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# Asymmetric synthesis of chiral tectons with tetrapodal symmetry: fourfold asymmetric reactions

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Dedicated to Professor Henri Kagan on the occasion of his 80th birthday

ABSTRACT

The diastereoselective fourfold addition to Ellman-type imines furnished after deprotection the tetrapodal amines in excellent yields. The unprecedented asymmetric fourfold addition of hydride and alkylzinc reagents to tetrapodal ketones and aldehydes, respectively, is achieved by employing CBS-reduction or [2.2]paracyclophane-based ketimine ligands with good to excellent global enantiomeric ratios.



## 1. Introduction

Highly porous materials such as inorganic zeolites and metal organic frameworks (MOFs)—also known as coordination polymers (CPs)—have been used for some time now for their sorption properties. Their permanent porosity is mostly exploited for catalysis,[1] gas separation[2] or gas adsorption/storage,[3] and in opto-electronic devices.[4] Recently, purely organic compounds—amorphous hypercross-linked polymers (HCPs)[5] and polymers of intrinsic microporosity (PIMs)[6] as well as crystalline covalent organic frameworks (COFs)[7]—have been added to the list of materials offering permanent porosity. Apart from zeolites, all these materials contain organic building units, so-called 'tectons' from the Greek word for builder. These frameworks are especially attractive due to the relative ease by which these organic molecules can be tuned. The synthesis of enantiomerically pure building units and consequently the generation of enantiopure networks is of great interest. The latter offer the possibility to use their chiral nanospace for applications intrinsically linked to their chirality such as racemic resolution[8] or asymmetric catalysis.[9] Framework formation occurs generally in a one-step process involving the discrete building units. Molecular tectonics operate under self-assembly conditions using iterative intermolecular recognition events.[10] The recognition patterns behave as structural nodes of the network and the repetitive nature of the process generates the translational symmetry.[11] Among all the possible organic building blocks, those bearing tetrahedral topology have been used relatively often to generate porous periodic networks. This is partially due to the inefficient packing in the solid state of such tetrapodal structures leading to permanent porosity.

## 2. Results and discussion

Adamantane-1,3,5,7-tetracarboxylic acid **1** was used as a building block in purely organic hydrogen-bonded networks and as ligand in MOFs (Fig. 1).[12] The synthesis of enantiomerically pure central chiral building blocks bearing tetrahedral topology is however a challenging task. Wuest et al. were among the first to prepare peripheral chiral tetraphenylmethanes (e.g., **2**, Fig. 1) and -silanes.[13] Fourfold addition of enantiopure alcohols and amines to tetrakis(4-isocyanatophenyl)methane gave enantiomerically pure building blocks which generated chiral porous hydrogen-bonded networks. Recently we became interested in the synthesis and the applications of tetrapodal systems[14–16] and developed a

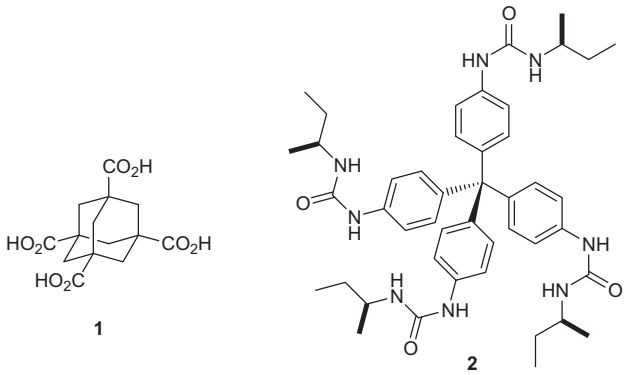


**Figure 1.** Adamantane and methane building units **1** and **2**.

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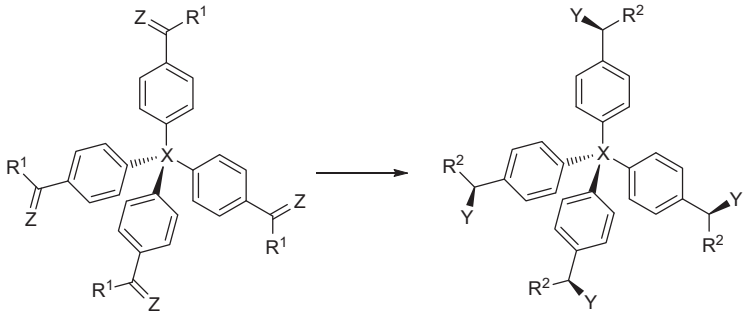



**Scheme 1.** Synthesized chiral tetrapodal systems **5** and **6** (Ad = 1,3,5,7-adamantyl).

synthesis of chiral tetrahedral building blocks via Click chemistry.[17]

Here, we report the syntheses of a series of methane- and adamantane-based peripheral chiral molecules obtained by asymmetric 1,2-addition reactions (Scheme 1). To our knowledge, this is the first time that chiral tetrapodal tectons produced by asymmetric catalysis have been reported.[18]

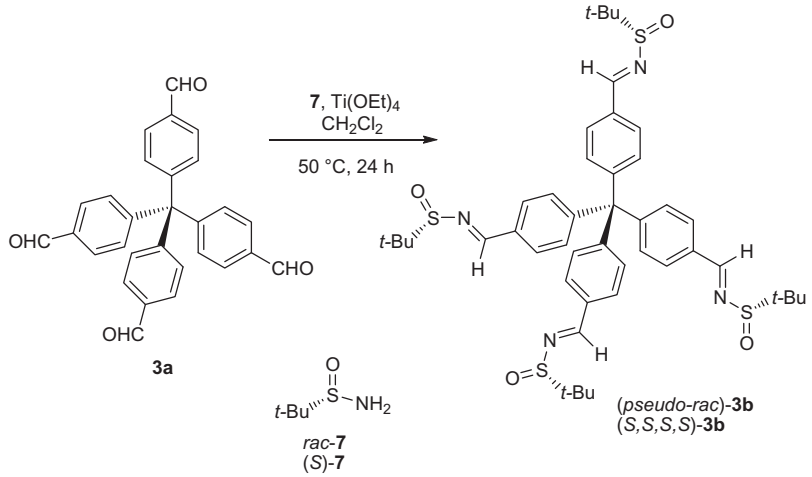
In order to explore chiral nitrogen-based tectons, we used a diastereoselective approach using the Ellman sulfinamide **7** (Scheme 2).[19–21] First, tetraaldehyde **3a** was reacted with the racemic sulfinamide (*rac*)-**7** to generate tetraimine **3b** in 85% yield. At this stage, $^{1}$H NMR and $^{13}$C NMR did not show the expected broadening of signals due to the formation of diastereomers. The same global structure (*S*,*S*,*S*,*S*)-**3b** was obtained by using the enantiomerically pure sulfinamide (*S*)-**7**.

Addition of methyl magnesiumbromide to this imine proceeded smoothly and delivered sulfinamide **5b** in quantitative yield (Scheme 3). The removal of the protecting group with hydrochloric acid led to chiral tetraamine **5c** in good yield (65%).

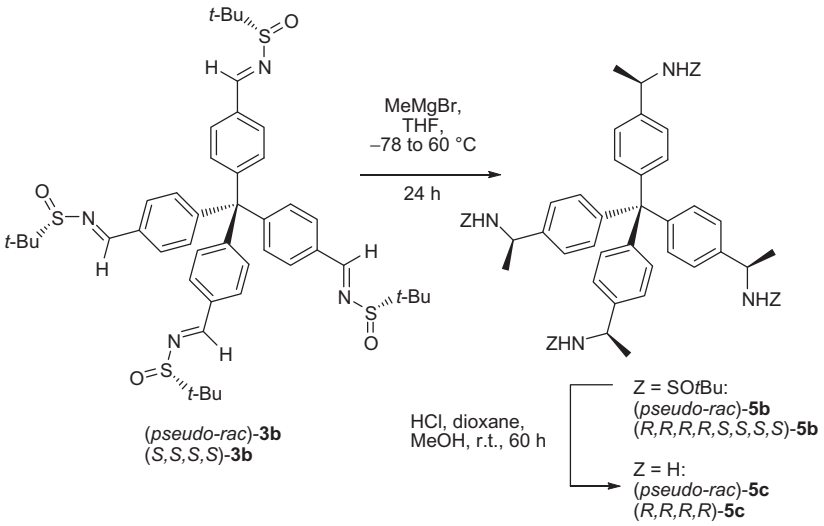
In the case of compounds **5b**, two sets of signals for both, the methyl group and the NH group, were observed in the $^{1}$H NMR spectra.[22] They appear to be due to the formation of diastereomers. For (*R*,*R*,*R*,*R*,*S*,*S*,*S*,*S*)-**5b**, each signal corresponds to a single diastereomer whereas in the case of (*pseudo-rac*)-**5b** each signal stands for a mixture of enantiomers. Integration of these signals gave an expected identical ratio in both cases. Both amines (*pseudo-rac*)-**5b** and (*R*,*R*,*R*,*R*,*S*,*S*,*S*,*S*)-**5b** are obtained in a 4:1 diastereomeric mixture.

Next, we turned to asymmetric reactions on achiral tetrapodal systems yielding chiral tetraalcohols. Due to our interest in the asymmetric 1,2-addition of organometallic reagents to aldehydes,[23] we first explored the tetrafold addition of diethylzinc to tetraaldehyde **3a** (Scheme 4).[24] To the best of our knowledge, asymmetric fourfold addition reactions of zinc reagents onto aldehydes are unknown.[25] Under standard conditions, full conversion of the tetraaldehyde was not observed. However, diols and triols were isolated in moderate yields (data not shown). By increasing the temperature to 80 °C, tetraol **5e** could be isolated in low yield of 29%. By using the Mosher ester strategy, we were able to determine the global ratio and absolute stereochemistry of the formed stereogenic centers.[26] A ratio of 4.8:1 was determined reflecting a global enantiomeric ratio $er_{global}$.[27] Upon comparison of the sign of rotation {$[\alpha]_D = -19.2$ (*c* 5.0, DMSO)}, a $^{1}$H NMR analysis (600 MHz) of the corresponding tetra-Mosher ester, and based on similar reactions[23] we assumed an all-(*S*)-configuration for the main product. The high reaction temperature which this system requires is probably the reason for the moderate global enantiomeric ratio.

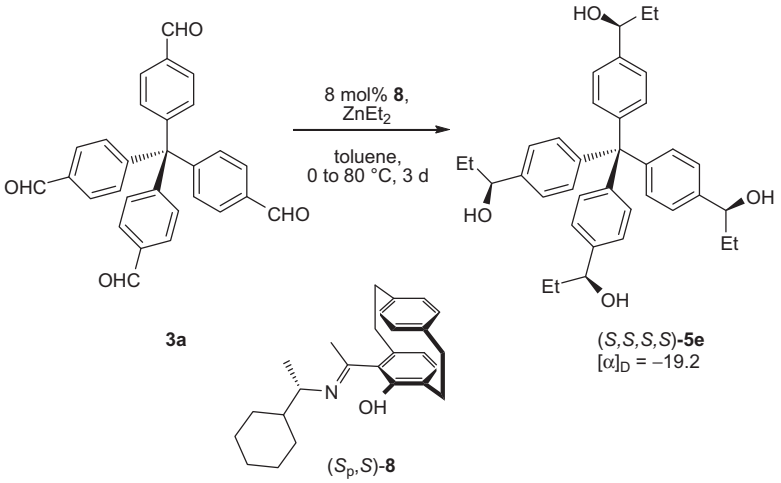
Next, we turned to the well-established CBS-reduction[28] which was performed on tetrapodal compounds **3d**[29] and **4d**[29]



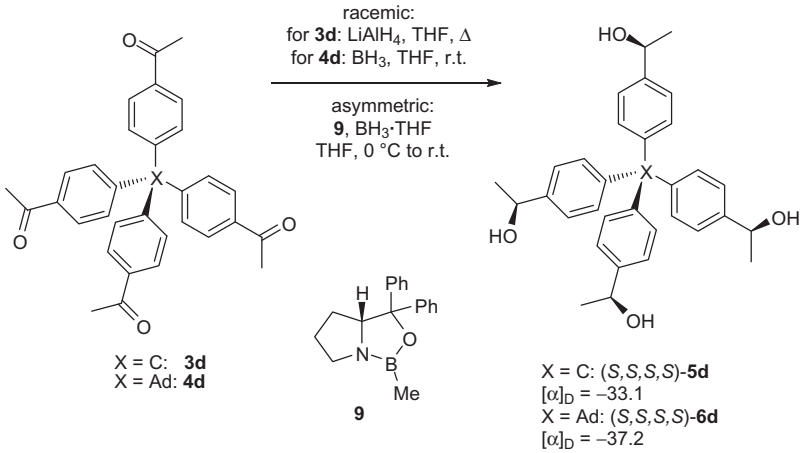

**Scheme 2.** Synthesis of tetraimine **3b**.




**Scheme 3.** Synthesis of tetraamine **5c**.




**Scheme 4.** Synthesis of tetraol **5e**.




**Scheme 5.** Asymmetric synthesis of tetraols **5d** and **6d**.

(Scheme 5). In parallel, **3d** was reacted with lithium aluminum hydride and **4d** with sodium borohydride to generate the pseudo-racemic tetraalcohols (*pseudo-rac*)-**5d** and (*pseudo-rac*)-**6d**, respectively.

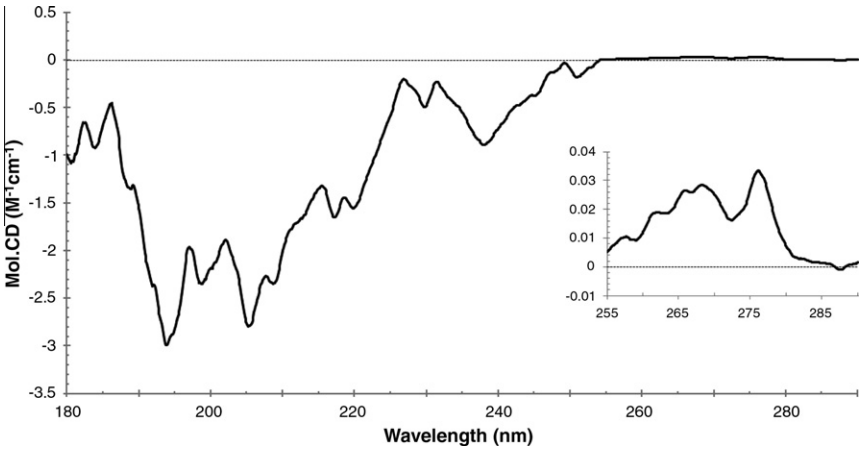



**Figure 2.** CD spectrum of compound **5d**.

For compound **3d**, the overall reactivity is low resulting in quite long reaction times of 60 h (*pseudo*-racemic: 67%, asymmetric: 50%). Using compound **4d**, better yields were obtained overnight (*pseudo*-racemic: 89%, asymmetric 93%).[30] The specific rotation of compound **5d** {$[\alpha]_D = -33.1$ (*c* 7.7, THF)} is quite similar to **6d** {$[\alpha]_D = -37.2$ (*c* 2.9, MeOH)} and comparable to the specific rotation of enantiomerically pure (*S*)-α-methylbenzyl alcohol ($[\alpha]_D = -41$ to $-44$).

Furthermore, CD spectra[32] of compounds (*S*,*S*,*S*,*S*)-**5d** and (*S*,*S*,*S*,*S*)-**6d** were measured and clearly indicate a non-racemic mixture of both compounds. A strong negative effect could be observed in both cases in the lower nm range (Figs. 2 and 3).

In order to determine the corresponding global ers, conversion of the tetraols **5d** and **6d** into the corresponding tetra-Mosher esters was undertaken and the global ratio of generated (*R*)- and (*S*)-isomers could be evaluated. The 600 MHz $^1$H NMR spectra

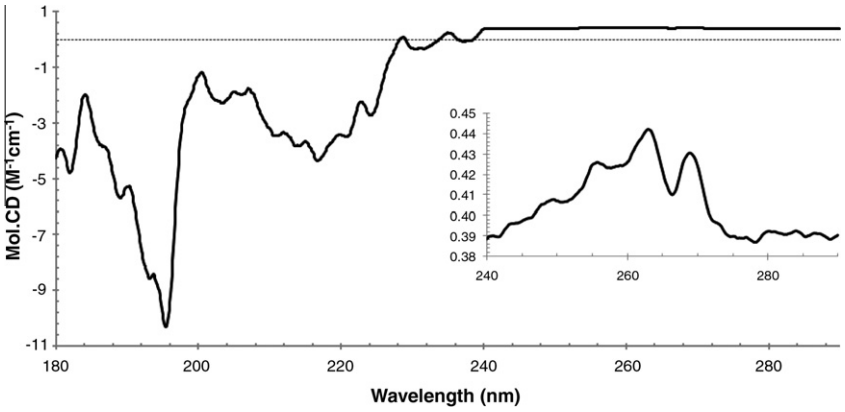



**Figure 3.** CD spectrum of compound **6d**.

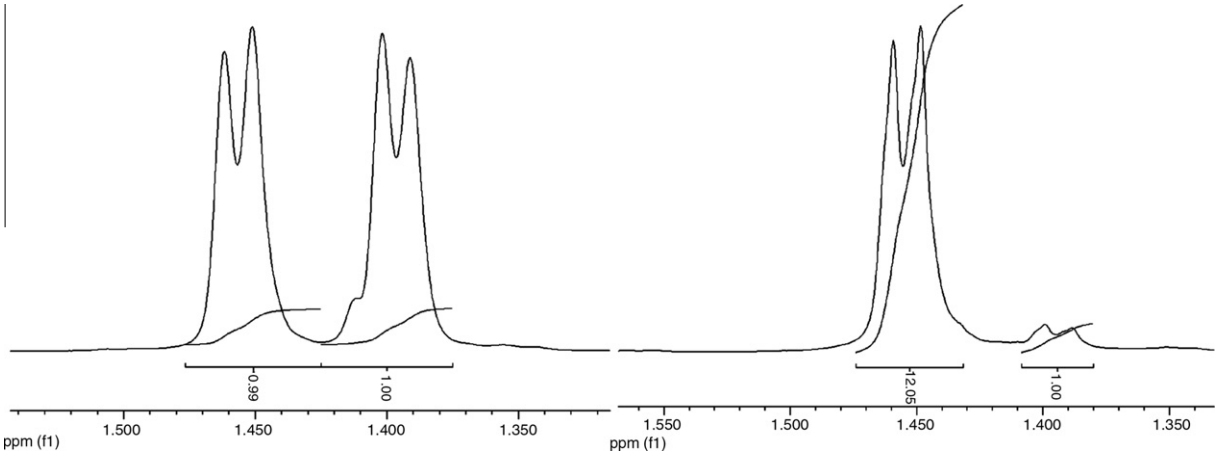
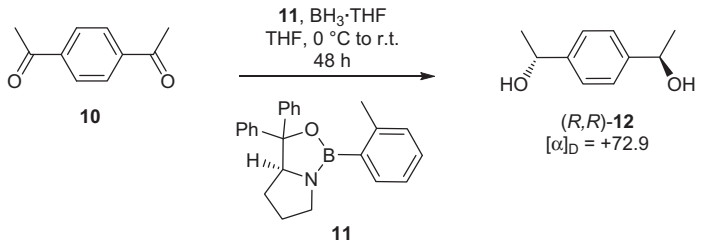



**Figure 4.** Separated NMR signals (methyl group) after conversion into the Mosher ester. Left: (*pseudo-rac*)-**6d**-tetra-Mosher ester, right: (*S*,*S*,*S*,*S*)-**6d**-tetra-Mosher ester.




**Scheme 6.** CBS-reduction of 1,4-diacetylbenzene **10**.

showed a ratio of 10.5:1 (*S*:*R*) ($er_{global}$) for compound **5d** and 12:1 (*S*:*R*) ($er_{global}$) for compound **6d**. An example of a separated NMR signal of the methyl group for (*pseudo-rac*)-**6d** and (*S*,*S*,*S*,*S*)-**6d** is shown in Figure 4. We were unable to separate the respective diastereomeric mixtures of tetraols **5d** and **6d** by HPLC using various columns and conditions.

Finally, to compare and confirm our results of the asymmetric reactions on the tetrapodal systems 1,4-diacetylbenzene **10** was reduced using the other enantiomer of the CBS-catalyst. Its reduction proceeded smoothly under standard conditions in 74% yield after column chromatography (Scheme 6).

We were able to obtain a crystal structure of (*R*,*R*)-**12** which is shown in Figure 5. (*R*,*R*)-**12** crystallized in the chiral space group $P2_1$ with one molecule in the asymmetric unit (Fig. 5). The absolute configuration of (*R*,*R*)-**12** could not be determined reliably by refinement of Flack's *x*-parameter [$x = -1.2(13)$][35] and calculation of Hooft's FLEQ parameter [FLEQ = −0.9(6)].[36] Therefore only the 'relative absolute' configuration could be determined. But using the high likelihood from Hooft's FLEQ parameter the absolute configuration of the enantiopure compound **12** was assigned as (*R*,*R*).

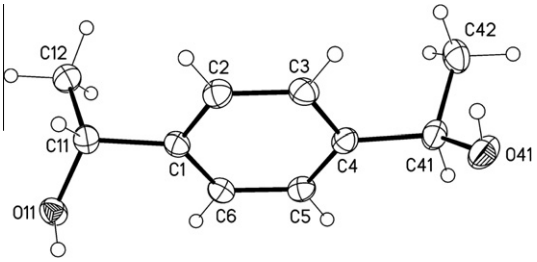



**Figure 5.** ORTEP-style representation of a molecule of (*R*,*R*)-**12** in the crystal (displacement parameters drawn at 50% probability level).

The specific rotation {$[\alpha]_D = 72.9$ (*c* 1.8, acetone)} is in accordance with the literature value {$[\alpha]_D = 86.3$ (*c* 1.7, acetone) for ee >99%}[31] taking into account the different ees. The corresponding di-Mosher ester showed a ratio of 13:1 (*R*:*S*). Furthermore, the CD spectrum shows a positive effect. Regarding the spectrum, the curve progression is comparable to the ones of compounds **5d** and **6d** (Figs. 2 and 3) in an opposite manner. This clearly indicates that their stereogenic centers have the opposite configuration.

The proposed (*R*,*R*)-configuration for compound **12** is in agreement with the CD spectra[32] (Fig. 6), the sign of rotation,[31] and corresponds to the expected stereochemistry when using (*S*)-*o*-tolyl-CBS-catalyst **11**.[33] Finally, the absolute stereochemistry could be confirmed by Mosher ester analysis.[26] By verifying that the absolute stereochemistry of compound **12** is (*R*,*R*) we conclude that the stereogenic centers of compounds **5d** and **6d** have the expected (*S*)-configuration. This is in accordance with the corresponding analytic data as well.

## 3. Conclusion

In conclusion, we have reported the first study dedicated to the asymmetric catalytic addition of reagents to achiral substrates giving rise to chiral tetrapodal tectons.

## 4. Experimental

### 4.1. X-ray crystal structure analysis of (*R*,*R*)-12

*(R,R)*-**12***:* colorless crystals, $C_{10}H_{14}O_2$, $M = 166.21$, crystal size $0.40 \times 0.16 \times 0.08$ mm, monoclinic, space group $P2_1$ (No. 4): $a = 8.285(1)$ Å, $b = 6.116(1)$ Å, $c = 9.836(1)$ Å, $\beta = 114.32(1)°$, $V = 454.2(1)$ Å$^3$, $Z = 2$, $\rho(\text{calcd}) = 1.215$ Mg m$^{-3}$, $F(0\,0\,0) = 180$, $\mu = 0.083$ mm$^{-1}$, 6196 reflections ($2\theta_{max} = 55°$) measured on a Bruker-Nonius Kappa-CCD diffractometer at 123(2) K using Mo Kα

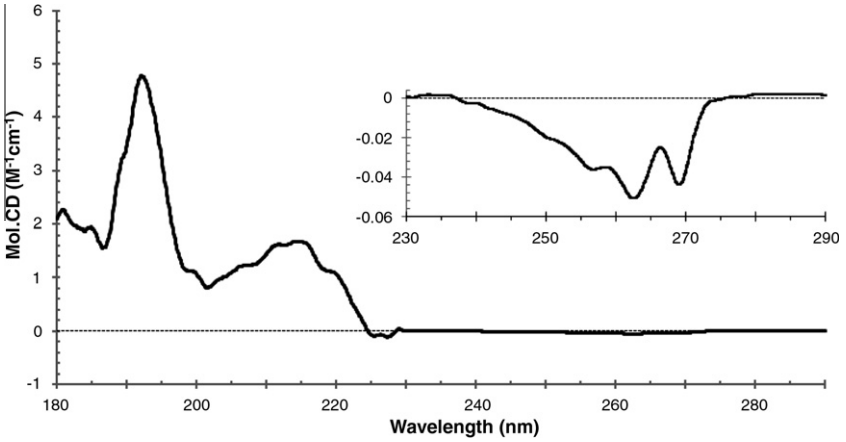



**Figure 6.** CD-spectra of compound (*R*,*R*)-**12**.

radiation ($\lambda$ = 0.71073 Å), 2072 unique [$R_{int}$ = 0.049] used for structure solution (direct methods, SHELXS-97[34]) and refinement (full-matrix least-squares on $F^2$, SHELXL-97[34]) with 117 parameters and 3 restraint, H-atoms with a riding model (H(O) free), $R1$ ($I > 2\sigma(I)$) = 0.040, *wR2* (all data) = 0.100, $S$ = 1.05, largest diff. peak and hole 0.298 and −0.194 e Å$^{-3}$. The absolute configuration could not be determined reliably by refinement of Flack's $x$-parameter[35] and calculation of Hooft's FLEQ parameter[36] ($x$ = −1.2(13); FLEQ = −0.9(6)).

Crystallographic data (excluding structure factors) for the structures reported in this work have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-772939 ((*R*,*R*)-**12**). Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge DB2 1EZ, UK (Fax: int.code+(1223)336 033; e-mail: deposit@ccdc.cam.ac.uk).

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