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Enantiodifferentiation of polyethers by the dirhodium method. Part 2: Cyclotriveratrylenes and cryptophanes☆

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Edison Díaz Gómez dedicates this paper to the late Ing. César Gómez Vacacela, Guayaquil, Equador

Abstract—Cycloveratrylenes and cryptophanes **1**–**12** are chiral compounds and were studied in their racemic form. Although most of them are non-polar oligocyclic ethers, their enantiomers can be easily differentiated by ^{1}H and ^{13}C NMR spectroscopy in the presence of an equimolar amount of $Rh_2[(R)$-(+)-MTPA$]_4$ (the standard protocol for the dirhodium method). Coordination mechanisms were studied. Various functionalities (sulfide, various ethers, olefin and phenol) were also sequenced according to their donor properties.

1. Introduction

Cryptophane molecules are fascinating supramolecular objects that can exist either as chiral or achiral derivatives. Since the 1980s, the chiral derivatives have received much attention as these compounds demonstrate remarkable binding properties towards small neutral molecules. For instance, the well-known *anti*-cryptophane-A **8** (D_3-symmetry), a molecule that consists of two chiral cyclotriveratrylene units (CTV) having the same absolute configuration and connected together by three identical ethanedioxy bridges, shows remarkable binding properties towards methane and halomethane derivatives,[1] and even xenon in organic solution.[2] More recently, new cryptophanes, with symmetries different to that of cryptophane-A, have been synthesized. For instance, *anti*-cryptophane-223 **11** and *anti*-cryptophane-233 with a C_2-symmetry have been prepared and used for the recognition of xenon atoms in organic or aqueous solution.[3] Chiral cryptophanes with a C_1-symmetry have also been reported for the design of biosensors[4] in combination with laser-polarized xenon[5] and for the synthesis of diastereomeric molecules that can be separated by crystallization. The optical resolution of cryptophanol-A via the separation of diastereomeric molecules provides a novel approach for the synthesis of new enantiomerically pure cryptophane enantiomers with an enantiomeric excess close to ee = 100%, and allowed the investigation of the chiroptical properties of cryptophanes by electronic circular dichroism (ECD) or vibrational circular dichroism (VCD) spectroscopies.[6]

The determination of the enantiomeric excess (ee) of cyclotriveratrylene and cryptophane molecules is not an easy task and, unfortunately, HPLC still remains the method of choice for the determination of the ee of these molecules despite the high cost of HPLC columns and solvents. Thus, there is still a need for a simple and direct method for enantiodifferentiation of CTV and cryptophane compounds. The enantiodifferentiation of the two enantiomers by ^{1}H NMR spectroscopy using a chiral agent would be suitable since NMR spectroscopy is commonly used in chemical laboratories; this approach would also provide an easy determination of the ee of CTVs and cryptophanes molecules in a few minutes. However, previous attempts to discriminate between the two enantiomers of a racemic mixture of cryptophane derivatives with europium complexes failed with no enantiodifferentiation observed over a large range of concentrations of europium salts. This result could be explained by the low affinity of the lanthanide salts for weak Lewis acid and bases, as the salts show a better affinity for hard Lewis bases such as OH, NH_2 or ketone functionalities. Recently, the dirhodium method developed by Duddeck et al.[7] appeared as a promising tool

☆ For Part 1 see Ref. 8.

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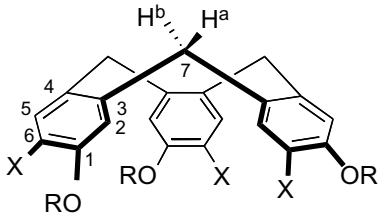
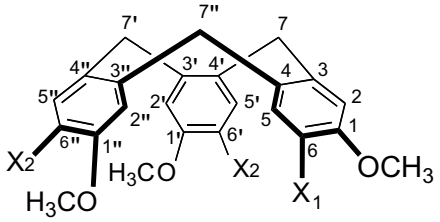
to discriminate between the two enantiomers of a series of cyclic ether derivatives such as the compounds prepared by de Meijere et al.[8] For instance, the ability of the chiral dirhodium tetracarboxylate complex **Rh*** (Scheme 1)[9] to differentiate between the two enantiomers of 2,8,12-trioxahexacyclo[8.3.0.0^{3,9}.0^{4,6}.0^{5,13}.0^{7,11}]tridecane and 4,7,11-trioxapentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane by ^{1}H and ^{13}C NMR spectroscopy was demonstrated, with signals being duplicated by up to $\Delta\nu = 16$ Hz.[8] The complexation of a very weak Lewis base such as the ether moieties encountered in this cyclic ether derivative, prompted us to test the dirhodium method with a series of CTV and cryptophane molecules. We selected six chiral CTV **1**–**6** and four chiral cryptophanes **7**–**10** for detailed analysis, each having different symmetry and substituents (Scheme 1); two more less symmetric cryptophane analogues, **11** and **12**, were studied as well. All compounds were racemates. Herein, we report that the dirhodium discrimination method can be applied successfully to a large series of CTV and cryptophane derivatives each having different symmetry and bearing a variety of substituents. This method provides a novel approach for an easy determination of the enantiomeric excess of these molecules in organic solution.

2. Results and discussion

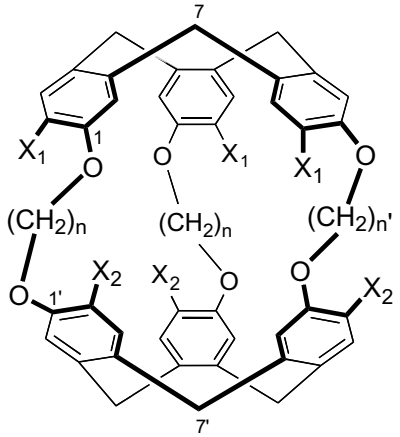
The NMR spectra of all compounds **1**–**10** were recorded in $CDCl_3$ (9.4 T: 400 MHz ^{1}H and 100.6 MHz ^{13}C). An equimolar amount of **Rh*** (except for **4**; see below) was then added and the measurements were repeated. NMR signal assignments were assisted by DEPT, COSY and HMQC experiments. In most cases, ^{1}H and ^{13}C chemical shifts (δ) were assigned unequivocally. Whereas the relative stereochemical position of the two diastereotopic H-7 protons (bridging methylene groups in the CTV moieties) was assigned unambiguously by NOE-difference experiments (NOE contact: H-7a→H-2 and H-5), those of other



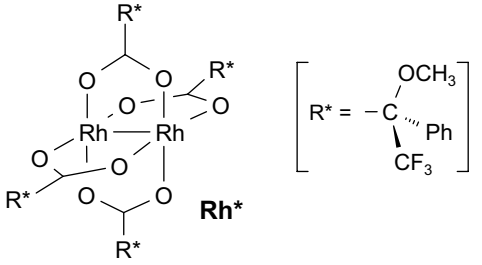
1 : R = CH_3, X = H
2 : R = CH_3, X = $OCH_2CH{=}CH_2$
3 : R = H, X = OCH_2CH_3
4 : R = CH_3, X = SCH_3



5 : X_1 = OCH_3, X_2 = $OCH_2CH{=}CH_2$
6 : X_1 = OH, X_2 = OCH_3



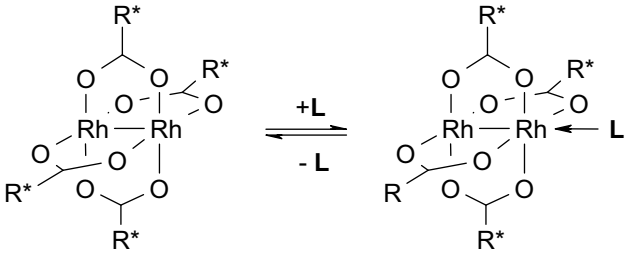
7 : X_1 = X_2 = H, n = 2
8 : X_1 = X_2 = OCH_3, n = n' = 2
9 : X_1 = X_2 = OCH_3, n = n' = 3
10 : X_1 = H, X_2 = OCH_3, n = n' = 2
11 : X_1 = H, X_2 = OCH_3, n = 2, n' = 3
12 : X_1 = H, X_2 = OCH_3, n = 2, n' = 4



Scheme 1. Structures of the chiral dirhodium complex **Rh***, the racemic cyclotriveratrylenes **1**–**6** and the racemic cryptophanes **7**–**12** investigated.

diastereotopic protons in some methylene groups remained open, particularly in the dioxyalkylene groups linking the CTV moieties of the cryptophanes. Occasionally, some signals could not be identified safely in the presence of **Rh*** due to signal overlap.

The dirhodium complex **Rh*** and the ligands (**L**; Scheme 2) form adducts, which cause shifts of the ligand signals (complexation shift $\Delta\delta$; in ppm; positive values correspond to deshielding).[7] These can be determined by comparing the δ-values of the free ligands **1**–**10** with the corresponding ones in the presence of **Rh***. In addition, signal splittings due to the existence of diastereomeric adducts (dispersion $\Delta\nu$; in Hz) appear in the spectra. All NMR data, δ, $\Delta\delta$ and $\Delta\nu$, are listed in Tables 1–4.



Scheme 2. Adduct formation of the dirhodium complex **Rh*** and the ligands **L** (**1**–**12**), respectively. This scheme is simplified; for a more detailed discussion see Ref. 7.

2.1. Enantiodifferentiation

As can be seen in Tables 2 and 4, there is not a single compound among the CTVs and cryptophanes **1**–**10** which does not show a number of diastereomeric splittings. A typical case is demonstrated in Figure 1 for both H-7 and the methoxy proton signals of cryptophane **8**; for more signal splittings for this and other molecules see Tables 2 and 4. Since the series **1**–**10** constitute a representative selection in this compound class, it can be put on record that the dirhodium method offers an excellent and easy-to-perform technique for chiral recognition.

It should be mentioned here that we investigated some other chiral cryptophanes, namely cryptophane-223 **11** and cryptophane-224 **12** (Scheme 1) which differ from **8** (cryptophane-222) in one ethenediol linker ('2') being replaced by 1,3-propanediol ('3') and 1,4-butanediol ('4'), respectively. This reduces the symmetry from D_3 to C_2. Consequently, the number of signals increases drastically. Inevitably, there is plenty of signal overlap but the chemical shift ranges of the various molecular moieties remain the same. Exact signal assignments are extremely tedious because each of the protons and carbons gives rise

Table 1. ^{1}H and ^{13}C chemical shifts of the cyclotriveratrylenes **1**–**6**

	1	**2**	**3**	**4**	**5**[a]	**6**[a]
C-1	158.2	146.7	144.2	155.7	148.2/146.72/146.70	147.6[b]/147.7[b]/144.2
H-2	6.88	6.79	6.77	6.78	6.85[c]/6.84/6.83	6.81/6.81/6.80
C-2	115.4	113.5	115.3	111.6	113.59[c]/115.56/115.47	112.9[d]/113.1[d]/112.1
C-3	141.1	131.7	132.4	138	131.76/131.83/131.6	131.7[d]/131.1[d]/131.9
C-4	131.5	132.3	131.2	131.7	131.8/132.27/132.23	132.5[d]/131.8[d]/131.5
H-5	7.27	6.85	6.86	7.16	6.84[c]/6.79/6.78	6.82/6.82/6.90
C-5	131.0	115.5	113.2	129.3	113.5[c]/113.06/113.06	113.1/113.1/115.6
H-6	6.64	—	—	—	—/—/—	—/—/—
C-6	112.0	148.1	144.5	124.6	148.2/147.68/147.65	147.6[b]/147.7[b]/145.2
H-7a	3.63	3.51	3.46	3.60	3.54/3.52/3.52	3.53/3.53/3.51
H-7b	4.75	4.73	4.67	4.71	4.76/4.75/4.74	4.75/4.75/4.71
C-7	36.5	36.5	36.3	36.4	36.47/36.52/36.48	36.5/36.5/36.2
OCH_3	3.72	3.83		3.85	3.84[e]/3.83/3.84	3.83/3.83/3.83
OCH_3	55.2	56.1		55.8	56.1[e]/55.99/55.96	56.02/55.99/55.95
OCH_2–		4.59	4.06		—/4.59/4.59	
OCH_2–		70.1	64.6		—/70.2/70.2	
C–CH_3			1.38			
C–CH_3			14.8			
CH=		6.06			—/6.06/6.06	
CH=		133.7			—/133.7/133.7	
=CH_2		5.24 (*Z*), 5.37 (*E*)			—/5.24 (*Z*), 5.37 (*E*)	
=CH_2		117.5			—/117.50/117.48	
SCH_3				2.38		
SCH_3				15.6		
OH			5.47			5.41

[a] In compounds **5** and **6**, the values follow the atom numbering sequence $i/i'/i''$. All chemical shift assignments for each individual veratrylene subunits (1′–7′ and 1″–7″, respectively) are based on 2D NMR experiments. However, we were unable to determine which data set belongs to which subunit.
[b] Four different signals observed for C-1 and C-6 (δ = 147.59, 147.63, 147.68, 147.74 ppm); assignment was arbitrary.
[c] $\delta(^{1}H)$ and $\delta(^{13}C)$ values may be interchanged pairwise.
[d] Values may be interchanged pairwise.
[e] Two δ-values for the OCH_3 groups at C-1/C-1′ and C-6/C-6′, not assigned.

Table 2. ^{1}H and ^{13}C complexations shifts ($\Delta\delta$, values on the top in each entry; positive values correspond to deshielding) and diastereomeric dispersions ($\Delta\nu$, values on the bottom of each entry) of the cyclotriveratrylenes **1**–**6**; **Rh***: ligand = 1:1 except for **4** (3:1; see text)

		1	**2**	**3**	**4**	**5**[a]	**6**[a]
C-1	$\Delta\delta$	0.31	0.12	0.37	0.19	0.27/0.13/0.13	0.50/0.50/0.40
	$\Delta\nu$	0	5	2	0	0/n.d./n.d.	0/0/1
H-2	$\Delta\delta$	0.14	0.00	0.08	−0.14	0.04/0.04/0.04	0.10/0.10/0.08
	$\Delta\nu$	5	4	4	53	n.d.[b]/n.d./n.d.	n.d.[b]/n.d./7
C-2	$\Delta\delta$	0.92	0.66	0.40	−0.11	0.59/0.78/0.78	1.54/1.40/1.70
	$\Delta\nu$	10	0	6	45	n.d./6/7	0/0/13
C-3	$\Delta\delta$	0.04	1.04	0.57	n.v.[c]	0.23/0.29/0.17	0.52/0.35/0.59
	$\Delta\nu$	0	8	9	n.v.[c]	1.5/4/3	8/0/7
C-4	$\Delta\delta$	0.70	−1.0	0.15	n.v.[c]	0.23/0.39/0.31	0.94/0.62/0.52
	$\Delta\nu$	5	0	1	n.v.	1.5/5/6	5/5/15
H-5	$\Delta\delta$	0.01	0.04	0.03	0.50	0.04/0.01/0.01	0.12/0.12/0.04
	$\Delta\nu$	9	10	2	37	n.d.[b]/n.d./n.d.	2/2/7
C-5	$\Delta\delta$	−0.02	0.93	1.18	n.v.[c]	0.59/0.62/0.62	1.36/1.38/0.67
	$\Delta\nu$	1	0	16	n.v.[c]	n.d./0/0	0/0/9
H-6	$\Delta\delta$	0.15	—	—	—	—/—/—	—/—/—
	$\Delta\nu$	6	—	—	—	—/—/—	—/—/—
C-6	$\Delta\delta$	1.20	0.34	0.14	n.v.[c]	0.27/0.22/0.21	0.50/0.50/0.42
	$\Delta\nu$	1	0	2	n.v.[c]	0/n.d.[b]/n.d.	0/0/4
H-7a	$\Delta\delta$	−0.05	−0.07	−0.02	−0.76	−0.07/−0.04/−0.04	−0.05/−0.05/−0.06
	$\Delta\nu$	0	10	0	0	n.d.[b]/n.d./n.d.	0/0/0
H-7b	$\Delta\delta$	−0.04	−0.05	−0.02	−0.21	−0.04/−0.03/−0.02	−0.05/−0.05/−0.04
	$\Delta\nu$	0	6	0	52	n.d.[b]/n.d./n.d.	0/0/0
C-7	$\Delta\delta$	−0.10	−0.10	−0.06	−0.02	−0.10/−0.08/−0.09	−0.17/−0.17/−0.10
	$\Delta\nu$	1	0	2	0	0/0/0	0/0/4
OCH_3	$\Delta\delta$	0.16	−0.09		−0.21	0.01/−0.07/0.01	−0.20/−0.20/0.12
	$\Delta\nu$	3	15		0	n.d.[b]/n.d./n.d.	n.d.[b]/n.d./2
OCH_3	$\Delta\delta$	1.64	0.27		0.00	0.32/0.33/0.30	1.70/0.95–0.98
	$\Delta\nu$	5	7		0	n.d.[b]/n.d./n.d.	9/n.d.[b]
OCH_2–	$\Delta\delta$		0.09	0.10		—/0.07/0.07	
	$\Delta\nu$		0	4		—/n.d.[b]/n.d.	
OCH_2–	$\Delta\delta$		0.58	1.24		—/0.48/0.48	
	$\Delta\nu$		8	17		—/8/8	
C–CH_3	$\Delta\delta$			0.01			
	$\Delta\nu$			0			
C–CH_3	$\Delta\delta$			0			
	$\Delta\nu$			0			
CH=	$\Delta\delta$		0.44			—/0.36/0.36	
	$\Delta\nu$		2			—/10/10	
CH=	$\Delta\delta$		−1.80			—/−1/−1	
	$\Delta\nu$		0			—/n.d.[b]/n.d.	
=CH_2	$\Delta\delta$		0.45 (*Z*)/0.42 (*E*)			—/0.39 (*Z*), 0.36 (*E*)	
	$\Delta\nu$		0/0			—/(5 (*Z*)/7 (*E*))	
=CH_2	$\Delta\delta$		−1.11			—/−0.92 (*Z*), −0.91 (*E*)	
	$\Delta\nu$		0			—/n.d.[b]/n.d.	
SCH_3	$\Delta\delta$				0.78		
	$\Delta\nu$				0		
SCH_3	$\Delta\delta$				0.47		
	$\Delta\nu$				0		
OH	$\Delta\delta$			0.15			0.28
	$\Delta\nu$			6			20

[a] In compounds **5** and **6**, the values follow the atom numbering sequence $i/i'/i''$. All chemical shift assignments for each individual veratrylene subunits (1′–7′ and 1″–7″, respectively) are based on 2D NMR experiments. However, we were unable to determine which data set belongs to which subunit.
[b] Not detectable 'n.d.' due to signal overlap.
[c] Not visible 'n.v.'; the signals did not exceed the noise level significantly due to the low concentration of **4**.

to three signals, each even doubled in the presence of **Rh***. As a result, we refrained from a complete NMR interpretation. Nevertheless, there are some signals in both compounds, which allow enantiodifferentiation without a complete signal assignment. As an example, the aromatic H-2 and H-5 signals of **11** and **12**, is shown in Figure 2.

2.2. Ligand binding

As reported before,[7] the atomic site within the ligand molecule binding to **Rh*** can be estimated from the complexation shifts $\Delta\delta$. These parameters adopt significant positive values of moderate magnitudes if the nucleus under inspection is close to the ligating atom whereas $\Delta\delta$-values are

Table 3. ^{1}H and ^{13}C chemical shifts of cryptophanes **7**–**10**

	7	8	9	10[a]
C-1	156.8	146.6	147.1	157.1/146.8
H-2	6.69	6.76	6.61	6.70/6.83
C-2	117	120.8	112.3	118.9/121.1
C-3	131.6	131.6	131.0	140.8/131.8
C-4	140.9	134.1	131.0	132.3/134.7
H-5	6.50	6.67	6.69	7.10/6.70
C-5	113.5	113.7	112.1	130.8/113.9
H-6	7.11	—	—	6.67/—
C-6	130.8	149.6	147.1	113.3/149.93
H-7a	3.50	3.41	3.42	3.45/3.49
H-7b	4.64	4.60	4.66	4.62/4.61
C-7	36.3	36.2	36.1	36.3/36.0
O*C*H_3		3.80	3.83	—/3.80
O*C*H_3		55.7	55.6	—/56.1
O*C*H_2–	4.19	4.16	4.05, 3.87[b]	4.14, 4.28[b]/3.67, 4.27[b]
O*C*H_2–	65.5	69.3	63.6	66.0/71.4
C–CH_2–C			2.30	
C–*C*H_2–C			29.7	

[a] In compound **10**, the values follow the atom numbering sequence *i*/*i*′.
[b] Diastereotopic protons.

close to zero, sometimes even negative, if they are further away. The reason for this, is a slight increase of the inductive effect of the ligating atom compared to the free species. Both ^{1}H NMR and ^{13}C NMR are useful, but ^{13}C NMR provides clearer information mostly due to its higher chemical shift sensitivity and the fact that it is often closer to the ligating atom than the next-nearest hydrogen.

Most CTVs offer a variety of possible binding sites but **1** possesses only methoxy groups which can be considered. As expected, the ^{13}C atoms are the most informative: the strongest positive shifts can be observed for the methoxy carbon ($\Delta\delta = 1.64$ ppm) and for the carbons 2 ($\Delta\delta = 0.92$ ppm), 4 ($\Delta\delta = 0.70$ ppm) and 6 ($\Delta\delta = 1.2$ ppm). This indicates a decrease in the +M-effect of the oxygen atoms affecting *ortho*-and *para*-carbons, since its electron pairs are involved in rhodium complexation. Correspondingly, the methoxy protons ($\Delta\delta = 0.16$ ppm), H-2 ($\Delta\delta = 0.14$ ppm) and H-6 ($\Delta\delta = 0.15$ ppm) are distinctly deshielded. The low number of individual NMR signals suggests that, in the adduct, the ligand molecules **1** have the same symmetry as free **1** itself. This is, of course, impossible, and the observation can be explained by assuming that the ligand molecules rotate within the adduct with a high rate relative to the NMR time-scale, because each oxygen position is equivalent in its donor property. Thereby, equivalent nuclei give rise to the same signal due to time-averaging. The same phenomenon has been observed for deMeijere's polyethers,[8] as well, for example with 2,8,12-trioxahexacyclo[8.3.0.0^{3,9}.0^{4,6}.0^{5,13}.0^{7,11}]tridecane (compound **1** in Ref. 8), by applying variable-temperature ^{1}H and ^{13}C NMR spectroscopy. This experiment, hitherto unreported, proved that there are at least two mechanisms of molecular dynamics: (a) There is a coalescence behaviour of all NMR signals on lowering the temperature indicating an adduct formation as described in Scheme 2; at low temperature, both ligand species, free and complexed, can be observed separately, and a ligand exchange barrier of 44–45 kJ/mol can be estimated. (b) Even at low temperature, the NMR signals of the complexed species are still time-averaged. Thus, a second molecular dynamic with a much lower energy barrier exists which cannot be 'frozen out' by NMR. This is a fast internal rotation of the polyfunctional ligand. We expect that such a rotation occurs in all polyether ligands with equivalent binding sites, that is, for all compounds studied here as well, except for **4** with its sulfur sites (see below).

Table 4. ^{1}H and ^{13}C complexations shifts ($\Delta\delta$; positive values correspond to deshielding) and diastereomeric dispersions ($\Delta\nu$) of cryptophanes **7**–**10**; **Rh***: ligand = 1:1[a]

		7	8	9	10[b]
C-1	$\Delta\delta$	0.24	−0.04	−0.08	0.17/0.17
	$\Delta\nu$	0	1	5	0/0
H-2	$\Delta\delta$	0.06	0.09	0.03	0.06/0.07
	$\Delta\nu$	2	3	0	2/3
C-2	$\Delta\delta$	0.58	0.52	0.45	0.32/0.34
	$\Delta\nu$	0	0	10	0/3
C-3	$\Delta\delta$	0.28	0.10	0.41	0.04/0.04
	$\Delta\nu$	0	2	6	0/0
C-4	$\Delta\delta$	0.08	0.31	−0.01	0.15/0.27
	$\Delta\nu$	2	5	3	0/5
H-5	$\Delta\delta$	0.07	0.01	0.04	0.02/−0.01
	$\Delta\nu$	n.d.	5	1	0/0
C-5	$\Delta\delta$	0.43	0.34	0.37	0.04/0.28
	$\Delta\nu$	0	0	4	0/0
H-6	$\Delta\delta$	0.02	—	—	0.05/—
	$\Delta\nu$	1	—	—	4/—
C-6	$\Delta\delta$	0.54	0.07	0.22	0.43/0.13
	$\Delta\nu$	0	1	3	4/2
H-7a	$\Delta\delta$	−0.03	−0.06	−0.01	−0.06/−0.02
	$\Delta\nu$	5	7	0	3/0
H-7b	$\Delta\delta$	−0.03	−0.05	−0.01	−0.05/−0.02
	$\Delta\nu$	7	4	0	4/0
C-7	$\Delta\delta$	−0.06	−0.12	−0.07	−0.10/−0.01
	$\Delta\nu$	0	2	0	0/0
O*C*H_3	$\Delta\delta$		−0.08	−0.01	—/−0.04
	$\Delta\nu$		6	3	—/0
O*C*H_3	$\Delta\delta$		0.03	0.32	—/0.09
	$\Delta\nu$		0	4	—/0
O*C*H_2–	$\Delta\delta$	0.08	0.17	−0.01, 0.04[c]	0.12, 0.08[c]/0.14, 0.16[c]
	$\Delta\nu$	n.d.[d]	n.d.[d]	1, 1[c]	n.d.[d]/n.d.[d]
O*C*H_2–	$\Delta\delta$	0.87	0.45	0.14	0.42/0.41
	$\Delta\nu$	0	0	0	5/0
C–CH_2–C	$\Delta\delta$			−0.05	
	$\Delta\nu$			3	
C–*C*H_2–C	$\Delta\delta$			−0.13	
	$\Delta\nu$			5	

[a] $\Delta\delta$-values on the top and $\Delta\nu$-values at the bottom in each entry.
[b] In compound **10**, the values follow the atom numbering sequence *i*/*i*′.
[c] Diastereotopic protons.
[d] Not detectable 'n.d.' due to signal overlap.

In **2** with two different oxygen substituents at each benzenoic residue, the complexation shifts are different. As a result, five of the six aromatic carbons and the methylene carbon of the allyloxy group are affected; the $\Delta\delta$-values at the methoxy carbon ($\Delta\delta = 0.27$ ppm) are much less pronounced compared to that at **1**. This allows for the interpretation that both oxygen functionalities are involved simultaneously (dynamic equilibrium of adduct formation). Moreover, the strongly positive complexation shifts

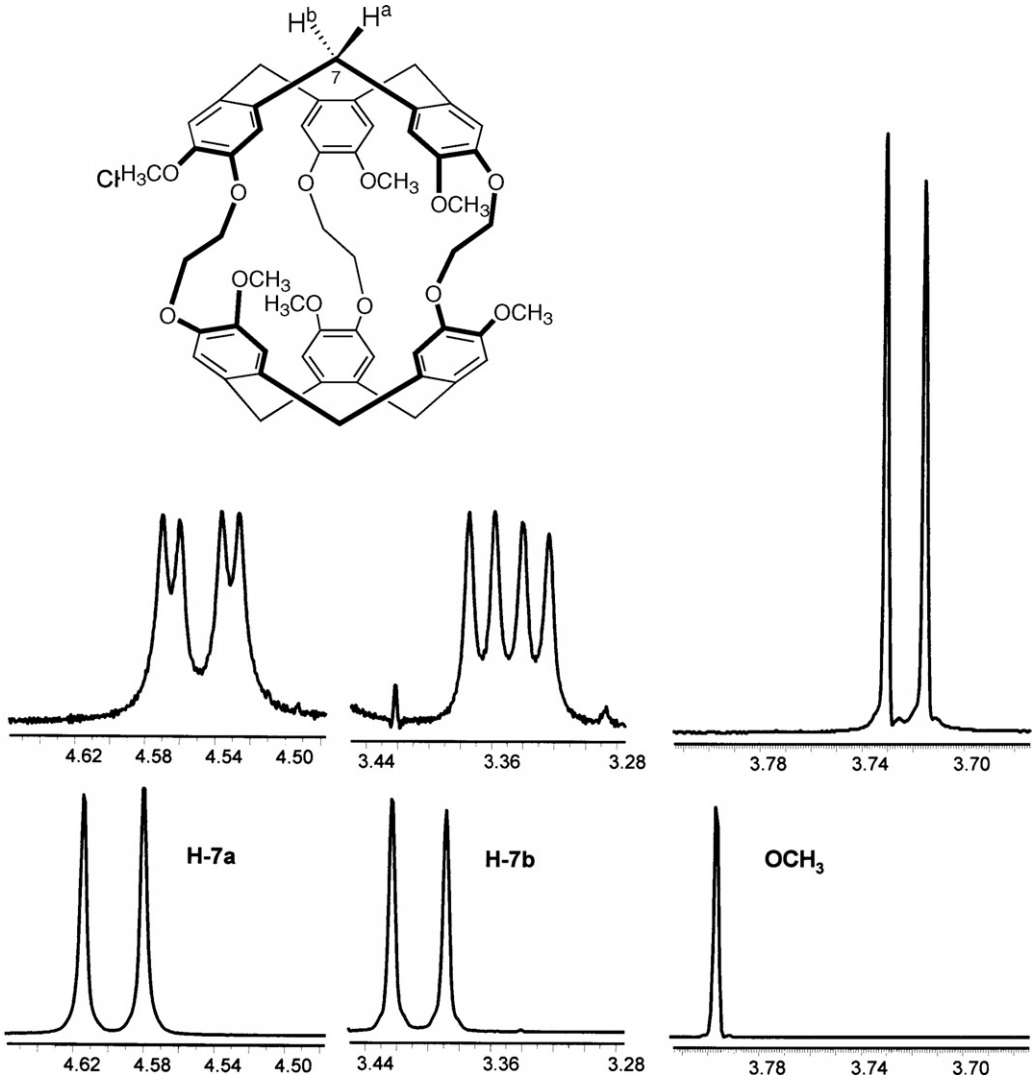


Figure 1. ^{1}H NMR signal dispersion effects of H-7a ($\Delta\nu = 7$ Hz), H-7b ($\Delta\nu = 4$ Hz) and OCH_3 ($\Delta\nu = 6$ Hz) of **8**, bottom: free ligand, top: in the presence of an equimolar amount of **Rh***.

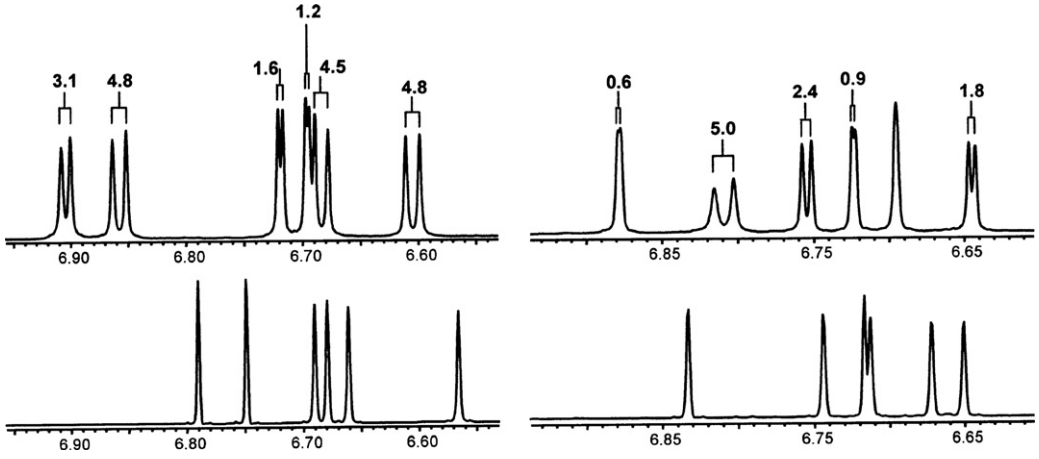
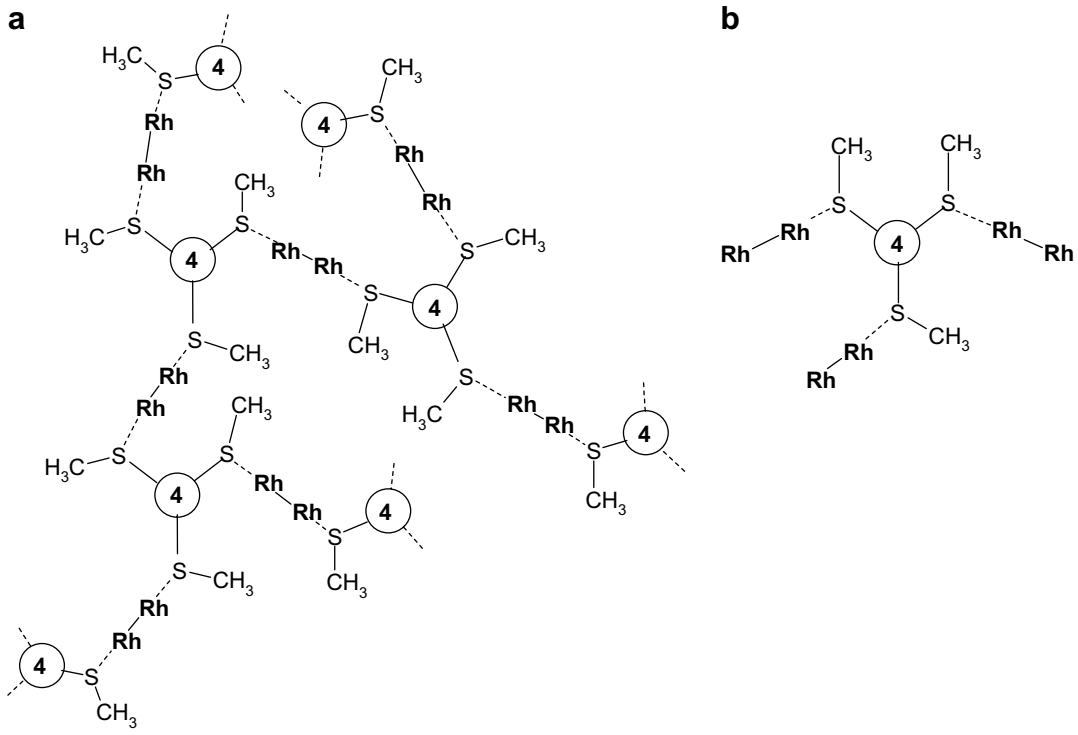


Figure 2. Dispersion effects $\Delta\nu$ (in Hz) at the aromatic H-2 and H-5 signals of **11** (cryptophane-223, left) and **12** (cryptophane-224, right); bottom: free ligand, top: in the presence of an equimolar amount of **Rh***.



Scheme 3. (a) Schematic representation of a 1:1-heteropolymer of **Rh*** and **4** formed at a molar ratio of 1:1; (b) 3:1-adduct formed at a molar ratio of 3:1 (here: **Rh*** is replaced by '**Rh**–**Rh**' for a clearer illustration).

of the olefinic hydrogens are not surprising since this had been found in early dirhodium experiments[9] with olefins as well. Here, a significant contribution of the ethenyl group to the ligation of **2** is indicated. Such an estimation, however, is only semi-quantitative and does not allow us to state whether or not there is any preference for one of the three possible binding sites.

CTV **3** contains hydroxy and ethoxy groups. All aromatic carbons are affected but to a different extent. The largest effects are observed for C-5 ($\Delta\delta = 1.18$ ppm) and C-3 ($\Delta\delta = 0.57$ ppm) indicating a preference in ethoxy ligation. Apparently, phenols are very weak donors, an interesting observation which we have encountered very recently when investigating a flavonolignane.[10]

Significant complexation shifts in the methylthio derivative **4** mainly involve the (*S*)-methyl atoms (^{13}C: $\Delta\delta = 0.47$ ppm; ^{1}H: $\Delta\delta = 0.78$ ppm) as well as some aromatic atoms in close vicinity whereas the methoxy group shows no effect at all. There is no doubt that sulfur is a much stronger donor than oxygen; this is supported with earlier observations.[7,11] Interestingly, we encountered a particular behaviour of **4** in the dirhodium experiment, namely that a dark-yellow solid material precipitated in the NMR tube when the standard dirhodium experiment conditions were applied (equimolar amount of both partners). Apparently, a non-soluble heteropolymer (Scheme 3a) was formed involving the three sulfur substituents (SCH_3) and the two rhodium sites of **Rh***. It should be noted that, in contrast to oxygen binding sites, sulfur ligands shift the adduct formation equilibrium (Scheme 2) completely towards the adduct.[7]

Therefore, we tripled the amount of **Rh*** (**Rh***:**4** = 3:1) so that, statistically, every sulfur atom in **4** is covered by one **Rh*** complex (3:1-adduct) and polymerization becomes unlikely (Scheme 3b). Indeed, there was no precipitation in this case. A further increase of the **Rh*** ratio sixfold (**Rh***:**4** = 6:1) caused the methoxy proton signal of the Mosher acid residues in the adduct ($\delta = 3.03$ ppm, Fig. 3, bottom) to split into two broadened signals ($\delta = 3.05$ and 3.16 ppm; Fig. 3, top) at ambient temperature; coalescence was observed when the solution was heated up to 333 K.

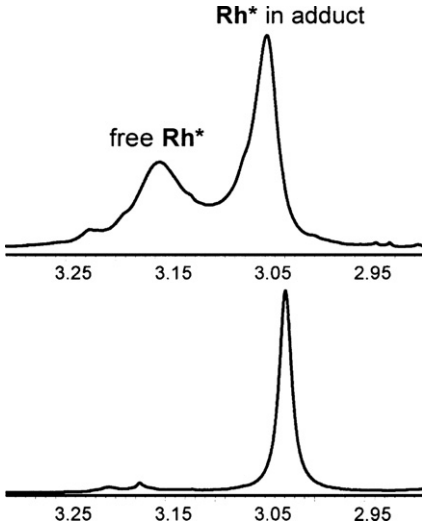


Figure 3. Sections of the ^{1}H NMR spectrum **4** in the presence of **Rh***; bottom: molar ratio **Rh***: **4** = 3:1, top: **Rh***: **4** = 6:1 (see text and Scheme 3b); recorded at ambient temperature.

The left-hand signal ($\delta = 3.16$ ppm) belongs to free **Rh*** molecules (three moles) and the right-hand one ($\delta = 3.05$ ppm) to the ligated **Rh*** (three moles). This behaviour indicates a **Rh*** exchange in the 3:1-adduct depicted in Scheme 3b, that is, a replacement of **Rh*** complexes bound to **4** by free **Rh*** complexes available in the solution. A barrier of ca 65 kJ/mol can be estimated for this process from the spectra. Analogous coalescence phenomena have been observed by us before.[7]

Compound **5** bears four methoxy but only two allyloxy groups. Thus, its symmetry is reduced to C_1 compared to C_3 in the previous derivatives. An inspection of positive $\Delta\delta$-values and their distribution in the molecule displays a close similarity to those of **2**, that is, all three ligands, $-OCH_3$, $-OCH_2$ and $-CH{=}CH_2$, are affected, and—as expected—none of the substituents seems to be favoured significantly.

No clear difference in complexation shift magnitudes was observed for the different rings in **6** with five methoxy and one hydroxy group. This was expected because the hydroxy group is essentially excluded from ligation (see above) but the phenol ring still possesses another methoxy which can act as a donor.

The adduct formation deshieldings in cryptophane **7** are quite similar to those in CTV **1** since both molecules contain only one sort of ether oxygens. Although the $\Delta\delta$-values of **7** are generally smaller in magnitude than those of **1**, we were unable to deduce which of the functionalities, $-O-CH_2-CH_2-O-$ **7** or $-OCH_3$ **1**, is the stronger donor because both compounds have been recorded in different experiments and external influences affecting the $\Delta\delta$-values cannot be excluded.

It seems that the oxygen atoms in the 1,2-ethenediol linkers of **8** are slightly better donors than the methoxy groups as inspected from attached aliphatic and *ortho*- and *para*-carbons. Cryptophane **9**, which is analogous to **8** except for the 1,3-propanediol linkers, shows very similar effects.

On the other hand, by far the majority of all complexation effects are very similar in the two different CTV-bowls of **10**, one with and one without additional methoxy groups, suggesting that there is no ligating preference for any of the two different oxygen functionalities. The values of the OCH_2 carbons in the linker should be noted: $\Delta\delta = 0.87$ ppm in **7**, 0.45 ppm in **8** and 0.42/0.41 ppm in **10**. The larger value of **7** can be interpreted as a consequence of the fact that in this molecule, there is no competition by methoxy groups diluting the effects by averaging.

3. Conclusion

In conclusion we have made three major findings:

(a) The dirhodium method can be successfully applied to a large range of CTV and cryptophane derivatives. This provides a useful approach to measure the enantiomeric excess (ee) by ^{1}H NMR spectroscopy, since the spectra reveal a good enantiodifferentiation in most cases. The overlapping between the ^{1}H NMR signals seems to be the only limitation of the method for CTV and cryptophane molecules having low symmetry.

(b) The dirhodium method, that is, enantiodifferentiation, works well, although most CTVs and cryptophanes possess only ether functionalities. Other soft-base ligands, for example, $-SCH_3$, even support its successful application.

(c) All oxygen functionalities have a comparable potential to act as a binding site whereas sulfur substituents are much stronger donors and outrun all oxygen atoms. On the other hand, a hydroxyl group is very weak and, therefore, uninvolved. In accordance with earlier findings,[7,10] the following sequence of donor characters was established:

$$S\mathrm{CH_3} > O\text{–}\mathrm{CH_3}/O\text{–}\mathrm{C_2H_5} \approx O\text{–}\mathrm{CH_2}\text{–}\mathrm{CH}{=}\mathrm{CH_2} \approx O\text{–}CH_2\text{–}\mathrm{CH_2}\text{–}\mathrm{O} \approx \mathrm{O}\text{–}\mathrm{CH_2}\text{–}CH{=}CH_2 > -O\mathrm{H}$$

4. Experimental

4.1. General

Column chromatographic separations were carried out over Merk-Silica Gel 60 (0.040–0.063 mm). Analytical thin layer chromatography (TLC) was performed on Merck Silica Gel F-254 TLC plates. Melting points were measured on a Perkin–Elmer DSC7 microcalorimeter. Elemental analyses were carried out by the Service Central d'Analyse, CNRS.

4.2. NMR spectroscopy

^{1}H (400.1 MHz) and ^{13}C (100.6 MHz) NMR spectra were performed on Bruker DPX-400 (9.4 T), except for compound **13** (Varian Unity 500 spectrometer at 499.83 and 126.7 MHz, respectively). Solutions were ca 0.07 molar in $CDCl_3$ with internal tetramethylsilane as standard ($\delta = 0$ ppm) for both ^{1}H and ^{13}C. Digital resolutions were 0.14 Hz/point in ^{1}H and 0.24 Hz/point in ^{13}C. Bruker standard software was used for recording DEPT, HMQC, HMBC and ROESY spectra. Notations: H^a, axial proton; H^e, equatorial proton; s, singlet; d, doublet; m, multiplet.

In a standard dirhodium experiment, **Rh*** and an equimolar amount of the ligands **1**–**3** and **5**–**12**, respectively, were dissolved in 0.7 mL $CDCl_3$; quantities of 10–25 mg of **Rh*** (ca 0.01–0.025 mmol concentration) were employed. In the case of **4**, the ratio **Rh***:**4** was 3:1 and 6:1 (see Fig. 3 and text). The dissolution process was accelerated by exposing the NMR sample tubes to an ultrasonic bath for a couple of minutes. All compounds **1**–**12** were investigated as racemic compounds.

Note that $\Delta\nu$-values have no signs because racemates have been investigated, and that they are B_0-dependent.[7] In this work, all dispersion values are given in Hz as determined at

$B_0 = 9.4$ T corresponding to 400 MHz ^{1}H and 100.6 MHz ^{13}C.

4.3. Synthesis of compounds

The preparation of the NMR auxiliary **Rh*** had been previously reported.[9] Cyclotriveratrylenes **1**–**6** and cryptophanes **8**–**12** have been previously reported. Compounds **2** and **4** have been prepared from (4-allyloxy-3-methoxybenzyl)methanol, and (3-methylthio-4-methoxyphenyl) methanol, respectively, according to a known procedure.[12] Compound **3** was prepared according to a procedure given by Collet et al.[13] CTV **1** was prepared in three steps from CTV **2** according to a known procedure.[12]

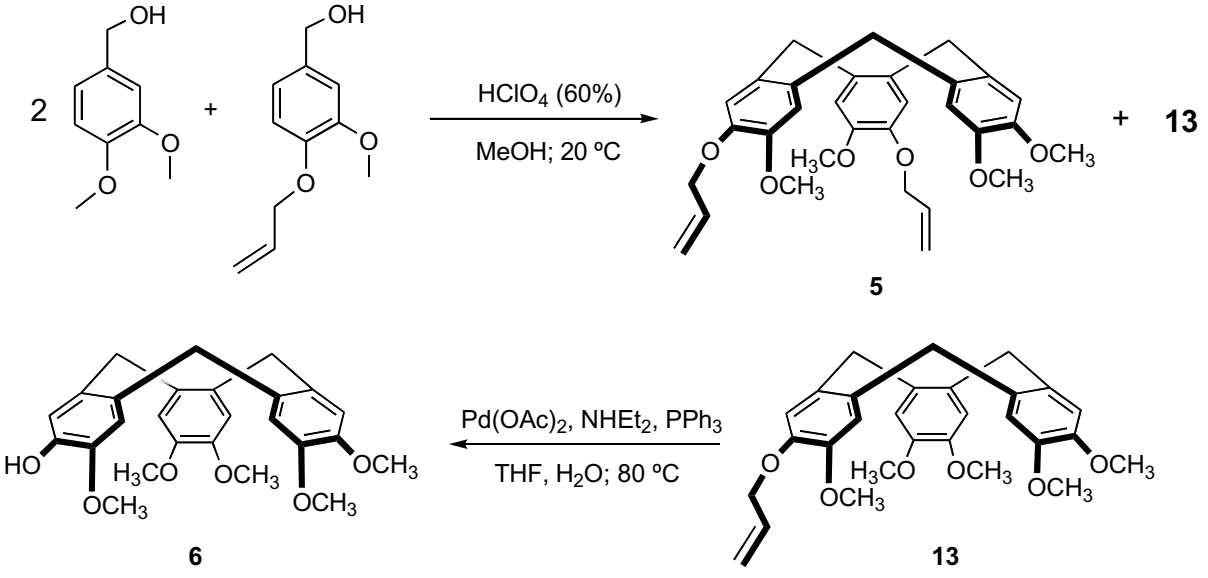
Derivatives **5** and **6** have been synthesized in an alternative way using 2 equiv of (3,4-dimethoxyphenyl)methanol and 1 equiv of (4-allyloxy-3-methoxyphenyl)methanol in the presence of perchloric acid (70%) in methanol (Scheme 4). The reaction gives rise to a mixture of mono-, bi- and trisubstituted derivatives, which can be separated by chromatography on silica gel. The deallylation procedure was performed using a palladium catalyst under basic condition to give rise to CTV **6** with 82% yield.

Synthetic procedure and analytical data of **5**, **6** and their precursors: An aqueous solution of 60% perchloric acid (55 mL) was added dropwise at 0 °C to a stirred solution of 4-allyloxy-3-methoxybenzylalcohol (7 g; 36 mmol) and 3,4-dimethoxybenzylalcohol (12.1 g; 72 mmol) in methanol (120 mL). The solution was allowed to reach room temperature and stirred at this temperature for 18 h, under an argon atmosphere. The deep purple solution was poured onto water and the products were extracted three times with CH_2Cl_2. The organic layers were then combined and washed three times with brine, then with a solution of $NaHCO_3$ (8%). The organic layer was then dried over Na_2SO_4 and the solvent removed by rotary evaporation under reduced pressure to leave a yellow residue. Diethylether was added and the mixture was stirred for 3 h. Filtration on a frit leaves a white residue (5 g) that contains compounds **5** and **13** (Scheme 4). Derivatives **5** and **13** were purified twice by column chromatography on silica gel (CH_2Cl_2/Et_2O: 95:5) to yield *rac*-**5** (1.1 g; 6.4%) and *rac*-**13** (0.23 g; 2.4%).

Compound **5**: Mp: 177.5 °C. Elemental Anal. Calcd for $C_{29}H_{32}O_6$ (476.57): C, 73.09; H, 6.77. Found: C, 72.93; H, 6.88. For NMR data see Table 1.

Compound **13**: Mp: 126.0 °C. Elemental Anal. Calcd for $C_{31}H_{34}O_6$ (502.61): C, 74.08; H, 6.82. Found: C, 74.11, H, 6.81. ^{1}H NMR (500 MHz, $CDCl_3$, 20°C): $\delta = 6.83$ (s, 1H; Ar), 6.82 (s, 2H; Ar), 6.81 (s, 1H; Ar), 6.77 (s, 1H; Ar), 6.76 (s, 1H; Ar), 6.035 (m, 2H), 5.35 (m; 2H), 5.22 (m; 2H), 4.75 (d, $^2J(^1H,^1H) = 13.5$ Hz, 1H; H_a), 4.74 (d, $^2J(^1H,^1H) = 13.5$ Hz, 1H; H_a), 4.73 (d, $^2J(^1H,^1H) = 13.5$ Hz, 1H; H_a), 4.56 (m, 4H), 3.82 (s, 6H; OCH_3), 3.815 (s, 3H; OCH_3), 3.81 (s, 3H; OCH_3), 3.53 (d, $^2J(^1H,^1H) = 13.5$ Hz, 1H; H_e), 3.50 (d, $^2J(^1H,^1H) = 13.5$ Hz, 1H; H_e). ^{13}C NMR (126.7 MHz, $CDCl_3$, 20 °C) $\delta = 148.09$ (2C), 147.63, 147.60, 146.66, 146.65, 133.65 (2C), 132.23, 132.18, 131.79, 131.71 (2C), 131.59, 117.50, 117.48, 115.47, 115.38, 113.50, 113.43, 112.97 (2C), 70.11 (2C; O*C*H_2), 56.06 (2C; O*C*H_3), 55.96 (1C; O*C*H_3), 55.93 (1C; O*C*H_3), 36.51 (1C; $C_{a,e}$), 36.45 (2C; $C_{a,e}$).

Compound **6**: A solution of **13** (1 g; 2.1 mmol), palladium acetate (0.035 g; 0.16 mmol), triphenylphosphine (0.060 g; 0.23 mmol), diethylamine (12.5 mL), tetrahydrofurane (30 mL) and water (6.5 mL) were stirred at 80 °C for 3 h. The solvents were then removed under reduced pressure to leave a dark residue which was extracted twice with ethyl acetate. The organic layer was then washed once with water followed by filtration with a filter paper to remove insoluble dark materials. After drying over Na_2SO_4 and removal



Scheme 4. Synthesis of the CTVs **5** and **6**.

of the solvent under reduced pressure, the dark residue was washed three times with diethyl ether to leave compound **6** as a white solid (0.75 g; 82%). Mp: 211–212 °C. Elemental Anal. Calcd for $C_{26}H_{28}O_6$ (436.50): C, 71.54; H, 6.47. Found: C, 71.62; H, 6.51. For NMR data see Table 1.

Cryptophanes **8**–**12** were prepared according to known procedures. Cryptophanes **8**[14] and **9**[15] (both D_3-symmetry) were synthesized from a procedure given by Collet et al. Compound **10** (C_3-symmetry) was prepared according to a procedure reported by Brotin et al.[12] Cryptophanes **11** and **13** (both C_2-symmetry) have been prepared using a known procedure.[3a] D_3-symmetry cryptophane **7** was prepared in three steps from C_3-symmetry cryptophane **10**.[16]

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