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D-Isomannide in synthesis: asymmetric Diels–Alder reactions with novel homochiral bis-imine Cu^{2+}-catalysts

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Abstract—The synthesis of a set of novel homochiral bis-imine ligands **4** derived from D-isomannide **6**, and their application in the Cu^{2+}-catalyzed asymmetric Diels–Alder reaction of cyclopentadiene and *N-tert*-crotonoyloxazolidinone **1** is reported.

1. Introduction

Although D-isomannide was described for the first time in 1882 by Fauconnier[1] and its structure was elucidated in 1945 by Fletcher[2] and Wiggins,[3] reports on its synthetic application as a valuable commercially available chiral pool compound are remarkably scarce. D-Isomannide has been used successfully as a building block for (−)-*endo*- and (−)-*exo*-Brevicomin and (+)-Dodecanolide, in a strategy based on a chiral intermediate obtained via selective ring opening via reductive elimination.[4] An analogous ring opening with trimethylsilyl iodide has also been reported.[5] D-Isomannide has been employed as starting material for the synthesis of novel bicyclic dideoxynucleosides, which are potential antiviral agents.[6] It has also been transformed into the corresponding *exo*-bis-phosphine, which was investigated as a homochiral ligand in the Rh-catalyzed asymmetric hydrogenation of *N*-acyl-α-aminoacrylate esters, with rather poor enantioselectivity.[7] Amino ethers derived from D-isomannide have been evaluated as chiral auxiliaries for the asymmetric alkylation of phenylacetic acid[8] and monobenzyl and monomethyl ethers derived from D-isomannide have been used as chiral auxiliaries for the stereoselective synthesis of tertiary α-hydroxy acids.[9] Finally, acrylate esters from monobenzylated D-isomannide were reported to undergo highly *endo*- and diastereoselective Lewis acid-promoted Diels–Alder reactions with cyclopentadiene.[10]

The Diels–Alder reaction is a powerful tool in synthetic organic chemistry, especially in its asymmetric version with a homochiral catalyst. The first example of this type was reported by Koga,[11] using (−)-menthoxyaluminum dichloride as a catalyst. Since then, asymmetric Diels–Alder reactions catalyzed by chiral Lewis acids have been studied extensively.[12] Several metal cations have been investigated. In particular, highly efficient Cu^{2+}-catalysts derived from homochiral bis-oxazoline ligands **3** (Fig. 1) have been reported by Evans' group.[13]

Herein, we wish to report on the synthesis of homochiral ligands of the type **4** and their use in the Cu^{2+}-catalyzed asymmetric Diels–Alder reaction of cyclopentadiene and *N-tert*-crotonoyloxazolidinone **1** (Scheme 1). For these catalysts, an efficient chirality transfer was anticipated because of their rather rigid conformation and the presence of a C_2-symmetry axis,

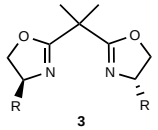

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Figure 1.

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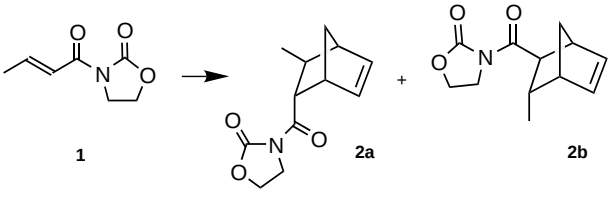
reducing the number of possible diastereomeric complexes.

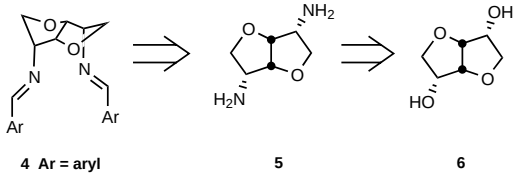
2. Results and discussion

Ligands **4** are readily accessible from diamine **5** (Scheme 2), which in turn is prepared from D-isomannide **6** in five steps.

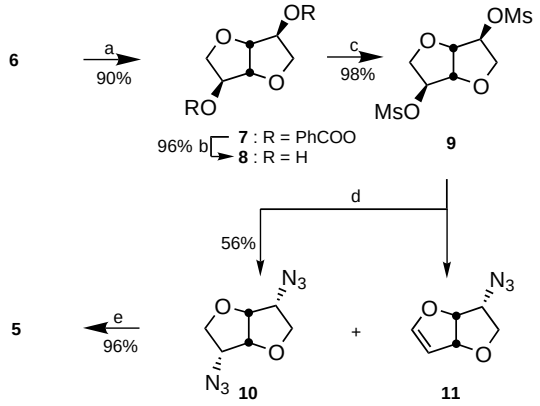
Mitsunobu inversion[14] of **6** (Scheme 3) and subsequent cleavage of the dibenzoate ester **7** afforded 1,4:3,6-dianhydro-L-iditol **8**, which was easily transformed into dimesylate **9** in 85% overall yield. Substitution with sodium azide in DMSO at 125°C afforded diazide **10** in 56% yield, along with the elimination product **11**. Hydrogenation of **10** finally yielded the desired diamine **5** in 46% overall yield from **6**. This constitutes a considerable improvement as compared to an analogous sequence described by Thiem et al.,[15] reporting an overall yield of only 5%. A set of bis-imine ligands **4a**–**g** was prepared (Scheme 4) by stirring a dichloromethane solution of **5** with aromatic aldehydes **12a**–**g** (2 equiv.) for 16 h at room temperature in the presence of anhydrous magnesium sulfate (2 equiv.). As the bis-imines thus obtained hydrolyze upon chromatographic purification on silica, they were either recrystallized (CH_2Cl_2/hexane) or used directly without purification. The catalysts **13a**–**g** (10 mol% as compared to **1**) were prepared in situ by combining the bis-imines **4a**–**g** (0.05 mmol) with anhydrous $Cu(OTf)_2$ (0.9 equiv. as compared to **4a**–**g**) and powdered molecular sieves (4 Å, 100 mg) in dichloromethane (1.5 ml) at room temperature for 16 h, resulting in a green solution, indicating formation of the catalyst.[13] Diels–Alder reactions were then performed by cooling the reaction mixture (Table 1) and adding a solution of **1** (0.5 mmol) in dichloromethane (1 ml) followed by freshly distilled cyclopentadiene (10 mmol) and stirring for the time indicated in Table 1. After filtration through a plug of silica with ether and washing of the eluent with HCl (1 M) and brine, the *endo*/*exo* ratio was determined by ^1H NMR from the integration of the methyl doublet (**2a**: 1.13 ppm, **2b**: 0.86 ppm in $CDCl_3$). After HPLC separation of the adducts (*n*-hexane/EtOAc 7:3), the enantiomeric purity of the *endo* adduct **2a** was estimated by measuring the optical rotation in $CHCl_3$ and comparing it with the value cited in the literature.[16a] The e.e. values thus obtained were in agreement with those derived from a ^1H NMR experiment with $Eu(hfc)_3$ as chiral shift reagent.



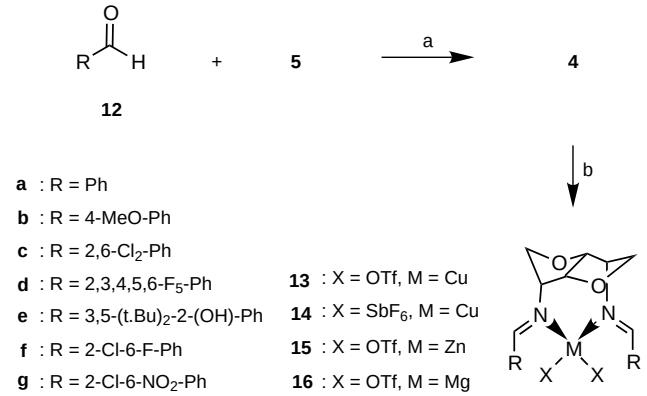
Scheme 1. *Reagents and conditions*: cyclopentadiene, CuX_2, chiral ligand.



Scheme 2.



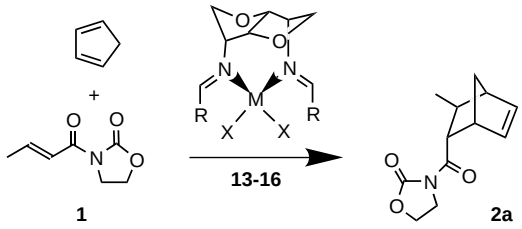
Scheme 3. *Reagents and conditions*: (a) DEAD, Ph_3P, PhCOOH, THF, 25°C, 15 h; (b) KCN (cat.), NaOMe, MeOH, 25°C, 2 h; (c) MsCl, pyridine, CH_2Cl_2, −10°C, 24 h; (d) NaN_3, DMSO, 125°C, 15 h; (e) Pd/C (10%), H_2, MeOH, 25°C, 4 bar, 6 h.



Scheme 4. *Reagents and conditions*: (a) CH_2Cl_2, $MgSO_4$; **4a** (80%), **4b** (85%), **4c** (79%), **4d** (96%), **4e** (98%), **4f** (91%), **4g** (75%); (b) **13**: $Cu(OTf)_2$, CH_2Cl_2; **14**: $AgSbF_6$, $CuCl_2$, CH_2Cl_2; **15**: $Mg(OTf)_2$, CH_2Cl_2; **16**: $Zn(OTf)_2$, CH_2Cl_2.

The presence of molecular sieves has an important influence on the enantioselectivity as well as on the *endo*/*exo* ratio (entry 1 versus 2, and 3 versus 4, although in the latter case the temperature can also play a role). The aryl substitution pattern also plays a crucial role in governing the selectivity of the reaction. The presence of electron-donating substituents leads to improved *endo*-selectivity for **13b** (R = OMe), together with comparably low yields and enantioselectivities (entry 3 versus 1, and 4 versus 2). In the case of **13e**, which bears bulky *tert*-butyl substituents (entry 10), the *endo*-selectivity also decreases. Using ligands with electron-withdrawing substituents, only the 2,6-dichlorophenyl derivative **13c** remarkably affords 100% yield and an enantiomeric excess of the *endo*-adduct of

Table 1. Selectivity for the Diels–Alder reaction of cyclopentadiene and *N*-*tert*-crotonoyloxazolidinone **1** performed on 1 mmol scale



1 **2a**

Entry	Catalyst[a]	Time (h)	*T* (°C)	**2a**:**2b**	Yield (%)	E.e.[e] (%) **2a**
1	**13a**[b]	24	−15	3:1	11	0
2	**13a**	114	−10	10:1	10	25
3	**13b**[b]	24	+20	5:1	20	0
4	**13b**	63	−30	19:1	19	16
5	**13c**	88	−10	2:1	100	57
6	**13c**[c]	39	−10	2:1	100	63
7	**13c**	63	−30	3.7:1	31	55
8	**13c**[d]	84	−10	2:1	17	40
9	**13d**	76	−10	4:1	22	5[f]
10	**13e**	63	0	1.6:1	27	24
11	**13f**	135	−10	10:3	6	42
12	**13g**	66	−10	3:1	3	17
13	**14c**	113	−10	2.6:1	42	8[f]
14	**15c**	71	0	4.6:1	32	0
15	**16c**	71	0	–	0	–

[a] 0.1 equiv. of catalyst were used in CH_2Cl_2.
[b] Reaction performed without powdered molecular sieves 4 Å.
[c] Reaction performed under a continuous argon flow.
[d] Dichloromethane/toluene (1:3).
[e] The e.e. was determined by comparing the specific rotation value of **2a** with the value reported in the literature,[16a] and was confirmed by a chiral shift ^{1}H NMR experiment with Eu(hfc)$_3$ in $CDCl_3$.
[f] Enantiomeric *ent*-**2a** was formed in excess.

57% (entry 5), which can be improved to 63% by performing the reaction under a continuous flow of argon (entry 6). Attempts to obtain higher enantioselectivity by performing the reaction at −30°C only resulted in a slower reaction and an improved *endo*/*exo* ratio, without however influencing the e.e. (entry 7). At lower temperatures, the reaction rates generally became impracticably low. Although solvent variation is restricted (polar solvents interfere by chelating the metal, while in apolar solvents solubility is poor) a mixture of dichloromethane and toluene (1:3) was tried (entry 8), resulting however in a much slower reaction and a lower enantiomeric excess. Surprisingly, a small change, such as replacing one of the chlorine atoms with fluorine as in **13f** has a dramatic influence (entry 11 versus 5): the reaction rate drops considerably, resulting in a very low yield, with comparable *endo*-selectivity, and decreased but still clear enantioselectivity. Enantioselectivity drops on replacing fluorine with the strongly electron-withdrawing nitro group (**13g**, entry 12). The same holds for the pentafluorophenyl derivative **13d** (entry 9). In this case, the opposite enantioselectivity is observed.

Evans and coworkers found that the counterion has a major influence on the enantioselectivity.[13a,16] Triflates are used with success because they easily dissociate from the metal, thus allowing the chelating dienophile to act as a bidentate ligand, resulting in a well defined transition state and high enantioselectivity. Evans also showed that the use of hexafluoroantimonate (SbF_6^-), which dissociates even more readily from the metal, results in higher enantioselectivity and a faster reaction. Therefore, **14c** was prepared according to Evans' procedure,[13a] by mixing $CuCl_2$ (0.09 mmol), **4c** (0.1 mmol) and $AgSbF_6$ (0.18 mmol) in CH_2Cl_2 (1 ml). After stirring for 6 h at ambient temperature, the green reaction mixture was filtered through a plug of cotton wool to give a clear solution of **14c**, which was used directly in the Diels–Alder reaction (Table 1, entry 13) in the presence of molecular sieves (4 Å). Contrary to our expectations however, this catalyst resulted in an almost complete loss of enantioselectivity, while there was no change in the diastereoselectivity as compared to entry 6. Moreover, *ent*-**2a** was obtained in excess.

As it was shown that the metal also influences the enantio- and diastereoselectivity,[13a,17] the Zn^{2+} catalyst **15c** and the Mg^{2+} catalyst **16c** were prepared following the same procedure as for **13c**, but using Zn(OTf)$_2$ and Mg(OTf)$_2$ respectively. However, catalyst **15c** (entry 14) resulted in complete loss of selectivity, while with catalyst **16c** (entry 15) no reaction was observed.

3. Conclusion

In conclusion, we have synthesized for the first time a set of *endo*-bis-imine ligands **4** from D-isomannide **6**, making use of an improved procedure for the preparation of the parent diamine **5** (46% overall yield from **6**). After complexation with copper(II) triflate, these bidentate ligands are capable of catalyzing the asymmetric Diels–Alder reaction of cyclopentadiene and *N*-*tert*-crotonoyloxazolidinone **1**. The best results (63% e.e.) were obtained with the 2,6-dichlorophenyl catalyst **13c**. We are currently investigating other derivatives and analogues of **6** in order to improve enantioselectivity.

4. Experimental

4.1. Materials and general methods

All reactions were carried out under an argon or nitrogen atmosphere with magnetic stirring. All solvents were purified or dried according to standard procedures. Solutions were dried over $MgSO_4$. The solvent was removed from the filtered solutions on a rotary evaporator. Column chromatographic separations were performed with silica gel (Merck 60F254); eluents are given in brackets. Isocratic HPLC separations were performed on a Kontron 422 delivery system with RI-detection (Meltz LCD 312); eluents are given in brackets. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. IR-spectra were recorded on a Perkin–Elmer FTIR-1600 spectrometer. EI-MS were recorded on an AEI MS-50, a Finnigan 4000 or an HP-5988A spectrometer. ES-MS was performed with the electrospray source in the positive mode on an Agilent 1100 series ES/MSD(VL). ^{1}H NMR spectra were recorded at 200 MHz (Varian Gemini) or at 500 MHz (Bruker Avance DRX 500). ^{13}C NMR spectra were recorded at 125.7 MHz (Bruker Avance DRX 500). Chemical shifts are expressed in ppm relative to TMS and coupling constants are reported in Hz. Melting points are uncorrected.

4.2. (3*S*,3a*R*,6*S*,6a*R*)-6-(Benzyloxy)hexahydrofuro[3,2-*b*]-furan-3-yl benzoate, 7

To a solution of D-isomannide **6** (10 g, 69 mmol) and triphenylphosphine (36 g, 137 mmol) in tetrahydrofuran (170 ml) was added dropwise a solution of benzoic acid (16.7 g, 137 mmol) and diethyl azodicarboxylate (21.6 ml, 137 mmol) in tetrahydrofuran (170 mmol) over a period of 3 h at ambient temperature. The mixture was stirred for 15 h and then additional benzoic acid (1.67 g, 13.7 mmol), triphenylphosphine (3.6 g, 13.7 mmol) and diethyl azodicarboxylate (2.16 ml, 13.7 mmol) were added and the mixture was further stirred for 3 h. The reaction mixture was concentrated in vacuo and the residue was subjected to column chromatography (hexane/ethyl acetate 85:15), giving **7** as a white solid (6.97 g, 90%). The crude product can also be purified by recrystallizing twice from ethanol; mp 105°C; R_f=0.18 (*n*-hexane/ethyl acetate 85:15); $[\alpha]_D^{20}$=+134.6 (*c* 1.13, $CHCl_3$); IR (KBr) ν_{max} cm^{-1}: 2964, 1722, 1265, 1097; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (m, 4H), 7.59 (m, 2H), 7.45 (m, 4H), 5.51 (m, 2H), 4.88 (s, 2H), 4.14 (dd, *J*=3.3 Hz, 10.7 Hz, 2H), 4.11 (dd, *J*=1.6 Hz, 10.7 Hz, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$): 165.4 (C), 133.3 (CH), 129.6 (CH), 129.3 (C), 128.4 (CH), 85.4 (CH), 77.9 (CH), 72.6 (CH_2); MS (*m*/*z*): 232 (15), 177 (35), 149 (23), 105 (68), 77 (100), 51 (75). Anal. calcd for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.66; H, 5.13%.

4.3. (3*S*,3a*R*,6*S*,6a*R*)-Hexahydrofuro[3,2-*b*]furan-3,6-diol, 8

To a suspension of the *exo*-dibenzoate **7** (6 g, 17 mmol) in methanol (17 ml) was added potassium cyanide (170 mg, 2.6 mmol). A solution of 0.1 M sodium methoxide in methanol (11 ml, 1.1 mmol) was added and the reaction mixture was stirred for 2 h at ambient temperature. The clear solution was neutralized with DOWEX 50×8 W and filtered. The filtrate was diluted with dichloromethane (100 ml) and the organic phase was extracted with water (dist., 5×70 ml). The combined aqueous phases were concentrated in vacuo and the product was dried for 24 h over phosphorus pentoxide in vacuo, giving **8** as a white solid (2.38 g, 96%); mp 38°C; R_f=0.17 (dichloromethane/methanol 9:1); $[\alpha]_D^{20}$=+20.4 (*c* 0.91, H_2O); IR (KBr) ν_{max} cm^{-1}: 3416, 3055, 2984, 1417, 1357, 1266, 1124, 1087, 1014, 896, 738; ^{1}H NMR (500 MHz, D_2O): δ 4.59 (s, 2H), 4.30 (m, 2H), 3.85 (dd, *J*=1.0 Hz, 10.4 Hz, 2H), 3.78 (dd, *J*=3.3 Hz, 10.4 Hz, 2H); ^{13}C NMR (125.7 MHz, D_2O): 86.3 (CH), 74.6 (CH), 73.7 (CH_2); MS (*m*/*z*): 98 (20), 86 (7), 73 (38), 69 (45), 58 (13), 49 (72), 43 (100). Anal. calcd for $C_6H_{10}O_4$: C, 49.31; H, 6.90. Found: C, 49.22; H, 6.88%.

4.4. (3*S*,3a*S*,6*S*,6a*S*)-6-[(Methylsulfonyl)oxy]hexahydrofuro[3,2-*b*]furan-3-yl methanesulfonate, 9

To a solution of the *exo*-diol **8** (500 mg, 3.4 mmol) in pyridine (16 ml) was added dropwise mesyl chloride (1.2 ml, 7.7 mmol) at −10°C and the reaction mixture was stirred for 24 h at this temperature. The reaction mixture was diluted with 2.4 M hydrochloric acid and extracted with dichloromethane (4×100 ml). The combined organic phases were washed with saturated sodium bicarbonate solution (200 ml), brine (200 ml), dried ($MgSO_4$), and concentrated in vacuo to afford **9** as a white solid (1.01 g, 98%); mp 158°C; R_f=0.28 (*n*-hexane/ethyl acetate 3:7); $[\alpha]_D^{20}$=+40.4 (*c* 1.02, acetone); IR (KBr) ν_{max} cm^{-1}: 2944, 1472, 1333, 1174; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.14 (dd, *J*=1.1 Hz, 3.5 Hz, 2H), 4.84 (s, 2H), 4.14 (dd, *J*=1.1 Hz, 11.2 Hz, 2H), 3.94 (dd, *J*=3.5 Hz, 11.2 Hz, 2H), 3.09 (s, 6H); ^{13}C NMR (125.7 MHz, $CDCl_3$): 85.2 (CH), 81.5 (CH), 72.3 (CH_2), 38.5 (CH_3); MS (*m*/*z*): 275 (4), 232 (3), 206 (9), 127 (35), 123 (33), 110 (14), 97 (63), 85 (52), 79 (85), 69 (100), 64 (54), 55 (43). Anal. calcd for $C_8H_{14}O_8S_2$: C, 31.78; H, 4.67. Found: C, 31.85; H, 4.65%.

4.5. (3*R*,3a*R*,6*R*,6a*R*)-3,6-Diazidohexahydrofuro[3,2-*b*]-furan, 10 and (3*R*,3a*R*,6a*R*)-2,3,3a,6a-tetrahydrofuro-[3,2-*b*]furan-3-yl azide, 11

The *exo*-dimesylate **9** (7.93 g, 26 mmol) was dissolved in dimethylsulfoxide (160 ml), and sodium azide (20.3 g, 312 mmol) was added. The suspension was stirred for 15 h at 125° C and then diluted with brine (800 ml). The reaction mixture was extracted with diethyl ether (4×700 ml) and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by column chromatography with gradient elution (*n*-hexane/diethyl ether 87.5:12.5, 7:3) to afford **10** as a colorless oil (2.85 g, 56%); $R_f=0.34$ (*n*-hexane/ethyl acetate 1:1); $[\alpha]_D^{20}=+307.4$ (*c* 1.32, $CHCl_3$); IR (KBr) ν_{max} cm^{-1}: 2359, 2107, 1260, 1104; ^1H NMR (500 MHz, $CDCl_3$): δ 4.70 (m, 2H), 4.08 (dd, $J=8.9$ Hz, 6.9 Hz, 2H), 3.90 (m, 2H), 3.80 (dd [app. t], $J=8.7$ Hz, 8.9 Hz, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$): 83.2 (CH), 70.5 (CH_2), 62.2 (CH); MS (*m*/*z*): 164 (8), 142 (19), 85 (27), 69 (100). Anal. calcd for $C_6H_8N_6O_2$: C, 36.74; H, 4.11. Found: C, 36.85; H, 4.09%.

The elimination product **11** was isolated as a side product (colorless oil; 636 mg, 16%); $R_f=0.40$ (*n*-hexane/ethyl acetate 1:1); $[\alpha]_D^{20}=+149.0$ (*c* 0.52, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 6.67 (d, $J=2.6$ Hz, 1H), 5.43 (dd, $J=2.6$ Hz, 6.0 Hz, 1H), 5.08 (dd [app. t], $J=2.6$ Hz, 2.6 Hz, 1H); 4.92 (dd [app. t], $J=6.0$ Hz, 6.0 Hz, 1H); 4.01 (dd, $J=6.5$ Hz, 8.8 Hz, 1H), 3.78 (ddd [app. dt], $J=6.0$ Hz, 6.5 Hz, 10.2 Hz, 1H), 3.43 (dd, $J=8.8$ Hz, 10.2 Hz, 1H).

4.6. (3*R*,3a*R*,6*R*,6a*R*)-6-Aminohexahydrofuro[3,2-*b*]-furan-3-ylamine, 5

The *endo*-diazide **10** (2.85 g, 14.5 mmol) was hydrogenated at 4 bar pressure H_2 in methanol (190 ml) with palladium on carbon 10% (200 mg) for 6 h at ambient temperature. The reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo to afford **14** as a white solid (2.02 g, 96%); mp 35°C; $R_f=0.15$ (dichloromethane/methanol 87.5:12.5); $[\alpha]_D^{20}=+61.2$ (*c* 0.97, H_2O); IR (KBr) ν_{max} cm^{-1}: 3385, 2615, 2513, 1636, 1508, 1405, 1139, 1113, 1041; ^1H NMR (500 MHz, D_2O): δ 4.42 (m, 2H), 4.03 (dd [app. t], $J=8.0$ Hz, 8.7 Hz, 2H), 3.51 (m, 2H), 3.29 (dd, $J=8.7$ Hz, 10.2 Hz, 2H); ^{13}C NMR (125.7 MHz, D_2O): 82.9 (CH), 72.3 (CH_2), 54.7 (CH); MS (*m*/*z*): 121 (22), 109 (23), 84 (100), 69 (81), 55 (42). Anal. calcd for $C_6H_{12}N_2O_2$: C, 49.99; H, 8.39. Found: C, 49.78; H, 8.37%.

4.7. Formation of the imines 4a–g: general procedure

The diamine **14** (50 mg, 0.35 mmol) was dissolved in dry dichloromethane (2 ml). Anhydrous magnesium sulfate (84 mg, 0.7 mmol) and the aldehyde (0.7 mmol) were added and the resulting mixture was stirred for 16 h at ambient temperature. As the products tend to decompose on silica gel, the reaction was not monitored by TLC. Magnesium sulfate was filtered off and rinsed with dichloromethane. After evaporation of the combined solvents, the imines **4** where crystallized or used as such. When the imine was a solid, the residue was dissolved in dichloromethane (1 ml), and *n*-hexane (10 ml) was added. Slow evaporation under reduced pressure yielded crystals, which were separated by filtration. The crystals were washed with *n*-hexane (2×3 ml).

4.7.1. *N*-[(*E*)-Phenylmethylidene]-*N*-(3*R*,3a*R*,6*R*,6a*R*)-6-{[(*E*)-phenylmethylidene]amino}hexahydrofuro[3,2-*b*]-furan-3-yl)amine, 4a

Mp 112°C; $[\alpha]_D^{20}=+320.3$ (*c* 0.75, $CHCl_3$); IR (KBr) ν_{max} cm^{-1}: 2875, 1644, 1453, 1263, 1102, 1042, 805; ^1H NMR (500 MHz, DMSO-d_6): δ 8.46 (s, 2H), 7.77 (m, 4H), 7.46 (m, 6H), 4.72 (m, 2H), 4.12 (m, 2H), 3.91 (dd [app. t], $J=8.2$ Hz, 8.2 Hz, 2H), 3.86 (dd, $J=6.8$ Hz, 8.2 Hz, 2H); ^{13}C NMR (125.7 MHz, DMSO-d_6): 163.3 (CH), 136.4 (C), 131.2 (CH), 129.0 (CH), 128.3 (CH), 84.7(CH), 72.2(CH_2), 71.9 (CH); MS (*m*/*z*): 219 (10), 217 (42), 187 (37), 156 (40), 130 (40), 117 (28), 106 (74), 69 (100), 41 (32). Anal. calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 74.81; H, 6.27; N, 8.72%.

4.7.2. *N*-[(*E*)-(4-Methoxyphenyl)methylidene]-*N*-(3*R*,3a*R*,6*R*,6a*R*)-6-{[(*E*)-(4-methoxyphenyl)methylidene]amino}hexahydrofuro[3,2-*b*]furan-3-yl)amine, 4b

Mp 152°C; $[\alpha]_D^{20}=+253.0$ (*c* 0.91, $CHCl_3$); IR (KBr) ν_{max} cm^{-1}: 2875, 1634, 1604, 1513, 1248, 1017, 825; ^1H NMR (500 MHz, DMSO-d_6): δ 8.38 (s, 2H), 7.71 (m [app. d], $J=8.8$ Hz, 4H), 7.01 (m [app. d], $J=8.8$ Hz, 4H), 4.68 (m, 2H), 4.06 (m, 2H), 3.90 (dd [app. t], $J=8.4$ Hz, 7.1 Hz, 2H), 3.82 (dd [app. t], $J=8.4$ Hz, 8.4 Hz, 2H), 3.80 (s, 6H); ^{13}C NMR (125.7 MHz, DMSO-d_6): 162.2 (CH), 161.4 (C), 129.7 (CH), 129.1 (C), 114.1 (CH), 84.4 (CH), 72.0 (CH_2), 71.7 (CH), 55.4 (CH_3); MS (*m*/*z*): 305 (11), 217 (69), 214 (82), 179 (26), 121 (70), 91 (54), 69 (100). Anal. calcd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36. Found: C, 69.58; H, 6.38; N, 7.33%.

4.7.3. *N*-[(*E*)-(2,6-Dichlorophenyl)methylidene]-*N*-(3*R*,3a*R*,6*R*,6a*R*)-6-{[(*E*)-(2,6-dichlorophenyl)methylidene]-amino}hexahydrofuro[3,2-*b*]furan-3-yl)amine, 4c

Mp 125°C; $[\alpha]_D^{20}=+156.5$ (*c* 1.10, $CHCl_3$); IR (KBr) ν_{max} cm^{-1}: 2875, 1654, 1579, 1553, 1428, 1104, 1039, 776; ^1H NMR (500 MHz, DMSO-d_6): δ 8.59 (s, 2H), 7.53 (m [app d], $J\cong 8.1$ Hz, 4H), 7.44 (dd, $J=8.7$ Hz, 7.4 Hz, 2H), 4.77 (m, 2H), 4.22 (m, 2H), 3.94 (dd, $J=7.2$ Hz, 8.3 Hz, 2H), 3.86 (dd [app. t], $J=8.3$ Hz, 8.3 Hz, 2H); ^{13}C NMR (125.7 MHz, DMSO-d_6): 159.0 (CH), 133.6 (C), 132.8 (C), 131.5 (CH), 129.0 (CH), 84.5 (CH), 72.1 (CH), 71.9 (CH_2); MS (*m*/*z*): 285 (18), 219 (10), 217 (18), 174 (60), 123 (38), 82 (25), 69 (100). Anal. calcd for $C_{20}H_{16}Cl_4N_2O_2$: C, 52.43; H, 3.52; N, 6.11. Found: C, 52.56; H, 3.51; N, 6.13%.

4.7.4. *N*-[(*E*)-(2,3,4,5,6-Pentafluorophenyl)methylidene]-*N*-(3*R*,3a*R*,6*R*,6a*R*)-6-{[(*E*)-(2,3,4,5,6-pentafluorophenyl)methylidene]amino}hexahydrofuro[3,2-*b*]furan-3-yl)amine, 4d

Oil, used without further purification; IR (KBr) ν_{max} cm^{-1}: 2923, 1654, 1526, 1500, 1098, 1010; ^1H NMR (500 MHz, DMSO-d_6): δ 8.56 (s, 2H), 4.77

(m, 2H), 4.23 (m, 2H), 3.92 (dd, $J=6.7$ Hz, 8.2 Hz, 2H), 3.85 (dd [app. t], $J=8.2$ Hz, 8.2 Hz, 2H); ^{13}C NMR (125.7 MHz, DMSO-d_6): 152.2 (CH), 145.3 (dm, $^1J_{C-F}=250.0$, C), 141.6 (dm, $^1J_{C-F}=252.1$, C), 137.4 (dm, $^1J_{C-F}=247.8$, C), 111.0 (m, C), 84.2 (CH), 72.3 (CH), 71.8 (CH_2); MS (m/z): 274 (4), 238 (2), 211 (17), 181 (15), 130 (5), 84 (14), 69 (100). HRMS calcd. for $C_{20}H_{11}F_{10}N_2O_2^+$ (MH^+): 501.0662. Found: 501.0651.

4.7.5. *N*-[(*E*)-(2-Hydroxy-3,5-di(*tert*-butyl)phenyl)-methylidene]-*N*-(3*R*,3a*R*,6*R*,6a*R*)-6-{[(*E*)-(2-hydroxy-3,5-di(*tert*-butyl)phenyl))methylidene]amino}hexahydrofuro[3,2-*b*]furan-3-yl)amine, 4e. Oil, used without further purification; IR (KBr) ν_{max} cm^{-1}: 3448, 2961, 1630, 1466, 1439, 1250, 1172, 1025; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.67 (s, 2H), 7.33 (d, $J=2.3$ Hz, 2H), 7.29 (d, 2.3 Hz, 2H), 4.77 (m, 2H), 4.22 (m, 2H), 4.06 (dd [app. t], $J=8.5$ Hz, 6.7 Hz, 2H), 3.81 (dd [app. t], $J=8.5$ Hz, 8.5 Hz, 2H), 1.39 (s, 18H), 1.27 (s, 18H); ^{13}C NMR (125.7 MHz, DMSO-d_6): 169.3 (CH), 158.0 (C), 139.9 (C), 136.0 (C), 126.9 (CH), 126.8 (CH), 118.1 (C), 84.4 (CH), 72.2 (CH_2), 70.1 (CH), 34.9 (C), 34.2 (C), 31.6 (CH_3), 29.6 (CH_3); MS (m/z): 576 (M^+) (7), 347 (1), 300 (7), 273 (10), 219 (100), 163 (7), 91 (15), 57 (7). HRMS calcd. for $C_{36}H_{53}N_2O_4^+$ (MH^+): 577.4006. Found: 577.4018.

4.7.6. *N*-[(*E*)-(2-Chloro-6-fluorophenyl)methylidene]-*N*-(3*R*,3a*R*,6*R*,6a*R*)-6-{[(*E*)-(2-chloro-6-fluorophenyl)-methylidene]amino}hexahydrofuro[3,2-*b*]furan-3-yl)-amine, 4f. Oil, used without further purification; IR (KBr) ν_{max} cm^{-1}: 2879, 1698, 1644, 1599, 1575, 1452, 1250, 1103, 1044, 906, 784; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.62 (s, 2H), 7.51 (m, 2H), 7.41 (m, 2H), 7.31 (m, 2H), 4.76 (m, 2H), 4.19 (m, 2H), 3.92 (dd, $J=8.3$ Hz, 6.8 Hz, 2H), 3.85 (dd [app. t], $J=8.3$ Hz, 2H); ^{13}C NMR (125.7 MHz, DMSO-d_6): 160.6 (d, $^1J_{C-F}=256.3$ Hz, C), 156.6 (CH), 134.1 (d, $J_{C-F}=4.0$ Hz, C), 132.3 (d, $J_{C-F}=10.0$ Hz, CH), 126.1 (d, $J_{C-F}=3.0$ Hz, CH), 122.5 (d, $J_{C-F}=13.0$ Hz, C), 115.7 (d, $J_{C-F}=21.9$ Hz, CH), 84.4 (CH), 72.4 (CH), 71.9 (CH_2); MS (m/z): 327 (2), 283 (4), 269 (18), 201 (15), 158 (70), 143 (35), 107 (55), 69 (100). HRMS calcd. for $C_{20}H_{17}Cl_2F_2N_2O_2^+$ (MH^+): 425.0636. Found: 425.0628.

4.7.7. *N*-[(*E*)-(2-Chloro-6-nitrophenyl)methylidene]-*N*-(3*R*,3a*R*,6*R*,6a*R*)-6-{[(*E*)-(2-chloro-6-nitrophenyl)methylidene]amino}hexahydrofuro[3,2-*b*]furan-3-yl)amine, 4g. $[\alpha]_D^{20}=+49.2$ (c 0.06, $CHCl_3$); IR (KBr) ν_{max} cm^{-1}: 2845, 1645, 1540, 1373, 1347, 1106, 1050, 804, 762; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.69 (s, 2H), 7.86 (bd, $J=8.0$ Hz, 2H), 7.66 (bd, $J=8.0$ Hz, 2H), 7.46 (dd [app. t], $J=8.0$ Hz, 8.0 Hz, 2H), 4.83 (m, 2H), 4.22 (m, 2H), 4.13 (dd [app. t], $J=8.0$ Hz, 8.0 Hz, 2H), 4.00 (dd, $J=8.0$ Hz, 9.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 158.2 (CH), 135.5 (C), 135.2 (C), 134.2 (CH), 130.5 (C), 130.2 (CH), 122.8 (CH), 85.1 (CH), 73.5 (CH_2), 72.1 (CH); MS (m/z): 263 (8), 199 (5), 169 (18), 155 (39), 99 (49), 75 (100). Anal. calcd for $C_{20}H_{16}Cl_2N_4O_6$: C, 50.12; H, 3.36; N, 11.69. Found: C,50.01; H, 3.35; N, 11.72%.

4.8. Metal-catalyzed Diels–Alder reaction of cyclopentadiene and *N*-*tert*-crotonoyl-2-oxazolidinone, 1: general procedure

To a solution of a ligand **4** (0.05 mmol) in dry methylene chloride (1.5 ml) were added $Cu(OTf)_2$ (17 mg, 0.047 mmol) and powdered molecular sieves (4 Å, 100 mg). After a few minutes, the solution changed color to bright green. The reaction mixture was stirred for 18 h at ambient temperature. The solution of the catalyst was subsequently chilled to the temperature indicated in Table 1, and a solution of *N*-*tert*-crotonoyl-2-oxazolidinone (**1** (78 mg, 0.5 mmol) in methylene chloride, followed by freshly distilled cyclopentadiene (820 μl, 10 mmol) was added. The reaction mixture was stirred at the same temperature for the time indicated in Table 1. After filtration through a plug of silica (2 g), eluting with ether (40 ml), the eluent was washed with HCl (1 M) and brine. The organic phase was dried over anhydrous $MgSO_4$. After filtration and concentration, the *endo*/*exo* ratio was determined by ^{1}H NMR from the integration of the methyl doublet (**2a**: 1.13 ppm, **2b**: 0.86 ppm in $CDCl_3$). The crude product was purified via HPLC (*n*-hexane/EtOAc 7:3), affording the *endo*-adduct **2a** as a white crystalline product, as well as the *exo*-adduct **2b** as a colorless oil (for *endo*/*exo* ratios and yields: see Table 1). The spectroscopic data of **2a** and **2b** were in accordance with those reported in the literature.[16a] The enantiomeric purity of the *endo*-adduct **2a** was estimated by measuring the specific rotation in $CHCl_3$ and comparing it with the value cited in the literature for *ent*-**2a**: $[\alpha]_D^{20}=-209$ (c 0.5, $CHCl_3$).[16a] The enantiomeric purity was further confirmed by a ^{1}H NMR experiment with $Eu(hfc)_3$ as chiral shift reagent.

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