlorides **19** with alcohols to generate carbamates and esters respectively. In addition, carbamates were synthesized by a two step procedure using carbonyl diimidazole and different primary and secondary amines **17**. The diene moiety was functionalized by Diels-Alder cycloaddition to yield fused seven-six membered bicyclic systems. A collection of 22

diene oxepanes (library 2) has been synthesized by means of a cross metathesis reaction followed by diversification of alcohols **23** to esters **24** and carbamates **25** (Scheme 4). A small collection of 16 compounds (library 3 and library 4) was synthesized using PCC oxidation of secondary alcohols **28** to ketones **29** and functionalization to oximes **32** after Diels-Alder reaction (Scheme 5). A total of 115 oxepane molecules have been obtained by solution phase parallel synthesis using polymer-supported reagents and scavengers.

Among the substituted propargyl alcohol building blocks **6**, all propargyl alcohols gave moderate to good yields except propargyl alcohol (**6d**) itself. It was noted that the propargyl alcohol is difficult to handle due to its volatility and that is reflected in the low yields of the oxepane molecules using this building block. Bromo ethyl acetate (**5a**) showed the best reactivity and yields than the other two building blocks among the substituted α-bromo ethyl acetates (**5b** and **5c**). Among the isocyanate building blocks **18**, the 2,4-dimethoxyphenyl isocyante (**18d**) showed the lowest reactivity and yield due to its electron donating substituents as well as the bulky *ortho*-substituent. The naphthyl- (**18a**) and phenyl isocyante (**18b**) showed moderate reactivity. The best reactivity was observed with *p*-chlorophenyl isocyanate (**18c**) due to the electron withdrawing chlorine. It was noted that the aliphatic acid chlorides (**19f-i**) are more reactive than the aromatic acid chlorides (**19a-e**). Among the aromatic acid chlorides 2-fluorobenzoyl chloride (**19c**) and 3,4-dichlorobenzoyl chloride (**19e**) are most reactive due to their electron withdrawing character. On the other hand *p*-methoxy- (**19b**) and *p*-methylbenzoyl chlorides (**19d**) are least reactive due to their electron donating substituents. It was observed that all primary and secondary amines **17** showed similar reactivity. It was experienced that among the dienophiles *N*-phenyl maleimide (**20b**), maleimide (**20a**) and maleic anhydride (**20c**) showed the best reactivity, whereas *p*-benzoquinone (**20d**) and diemthyl acetylene diacarboxylate (**20e**) are not particularly reactive.

Our results demonstrate that the solution phase synthesis of the oxepane collection using solid-supported scavengers is very practical and allows to synthesize a diversely functionalized oxepanes in an efficient manner.

Acknowledgments

This research was financially supported by the International Max-Planck Research School in Chemical Biology (IMPRS-CB) and the Max-Planck Society.

References and notes

1. (a) Breinbauer, R.; Vetter, I.; Waldmann, H. *Angew. Chem. Int. Ed.* **2002**, *41*, 2878; (b) Kumar, K.; Waldmann, H. *Angew. Chem. Int. Ed.* **2009**, *48*, 3224; (c) Kaiser, M.; Wetzel, S,; Kumar, K.; Waldmann, H. *Cell. Mol. Life Sci.* **2008**, 65, 1186.
2. Ley, S. V.; Baxendale, I. R. *Nature Reviews Drug Discovery* **2002**, *1*, 573 and the references therein.
3. Macías, F. A.; Molinillo, J. M. G.; Varela, R. M.; Torres, A. *J. Org. Chem.* **1994**, *59*, 8261.
4. (a) Bon, C. F.–L.; Berrué, F.; Thomas, O. P.; Reyes, F.; Amade, P. *J. Nat. Prod.* **2005**, *68*, 1284; (b) Rudi, A.; Goldberg, I.; Stein, Z.; Kashman, Y. *J. Nat. Prod.* **1995**, *58*, 1702.
5. Guella, G.; Mancini, I.; Chiasera, G.; Pietra, F. *Helv. Chim. Acta* **1992**, *75*, 310.
6. Levine, S. D.; Adams, R. E.; Chen, R.; Cotter, M. L.; Hirsch, A. F.; Kane, V. V.; Kanijoa, R. M.; Shaw, C. J.; Wachter, M. P.; Chin, E.; Huetteman, R.; Ostrowski, P.; Mateos, J. L.; Noriega, L.; Guzmán, A.; Mijarez, A. Tovar, L. *J. Am. Chem. Soc.* **1979**, *101*, 3404.
7. (a) Marcelle, G. B.; Bunyapraphatsara, N.; Cordell, G. A.; Fong, H. S.; Nicolaou, K. C.; Zipkin, R. E. *J. Nat. Prod.* **1985**, *48*, 739; (b) Kanojia, R. M.; Chin, E.; Smith, C.; Chen. R.; Rowand, D.; Levine, S. D.; Wachter, M. P.; Adams, R. E.; Hahn, D. W. *J. Med. Chem.* **1985**, *28*, 796.
8. (a) Wetzel, S.; Bon, R. S.; Kumar, K.; Waldmann, H. *Angew. Chem. Int. Ed.* **2011**, *50*, 10800; (b) Bon, R. S.; Waldmann, H. *Acc. Chem. Res.* **2010**, *43*, 1103.
9. (a) Nören-Müller, A.; Reis-Correa, I.; Prinz, H.; Rosenbaum, C.; Saxena, K.; Schwalbe, H. J.; Vestweber, D., Cagna, G.; Schunk, S.; Schwarz, O.; Schiewe, H.; Waldmann, H. *Proc. Natl. Acad. Sci. U. S. A*. **2006**, *103*, 10606; (b) Nören-

Müller, A.; Wilk, W.; Saxena, K.; Schwalbe, H.; Kaiser, M.; Waldmann, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 5973; (c) Waldmann, H.; Khedkar, V.; Dückert, H.; Schürmann, M.; Oppel, I. M.; Kumar, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 6869; (d) Antonchick, A. P.; Gerding-Reimers, C.; Catarinella, M.; Schurmann, M.; Preut, H.; Ziegler, S.; Rauh, D.; Waldmann, H. *Nat. Chem.* **2010**, *2*, 735; (e) Basu, S.; Ellinger, B.; Rizzo, S.; Deraeve, C.; Schurmann, M.; Preut, H.; Arndt, H. D.; Waldmann, H.; *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 6805; (f) Dueckert, H.; Pries, V.; Khedkar, V.; Menninger, S.; Bruss, H.; Bird, A. W.; Maliga, Z.; Brockmeyer, A.; Janning, P.; Hyman, A.; Grimme, S.; Schurmann, M.; Preut, H.; Hubel, K.; Ziegler, S.; Kumar, K.; Waldmann, H. *Nat. Chem. Biol.* **2012**, *8*, 179; (g) Potowski, M.; Bauer, J. O.; Strohmann, C.; Antonchick, A. P.; Waldmann, H. *Angew. Chem. Int. Ed.* **2012**, *51*, 9512; (h) Potowski, M.; Schurmann, M.; Preut, H.; Antonchick, A. P.; Waldmann, H. *Nat. Chem. Biol.* **2012**, *8*, 428-430.; (i) Over, B.; Wetzel, S.; Grütter, C.; Nakai, Y.; Renner, S.; Rauh, D.; Waldmann, H. *Nat. Chem.* **2013**, *5*, 21; (j) Dakas, P.-Y.; Parga, J. A.; Höing, S.; Schöler, H. R.; Sterneckert, J.; Kumar, K.; Waldmann, H.; *Angew. Chem. Int. Ed.* **2013**, *52*, 9576; (k) Voigt, T.; Gerding-Reimers, C.; Tuyen, T. N. T.; Bergmann, S.; Lachance, H.; Scholermann, B.; Brockmeyer, A.; Janning, P.; Ziegler, S.; Waldmann, H. *Angew. Chem. Int. Ed.* **2013**, *52*, 410; (l) Antonchick, A. P.; López-Tosco, S.; Parga, J.; Sievers, S.; Schürmann, M.; Preut, H.; Höing, S.; Schöler, H. R.; Sterneckert, J.; Rauh, D.; Waldmann, H. *Chem. Biol.* **2013**, *20*, 500; (m) Potowski, M.; Antonchick, A. P.; Waldmann, H. *Chem. Commun.* **2013**, *49*, 7800; (n) Takayama, H.; Jia, Z.-J.; Kremer, L.; Bauer, J. O.: Strohmann, C.; Ziegler, S.; Antonchick, A.; Waldmann, H. *Angew. Chem. Int. Ed.* **2013**, *52*, 12404; (o) Narajan, R.; Bauer, J. O.; Strohmann, C.; Antonchick, A.; Waldmann, H. *Angew. Chem. Int. Ed.* **2013**, *52*, 12892; (p) Eschenbrenner-Lux, V.; Kuechler, P.; Ziegler, S.; Kumar, K.; Waldmann, H. *Angew. Chem. Int. Ed.* **2014**, *53*, 2134.

10. (a) Moreno-Mañas, M.; Pleixats, R.; Santamaria, A. *Synlett.* **2001**, 1784; (b) Majumdar, K. C.; Rahaman, H.; Muhuri, S.; Roy, B. *Synlett.* **2006**, 466.
11. Crimmins, M. T.; DeBaillie, A. C. *Org. Lett.* **2003**, *5*, 3009.
12. Jadav, P. K.; Bhat, K. S.; Perumal, T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432.

13. Storer, R. I.; Takemoto, T.; Jackson, P. S.; Brown, D. S.; Baxendale, I. R.; Ley, S. V. *Chem. Eur. J.* **2004**, *10*, 2529.

14. Ahmed, M.; Barrett, A. G. M.; Braddock, D. C.; Cramp, S. M.; Procopiou, R. A. *Tetrahedron Lett.* **1999**, *40*, 8657.

15. Westhus, M.; Gonthier, E.; Brohm, D.; Breinbauer, R. *Tetrahedron Lett.* **2004**, *45*, 3141.

16. (a) Chadha, N. K.; Batcho, A. D.; Tang, P. C.; Courtney, L. F.; Cook, C. M.; Wovkulich, P. M.; Uskoković, M. R. *J. Org. Chem.* **1991**, *56*, 4714. (b) Cano, M.; Ladlow, M.; Balasubramanian, S. *J. Org. Chem.* **2002**, *67*, 129.

17. Harding, W. W.; Tidgewell, K.; Byrd, N.; Cobb, H.; Dersch, C. M.; Butelman, E. R.; Rothman, R. B.; Prisinzano, T. E. *J. Med. Chem.* **2005**, *48*, 4765.

18. Smith, A. B. III; Rucker, P. V.; Brouard, I.; Freeze, B. S.; Xia, S.; Horwitz, S. B. *Org. Lett.* **2005**, *7*, 5199.

19. Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2002**, *41*, 1668-1698.

20. (a) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3782. (b) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

21. (a) Kulkarni, B. A.; Roth, G. P.; Lobkovsky, E.; Porco, J. A., Jr. *J. Comb. Chem.* **2002**, *4*, 56-72. (b) Pelish, H. E.; Westwood, N. J.; Feng, Y.; Kirchhausen, T.; Shair, M. D. *J. Am. Chem. Soc.* **2001**, *123*, 6740.

22. Boger, D. L.; Tarby, C. M.; Myers, P. L.; Caporale, L. H. *J. Am. Chem. Soc.* **1996**, *118*, 2109.