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Enantioselective Access to Bicyclo[4.2.0]octanes by a Sequence of [2+2] Photocycloaddition/Reduction/Fragmentation

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Cyclobutanes are most concisely synthesized by [2+2] cycloaddition reactions upon thermal or photochemical activation.[1] Enantioselective access to chiral cyclobutanes can be achieved either by appropriately modifying the reaction conditions of the [2+2] cycloaddition reaction[2,3] or by subsequent transformations of a pre-formed cyclobutane.[4] A frequently encountered structural motif, in which a cyclobutane is involved, is the bicyclo[4.2.0]octane skeleton of several natural products[5] (Figure 1).

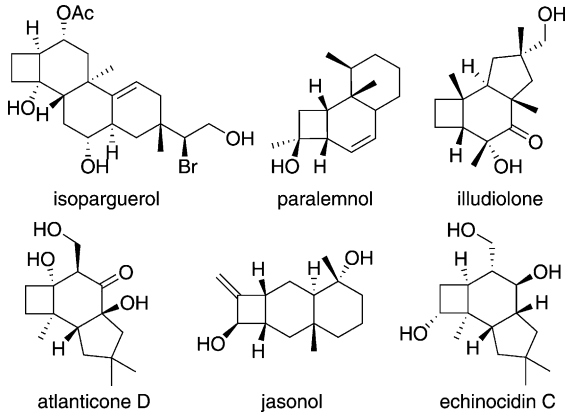

Figure 1. Examples of natural products, which display a bicyclo[4.2.0]octane skeleton.

Although an intermolecular [2+2] photocycloaddition reaction of enones to form bicyclo[4.2.0]octanes is feasible,[6] enantioselective access to this skeleton has only been possible by the use of stoichiometric auxiliaries.[7] An alternative approach, which we have tried to employ for some time, relies on an intramolecular Cu-catalyzed [2+2] photocycloaddition[8] to products of general type **A** and their subsequent desymmetrization by chiral reagents.[4e,f] However, it turned out to be difficult to perform desymmetrization reactions with Z=CO and only the enzymatic Baeyer–Villiger oxidation of ketone **1** was shown to be a sufficiently enantioselective process (Figure 2). When considering alternative ring-opening procedures, the 1,2-elimination of oxygen-bridged products of type **B** attracted our attention. It was envisaged that enantioselectivity could be achieved by employing precursors, which would facilitate elimination reactions and which would be readily available from furan. Indeed, it has now been found that imides **2** are suitable for this purpose and preliminary results of our experiments in this area are reported herein.

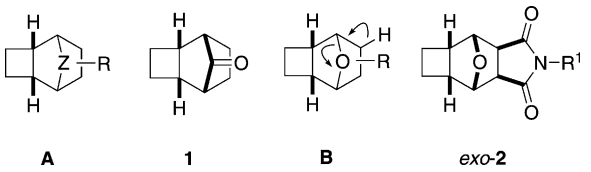

Figure 2. General structures **A** and **B** as well as specific structures **1** and **2** of bridged substrates, which allow for an enantiotopos-differentiating ring opening to the bicyclo[4.2.0]octane skeleton.

To access products **2**, a Diels–Alder reaction of imides **3** with furan[9] was followed by a ring-opening metathesis reaction with ethylene (Table 1; Grubbs I: $[RuCl_2(PCy_3)_2=CHPh]$,[10] Cy=cyclohexyl).[11] The resulting 1,6-dienes **5** were subjected to typical conditions of a Cu-catalyzed [2+2] photocycloaddition reaction employing $Cu(OTf)_2$ (10 mol%) as the catalyst[12] ($\lambda=254$ nm, room temperature, $c=15$ mM in Et_2O). Surprisingly, this reaction when performed with substrate **5a**, turned out to be sluggish and delivered after 17 h of irradiation only 21% of product **2a** (d.r.=*exo*/*endo*=76/24) and very little recovered starting material. Toluene emerged as the solvent of choice from a subsequently performed screen of solvents. Under otherwise identical conditions, the reaction in toluene delivered 89% yield of product **2a** (d.r.=82/18). The diastereoselectivity improved when the reaction temperature was lowered (d.r.=91/9 at −50°C), but the reaction was also significantly slower, which led us to run all other reactions (Table 1) at ambient temperature. Although *exo*- and *endo*-diastereoisomers **2** could not be separated at this stage (see below), the major product was clearly shown to be the *exo*-product based on NOE data (see Supporting Information for further details). In general, diastereomeric ratios were high (d.r.=80/20 to 91/9). Only in the case of product **2e**, there was a significant decrease in selectivity (d.r.=66/34).

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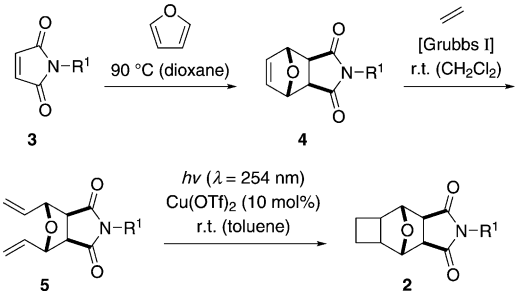
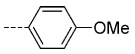
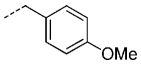
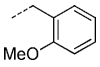
Table 1. Preparation of tetracyclic 12-oxa-4-azatetracyclo[5.4.1.0^{2,6}.0^{8,11}]dodecan-3,5-diones by a sequence of Diels–Alder reaction, ring opening metathesis, and intramolecular [2+2] photocycloaddition.



Substrate	R^1	Yield[a] **4** [%]	Yield **5** [%][d]	Yield[b] **2** [%][d]	d.r.[c] (*exo*/*endo*)
3a	---Me	90	87	89	82/18
3b		90	75	88	89/11
3c		81	76	74[e]	82/18
3d		59	69	97	91/9
3e		77	79	91	66/34
3f		76	72	95	80/20
3g		83	62	94	83/17

[a] The minor diastereoisomer of the Diels–Alder reaction could be separated by column chromatography. Yields refer to the isolated diastereoisomer **4** depicted in the reaction equation. [b] All [2+2] photocycloaddition reactions were conducted using a RPR-100 reactor with 16 Rayonet RPR-2540 Å lamps (quartz apparatus) as the irradiation source in deaerated toluene (c = 15 mM, t = 20 h). [c] Diastereomeric products *exo*-**2** (Figure 2) and *endo*-**2** were not separable by flash chromatography. The diastereomeric ratio (d.r.) was determined by ^{1}H NMR integration of the product mixture. [d] Yields refer to isolated products after chromatographic purification. [e] 24% of starting material was re-isolated.

The reaction sequence **3** → **2** proceeded smoothly for all substrates and only a few issues require special comment. In the Diels–Alder reaction, major product **4** was formed together with a diastereomeric by-product. The separation of the latter compound was facile and products **4** were obtained as single diastereoisomers. In the photocycloaddition of substrate **5c**, the reaction did not go to complete conversion after 20 h, which may be due to competing absorption by the *N*-phenyl chromophore. No side reactions were observed, though, and the yield based on conversion was 97%.

Attempts to achieve the conversion of products **2** to chiral ring-opening products by elimination were performed with different bases.[13] Unfortunately, the reactions did not lead to homogenous products but rather to product mixtures. Due to the fact that the α-carbonyl protons are more readily accessible in the *endo*-diastereoisomer *endo*-**2**, elimination products turned out to be enriched in the respective *endo*-isomer. Attempted ring-opening reactions with Lewis acids,[14] for example with BBr_3 in CH_2Cl_2, led to a cleavage of the central ether bond by nucleophilic displacement. The resulting halohydrins were unstable, however, and could not be isolated in enantiomerically pure form.

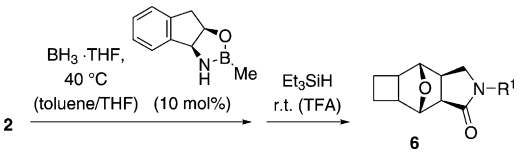
The desymmetrization of compounds **2** by an enantiotopos-selective reduction of the imide carbonyl groups[15,16] turned out to be the most reliable way to access enantioenriched compounds with a bicyclo[4.2.0]octane skeleton. After initial reduction to a hydroxylactam the reduction was completed with triethylsilane in trifluoroacetic acid (TFA) and the enantiomeric excess of the resulting products **6** was determined. Optimization experiments were performed with the *N*-benzyl-substituted substrate **2e**. The best compromise between high chemoselectivity and high enantioselectivity was to run the reaction with stoichiometric amounts of borane and an oxazaborolidine catalyst[17] derived from (1*S*,2*R*)-*cis*-1-amino-2-indanol in THF as the solvent at 40°C. After 12 h the reaction was stopped and product **6e** was separated from remaining starting material (15%). Higher enantioselectivities as compared to the 86% *ee* recorded for *exo*-**6e** in Table 2 were achieved with a higher catalyst loading (up to 91% *ee*). Oxazaborolidines derived from other amino alcohols or with other boron substituents than methyl did not show an improved performance.

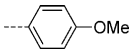
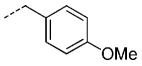
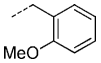
From the data presented in Table 2, it is apparent that the general procedure optimized for substrate **2e** was ideally suited for the enantioselective reduction of *N*-aryl (**2c**, **2d**) and *N*-benzyl (**2e**–**2g**) imides but it was less suited to achieve an enantioselective reduction of *N*-alkyl imides (**2a**, **2b**). In most cases, the chiral reagent showed no significant differentiation in the reduction of either *exo*- or *endo*-substrate and the d.r. of products **6** was similar to the d.r. of substrates **2**. Also the enantiomeric excess for *exo*- or *endo*-product did not vary extensively. Only with R = *ortho*-methoxybenzyl (substrate **2g**) was the *endo*-product apparently more readily reduced than the *exo*-product and the d.r. changed from 83/17 to 70/30. Separation of the diastereoisomers *exo*-**6** and *endo*-**6** was not possible by flash chromatography.

Gratifyingly, base treatment of compounds **6** not only induced the desired ring-opening of the central ether bond but it also led to products **7**, the two diastereoisomers of which were readily separable. Lithium bis(trimethylsilyl)-amide (LHMDS) was the base of choice[18] for this transformation. Upon elimination, major *exo*-isomers *exo*-**7** were accessed as shown for substrate **6c** in Scheme 1. In these compounds five contiguous stereogenic centers around the central bicyclo[4.2.0]octane skeleton exhibit a defined absolute and relative configuration. Apart from the depicted *exo*-product *exo*-**7c** the *endo*-isomer *endo*-**7c** was isolated in 18% yield. The total yield of the elimination was consequently 94%. As expected there was no significant change in the enantiomeric excess and product *exo*-**7c** was obtained in 97% *ee*.

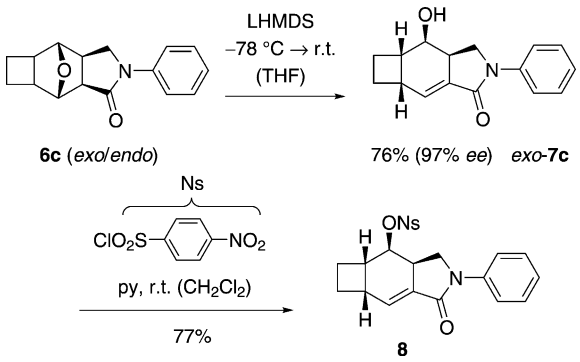
To substantiate the presumed relative configuration of product *exo*-**7c** and its congeners, the compound was con-

Table 2. Enantioselective reduction of imides **2** in the presence of a chiral oxazaborolidine catalyst followed by reduction to amides **6**.



Substrate	R^1	Yield[a] [%]	d.r.[b] (*exo*/*endo*)	*ee*[c] *exo* [%]	*ee*[c] *endo* [%]
2a	---Me	73	82/18	74	79
2b		53	88/12	84	83
2c		71	85/15	95	93
2d		75	92/8	93[d]	93[d]
2e		77	66/34	86	89
2f		78	82/18	89	87
2g		75	70/30	88	82

[a] Yields refer to isolated products after chromatographic purification. [b] Diastereomeric products *exo*-**6** and *endo*-**6** were not separable by flash chromatography. The diastereomeric ratio was determined by ^{1}H NMR integration of the product mixture. [c] The enantiomeric excess (*ee*) was determined by chiral HPLC analysis (see the Supporting Information). [d] The *ee* was determined after ring opening (see Figure 4 and Supporting Information).



Scheme 1. Base-induced ring opening of the oxygen bridge in the central oxybicyclo[2.2.1]heptane ring of substrates **6c** and conversion of product *exo*-**7c** into the respective nosylate **8**

verted into the crystalline *para*-nitrobenzenesulfonate **8**[19] (Figure 3). Single-crystal X-ray analysis[20] indeed established the relative configuration as *exo* but also proved the absolute configuration. The outcome of the desymmetrization is in line with previous work[15b–e] and suitable models to explain the preferential attack at one of the two enantiotopic imide carbonyl groups exist.

When submitting the other products **6d–g** to the elimination reaction conditions, the respective tricyclic products *exo*-**7d–g** were formed in high yields (Figure 4). The enantiomeric excess remained essentially unchanged and products *exo*-**7** offer a wide range of options for further functionalization. It was shown for example that the *para*-methoxymethyl group can be readily cleaved from product *exo*-**7f** under oxidative conditions[21] (see Supporting Information for further details).

In summary, we have delineated and executed an enantioselective access to molecules with a bicyclo[4.2.0]octane skeleton, which rests on three key steps. An intramolecular [2+2] photocycloaddition serves to generate the strained cyclobutane ring. Enantioselectivity is induced by an oxazaborolidine catalyzed desymmetrization, which is followed by a base-induced fragmentation of the central ether bond. It is believed that the method holds promise for a wider application in medicinal chemistry and in natural product total synthesis.

Experimental Section

General procedure for Cu-catalyzed intramolecular [2+2] photocycloaddition reaction: A 15 mL quartz tube with a rubber seal was charged with $Cu(OTf)_2$ (5.4 mg, 10 mol%), compound **5** (0.15 mmol) and anhydrous solvent (10 mL) under argon, and the solution was degassed by purging with argon in an ultrasonicating bath for 15 min. The tube was irradiated at room temperature ($\lambda = 254$ nm, Rayonet RPR-2537 Å) until conversion was complete (by GLC and TLC analysis). The solvent was removed under reduced pressure, and then the residue was directly subjected to purification by flash silica gel column chromatography to give compound **2**.

Acknowledgements

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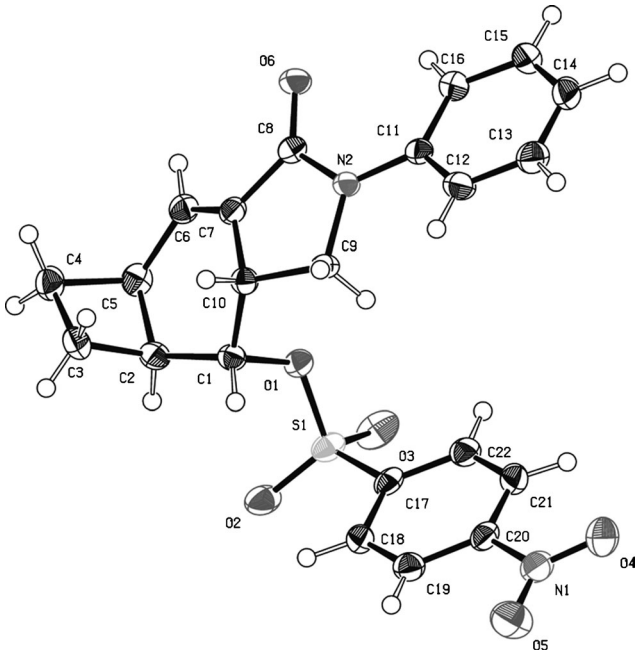
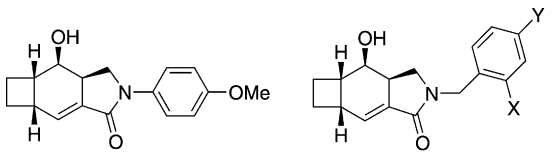


Figure 3. Structure of nosylate **8** in the crystal as determined by anomalous X-ray diffraction.



85% (93% *ee*) *exo*-**7d**

65% (85% *ee*) *exo*-**7e** X = Y = H
85% (89% *ee*) *exo*-**7f** X = H; Y = OMe
79% (85% *ee*) *exo*-**7g** X = OMe; Y = H

Figure 4. Structure of ring-opened *exo*-products *exo*-**7** as obtained by base-induced elimination of substrates **6**

Keywords: asymmetric synthesis · cycloaddition · enantioselectivity · photochemistry · reduction

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[20] Colorless fragment, $C_{22}H_{20}N_2O_6S$, $M_r = 440.47$; orthorhombic, space group $P2_12_12_1$ (no. 19), $a = 6.5141(2)$, $b = 12.6522(5)$, $c =$

24.2296(10) Å, $V=1996.95(13)$ Å^3, $Z=4$, $\lambda(Mo_{K\alpha})=0.71073$ Å, $\mu=0.207$ mm^{-1}, $\rho_{calcd}=1.465$ gcm^{-3}, $T=123(1)$ K, $F(000)=920$, $\theta_{max}=25.3°$, $R1=0.0260$ (3402 observed data), $wR2=0.0629$ (all 3640 data), GOF = 1.06, 360 parameters, $\Delta\rho_{max/min}=0.20/-0.22$ e Å^{-3}; CCDC-945497 (**8**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif; for more details, see Supporting Information.

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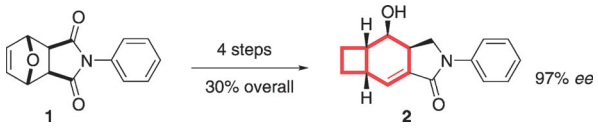
Photochemistry



Tricks of the trade: Because an intramolecular Cu-catalyzed access to bicyclo[4.2.0]octanes is not feasible, an oxygen bridge was introduced to facilitate the [2+2] photocycloaddition.

Starting from compounds similar to **1**, products such as **2** could be obtained enantioselectiviely in three steps after ring-opening metathesis (see scheme).