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New carbohydrate-based chiral auxiliaries in Diels–Alder reaction

Maria L. G. Ferreira,[a] Sergio Pinheiro,[a] Clarissa C. Perrone,[b] Paulo R. R. Costa[c] and Vítor F. Ferreira[a,*]

[a]*Instituto de Química, GQO, Universidade Federal Fluminense, CEG, Centro, 24210-150, Niterói, RJ, Brazil*
[b]*Instituto Nacional de Tecnologia, Av. Venezuela 82, 5° andar, 20081-380, Rio de Janeiro, RJ, Brazil*
[c]*Núcleo de Pesquisas de Produtos Naturais, Universidade Federal do Rio de Janeiro, CCS, 21941-590, Rio de Janeiro, RJ, Brazil*

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Abstract

The carbohydrate derivatives **1–5** were evaluated as chiral auxiliaries in the Diels–Alder reaction of its acrylate derivatives **6a–e** with cyclopentadiene promoted by Lewis acids. Although excellent *endo:exo* ratios (98:2) were obtained in many cases, the π-facial selectivities were from low to moderate (up to 60% d.e.). An effect of non-coordinating solvents reversing the stereoselectivities of adducts obtained from acrylates **6a,b** was also found.

1. Introduction

The unique feature of the Diels–Alder reaction to construct up to four new stereogenic centers in one step has made this reaction one of the most important tools in the field of asymmetric synthesis. Although the use of chiral Lewis acids has enjoyed a surge in popularity,[1] over the last few years the use of many chiral auxiliaries derived from available chiral pool compounds attached either to the diene or to the dienophile remains the most common method for effecting an asymmetric Diels–Alder reaction.[2,3]

Lewis acid-catalyzed [4+2]-cycloadditions using either monodentate B and Eu or chelating Ti and Sn have been among the most popular and successful synthetic applications of carbohydrate-based auxiliaries, especially in the cases where they are linked to the dienophile.[4] In fact, among others carbohydrates,[5] arabinose,[6] ribose,[6b,c] sorbitol[7] and galactose[8] have been used to build auxiliaries.

In Diels–Alder reactions involving chiral auxiliaries attached to dienophiles, the nature of both the Lewis acid catalyst[9] and the solvent[10] employed can induce a striking reversal in the stereoselectivity.

* Corresponding author. E-mail: CEGVITO@VM.UFF.BR

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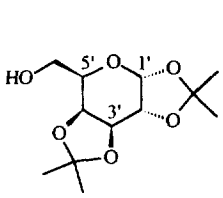
Coordinating solvents such as diethyl ether and chelating acids like $TiCl_4$ or $SnCl_4$ lead to stereoisomers of opposite configuration from those obtained from non-coordinating solvents such as toluene and monodentate acids like $EtAlCl_2$ or $BF_3 \cdot Et_2O$, showing that the metal coordination plays a key role in determining the π-facial selectivity of sugar-linked dienophiles.[9,10]

Some time ago we described the use of carbohydrate-based chiral auxiliaries in α-alkylation of esters enolates[11] and in Michael and aldol addition reactions.[12] Herein we report the use of the compounds **1**, **2–4** and **5** derived[13,14] from D-galactose, D-glucose and D-fructose, respectively, as structurally single chiral auxiliaries attached to the dienophile in the Diels–Alder reaction promoted by chelating and monodentate Lewis acids.



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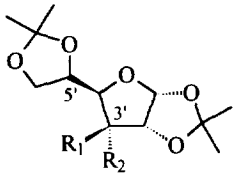
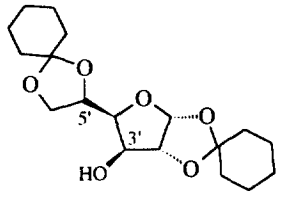


2: R_1=H, R_2=OH

3: R_1=OH, R_2=H



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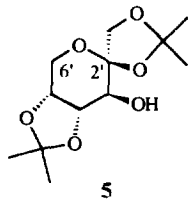

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2. Results and discussion

While the acrylates **6a,b** (Table 1) were prepared in 75% and 40% yields from the corresponding chiral auxiliaries **1** and **2** using acryloyl chloride in Et_3N,[6b,c] better yields for compounds **6c–e** (80%, 88% and 74%, respectively) were obtained by esterification of **3–5** with acrylic acid in the presence of DCC-DMAP.[15]

The Diels–Alder reactions between chiral acrylates **6a–e** and cyclopentadiene were carried out under thermal conditions[9] and in the presence of Et_2AlCl,[16] $EtAlCl_2$,[6b,c] $SnCl_4$,[9,17] $MgBr_2$ and Cp_2TiCl_2 as Lewis acids, following typical procedures already described in the literature. As expected,[2,3] the reactions performed under thermal conditions (entries 1, 8, 15, 17 and 19) furnished a mixture of adducts (*R*)-**7a–e** and (*S*)-**8a–e**, which were not separated, in low π-facial diastereoselectivities and moderate *endo*/*exo* ratios, these results being due to the fact that the s-*trans* conformations of the dienophiles **6a–e** are not fixed in the absence of Lewis acids.

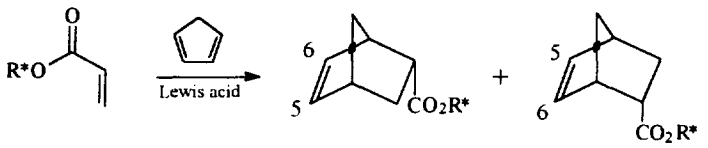
In spite of the decrease in chemical yields, many experiments conducted in the presence of Lewis acids show excellent *endo*/*exo* ratios (entries 2–4, 9–12 and 18). In dichloromethane, the use of $EtAlCl_2$ and Et_2AlCl led to adducts (*S*)-**8a,b,d** in moderate (*S*)-*endo* diastereoselectivity (40–60% d.e.) from the acrylates **6a,b,d** (entries 3, 9, 11 and 18). Conversely, in this solvent the acrylate **6c** led to (*R*)-**7c** in lower selectivity (entry 16).

A non-coordinating solvent-dependence stereoselectivity for acrylates **6a,b** in the presence of Et_2AlCl and $EtAlCl_2$ (entries 2, 3 and 9–12) is noteworthy. A striking reversal in stereoselectivity was obtained from **6a** for the experiments in dichloromethane and toluene (entries 2 and 3), with this tendency being less important for acrylate **6b** (entries 9–12).

In contrast to acrylates **6a** (entries 1 and 2) and **6d** (entries 17 and 18), no Lewis acid-induced reversal from the thermal conditions was observed for **6c** (entries 15 and 16) and **6e** (entries 19 and 20) showing that the metal coordination by these dienophiles was not important in determining the π-facial selectivity.

While $MgBr_2$ led to moderate and similar *endo*/*exo* ratios in CH_2Cl_2 and toluene (entries 7, 13 and 14),

Table 1
Stereoselectivities in the Diels–Alder reactions from acrylates **6a–e**



6a-e (*R*)-**7a-e** (*S*)-**8a-e**

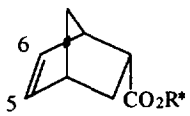
Entry	6	R*OH	Lewis acid[a]	T (°C)	Solvent	Yield (%)	Endo/ Exo[b]	7:8[c]
1	a	1	-----	0	CH_2Cl_2	85	85:15	4:6
2	a	1	Et_2AlCl	-78	toluene	37	> 98:2	7:3
3	a	1	Et_2AlCl	-78	CH_2Cl_2	11	> 98:2	3:7
4	a	1	$EtAlCl_2$	-78	CH_2Cl_2	38	> 98:2	1:1
5	a	1	Cp_2TiCl_2	-78	CH_2Cl_2	NR[d]	-----	-----
6	a	1	$SnCl_4$	-78	CH_2Cl_2	NR[d]	-----	-----
7	a	1	$MgBr_2$	-78	toluene	78	83:17	1:1
8	b	2	-----	0	CH_2Cl_2	90	83:17	1:1[e]
9	b	2	Et_2AlCl	-78	CH_2Cl_2	20	> 98:2	3:7[e]
10	b	2	Et_2AlCl	-78	toluene	31	> 98:2	1:1[e]
11	b	2	$EtAlCl_2$	-78	CH_2Cl_2	27	> 98:2	2:8[e]
12	b	2	$EtAlCl_2$	-78	toluene	30	> 98:2	1:1[e]
13	b	2	$MgBr_2$	-78	toluene	40	85:15	1:1[e]
14	b	2	$MgBr_2$	-78	CH_2Cl_2	40	80:20	1:1[e]
15	c	3	-----	0	CH_2Cl_2	98	80:20	6:4
16	c	3	Et_2AlCl (1.2 eq.)	-78	CH_2Cl_2	53	80:20	6:4
17	d	4	-----	0	CH_2Cl_2	99	84:16	6:4
18	d	4	Et_2AlCl (1.2 eq.)	-78	CH_2Cl_2	56	> 98:2	3:7
19	e	5	-----	0	CH_2Cl_2	96	80:20	1:1
20	e	5	Et_2AlCl (1.2 eq.)	-78	CH_2Cl_2	61	80:20	1:1

[a] 1.5 eq. of Lewis acids were employed unless indicated; [b] Ratios determined either by ^1H or ^{13}C NMR from the signals in positions 5 and 6; [c] By ^1H NMR from the signals due to H6 unless indicated; [d] No reaction occurred, even employing toluene as the solvent; [e] Ratios by ^1H NMR from the signals of H1'.

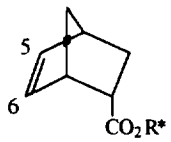
Cp_2TiCl_2 and $SnCl_4$ proved to be ineffective Lewis acids in the Diels–Alder reaction from **6a** (entries 5 and 6).

The *endo*/*exo* ratios were determined either from the relative intensities of the signals attributed to hydrogens H5 and H6 in the ^1H NMR spectra of mixtures of the adducts produced from acrylates **6c–e** or, alternatively, from the signals due to C6 in the ^{13}C NMR spectra of the adducts derived from **6a,b** employing the Off Resonance and the Gated Decoupled procedures (Table 2). These assignments in

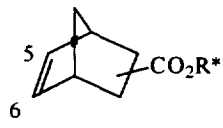
Table 2
Chemical shifts for positions 5 and 6 in ^1H and ^{13}C NMR



(*R*)-7



(*S*)-**8**



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Entry	Adduct	H5	H6	C6
1	(*R*)-7c [a]	6.24-6.19 (m)	5.98 (dd)	132.0
2	(*S*)-8c [a]	6.24-6.19 (m)	5.91 (dd)	131.9
3	9c [a]	6.17-6.06 (m)	6.17-6.06 (m)	135.5
4	(*R*)-7a [b]	6.19-6.11 (m)	6.06 (dd)	132.6
5	(*S*)-8a [b]	6.19-6.11 (m)	5.99 (dd)	132.5
6	9a [b]	6.19-6.11 (m)	6.19-6.11 (m)	135.5

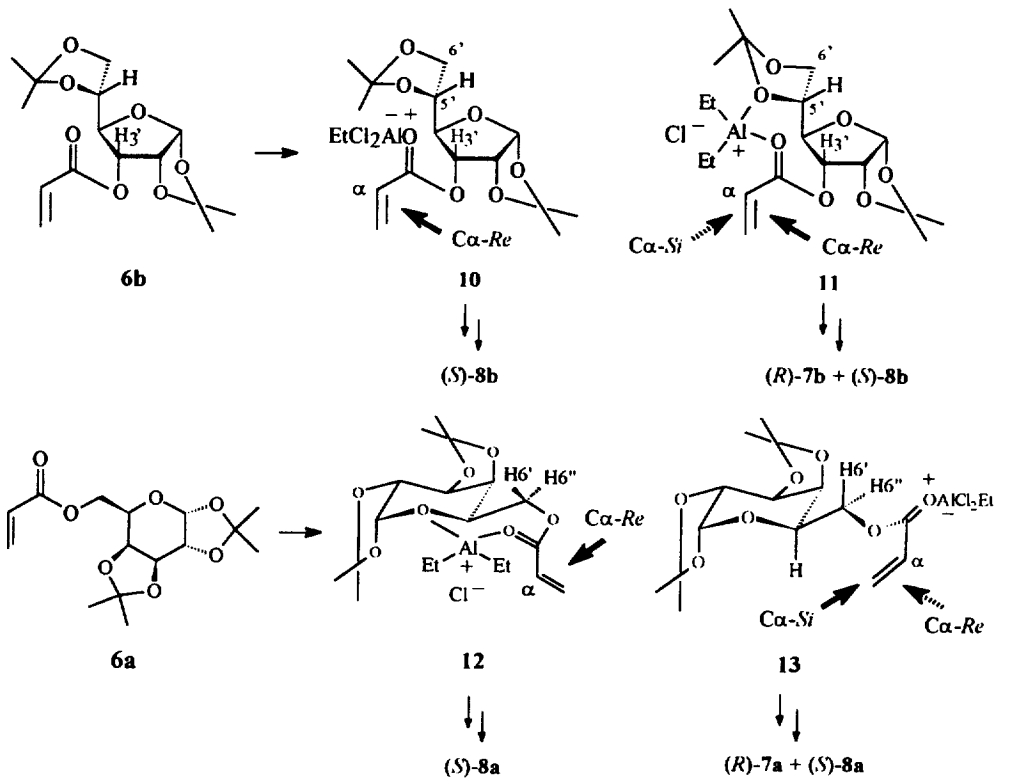
[a] By ^1H NMR (200 MHz); [b] By ^1H NMR (300 MHz).

^1H and ^{13}C NMR for the positions 5 and 6 of the *endo* adducts (*R*)-**7** and (*S*)-**8** as well as for the corresponding *exo* adducts **9** were performed based on previous reports for the Diels–Alder reaction of cyclopentadiene and chiral acrylates including those derived from carbohydrates.[5f,6b,18]

For the mixture **7c–9c** (entries 1–3), while the *endo*/*exo* ratio was obtained from the signals attributed to H5 and H6, the relative intensities of the signals of H6 furnished the *R*/*S* stereoselectivities between **7c** and **8c**. Similar assignments were employed to reach both the *endo*/*exo* and the *R*/*S* diastereoselectivities for **7d** and **7e**, but the spectral analysis did not allow us to determine the *R*/*S* ratio between the *exo* isomers **9c–e** in all cases.

For the adducts **7a–9a** (entries 4–6), where the signal due to H5 of the *endo* isomers (*R*)-**7a** and (*S*)-**8a** is enclosed by the signals of H5 and H6 of the respective *exo* isomers **9a**, the *endo*/*exo* selectivity was determined from the relative intensities of the characteristic[6b] signals of C6 for *endo* and *exo* isomers at 132.5 ppm and 135.5 ppm, respectively, in the ^{13}C NMR spectrum. While the *R*/*S* ratio between **7a** and **8a** was determined from the signals of H6 in the ^1H NMR spectrum, for the mixture of **7b** and **8b** the corresponding signals due to H1′ in the carbohydrate moiety at 5.45 ppm and 5.43 ppm furnished the stereoselectivity.

The stereoselectivities in Lewis acid-promoted Diels–Alder reactions from **6a,b,d** are explained as shown in Scheme 1. The ester **6b** reacts in its s-*trans* conformation leading to the intermediate **10**,[19] where the carbonyl adopts a *syn*-periplanar relationship to the hydrogen H3′.[20] The [4+2]-cycloaddition using $EtAlCl_2$ in CH_2Cl_2 (entry 11, Table 1) occurs mainly from the Cα-*Re* face of **10**, leading to (*S*)-**8b** since the rear face is blocked by the carbohydrate moiety in C5 and C6. The lower selectivity of (*S*)-**8b** obtained from the more chelating Et_2AlCl (entry 9, Table 1) can be attributed to an equilibrium between an intermediate similar to **10** and the metal chelate intermediate **11**, where both faces of the dienophile are disposable for attack. The lack of selectivity for the Diels–Alder reaction of **6b** catalyzed by $MgBr_2$ (entries 13 and 14) is attributed to an intermediate like **11**. The above rationale is also consistent with the stereoselectivity of (*S*)-**8d** from the reaction of acrylate **6d** in the presence of Et_2AlCl (entry 18, Table 1).



Scheme 1. Intermediates for the Lewis acid-promoted reactions of **6a,b** with cyclopentadiene

While the formation of adduct (*S*)-**8a** from Et_2AlCl in CH_2Cl_2 (entry 3, Table 1) is again explained by an equilibrium between the chelate **12** and non-chelate **13** intermediates, with the carbonyl being *syn*-periplanar either to H6′ or to H6″, the reversal (*R*)-selectivity of the reaction in toluene (entry 2, Table 1) remains unknown.

In summary, this first report on the use of the carbohydrate derivatives **1–5** as chiral auxiliaries in a Lewis acid-promoted Diels–Alder reaction shows that although from low to moderate *R/S* stereoselectivities are obtained, the excellent *endo/exo* ratios observed in some cases, in addition to the fact that they are inexpensive, can be further exploited in cycloaddition reactions.

An unexpected striking reversal in the stereoselectivity of the reaction in the presence of non-coordinating solvents dichloromethane and toluene is, to the best of our knowledge, without precedent.

3. Experimental

3.1. General

The diacetonides **1–3** were purchased from Aldrich Chem. Co. Melting points were determined with a Thomas–Hoover apparatus and are uncorrected. Optical rotations were recorded with a Acatec polarimeter. Column chromatrography was performed on silica gel 230–400 mesh (Merck). Infrared spectra were recorded either with a Perkin–Elmer 1420 or with a Perkin–Elmer 1760X spectrophotometer. High resolution electron impact mass spectra (HREIMS) and low resolution electron impact mass spectra (LREIMS) were measured on a V.G. Auto Spec. Q spectrometer. NMR spectra were recorded either

with a Varian Gemini-200 (200 MHz) or with a Varian VXR (300 MHz) for solutions in $CDCl_3$. HRGC analysis was performed using an HP 5890 series II chromatograph with an HP-1 column (12 m×0.2 mm×0.33 μm). Elemental analyses were determined with a Carlo Erba 1104 apparatus.

3.2. *Chiral acrylates **6a** and **6b**: general procedure*

To a −20°C cooled solution of diacetonides **1** or **2** (1.0 g, 3.8462 mmol) in dichloromethane (8 ml) and triethylamine (3 ml) under a nitrogen atmosphere was added dropwise acryloyl chloride (1.5 ml) and the mixture was stirred for 1.5 h and for an additional 5 h at room temperature. The reaction was quenched by cooling to 0°C and addition of conc. HCl (20 ml). The mixture was diluted in dichloromethane (100 ml), phases were separated and the organic layer was washed with water (2×100 ml), sat. $NaHCO_3$ (2×100 ml) and dried over anhydrous Na_2SO_4. Solvent removal in vacuum was followed by flash chromatography on silica gel using a 30% solution of ethyl acetate in n-hexane as eluant.

Compound **6a** was obtained as a pale yellow oil (0.91 g, 75%). $[\alpha]_D^{25}$ −26 (c 1; CH_2Cl_2). IR (neat, cm^{-1}): 2982; 2926; 1720; 1630; 1380; 1218; 1062; 990; 879. ^1H NMR ($CDCl_3$, 300 MHz, ppm): 6.44 (dd, 17.4 Hz, 1.5 Hz, H3); 6.19 (dd, 17.2 Hz, 10.5 Hz, H2); 5.84 (dd, 10.5 Hz, 1.5 Hz, H3); 5.55 (d, 5.1 Hz, H1′); 4.63 (dd, 7.8 Hz, 2.4 Hz, H3′); 4.38 (dd, 11.4 Hz, 4.8 Hz, H6′); 4.34 (dd, 7.8 Hz, 2.7 Hz, H2′); 4.28 (dd, 11.4 Hz, 7.5 Hz, H6′); 4.26 (dd, 7.8 Hz, 1.8 Hz, H4′); 4.07 (ddd, 7.4 Hz, 5.1 Hz, 2.0 Hz, H5′); 1.51 (s, CH_3); 1.46 (s, CH_3); 1.34 (s, CH_3); 1.33 (s, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): 165.7 (s, C1); 130.9 (t, C3); 128.0 (d, C2); 109.4 (s, C8′); 108.6 (s, C7′); 96.1 (d, C1′); 70.8 (d, C4′); 70.5 (d, C3′); 70.2 (d, C2′); 65.8 (d, C5′); 63.3 (t, C6′); 25.8 (q, CH_3); 25.7 (q, CH_3); 24.7 (q, CH_3); 24.2 (q, CH_3). LREIMS (70 eV, m/z): 314 (M^+, 17); 299 (42); 227 (17); 184 (21); 169 (21); 81 (80); 59 (47); 55 (99); 43 (100). Calcd for $C_{15}H_{22}O_7$: 57.3% C, 7.06% H. Found: 57.19% C, 6.99% H.

Compound **6b** was obtained as a white solid (0.48 g, 40%). Mp 73–75°C, $[\alpha]_D^{25}$ +134 (c 1; CH_2Cl_2). IR (KBr, cm^{-1}): 2978; 2908; 1722; 1628; 1376; 1279; 1068; 1012; 868. ^1H NMR ($CDCl_3$, 300 MHz, ppm): 6.47 (dd, 17.4 Hz, 1.5 Hz, H3); 6.18 (dd, 17.4 Hz, 10.5 Hz, H2); 5.90 (dd, 10.5 Hz, 1.5 Hz, H3); 5.85 (d, 3.6 Hz, H1′); 4.95 (dd, 8.4 Hz, 5.1 Hz, H3′); 4.86 (dd, 5.1 Hz, 3.9 Hz, H2′); 4.34–4.28 (m, H5′); 4.21 (dd, 8.7 Hz, 4.5 Hz, H4′); 4.07 (dd, 8.4 Hz, 6.9 Hz, H6′); 3.91 (dd, 8.7 Hz, 5.7 Hz, H6′); 1.55 (s, CH_3); 1.41 (s, CH_3); 1.34 (s, CH_3); 1.33 (s, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): 164.9 (s, C1); 131.8 (t, C3); 127.4 (d, C2); 113.0 (s, C7′); 109.8 (s, C8′); 104.0 (d, C1′); 76.9 (d, C2′); 76.4 (d, C4′); 74.9 (d, C5′); 72.5 (d, C3′); 65.5 (t, C6′); 26.6 (q, CH_3); 26.5 (q, CH_3); 26.1 (q, CH_3); 24.9 (q, CH_3). LREIMS (70 eV, m/z): 299 (46); 241 (18); 155 (68); 101 (28); 55 (100); 43 (61). Calcd for $C_{15}H_{22}O_7$: 57.3% C, 7.03% H. Found: 57.24% C, 7.03% H.

3.3. *Chiral acrylates **6c–6e**: general procedure*

A suspension of diacetonides **3** or **4** or **5** (11 mmol), acrylic acid (0.622 g, 11.1 mmol), DCC (2.27 g; 11 mmol) and DMAP (0.122 g; 1 mmol) in dichloromethane (100 ml) was stirred at room temperature for 4 days. The mixture was filtered and the filtrate was washed with water (3×30 ml), 5% aqueous HOAc (3×30 ml) and water (3×30 ml) and dried over anhydrous Na_2SO_4. Solvent removal under vacuum was followed by flash chromatrography on silica gel using a 20% solution of ethyl acetate in n-hexane as eluant.

Compound **6c** was obtained as a white solid (2.76 g, 80%). Mp 75–76°C, $[\alpha]_D^{25}$ −116 (c 2; $CHCl_3$). IR (KBr, cm^{-1}): 2962; 2914; 2880; 1726; 1622; 1404; 1382; 1248; 1206; 1154; 1026; 872. ^1H NMR ($CDCl_3$, 300 MHz, ppm): 6.49 (dd, 18.1 Hz, 1.2 Hz, H3); 6.17 (dd, 18.1 Hz, 9.7 Hz, H2); 5.96 (dd, 9.7 Hz, 1.2 Hz, H3); 5.93 (d, 4.8 Hz, H1′); 5.35 (d, 2.4 Hz, H3′); 4.57 (d, 4.8 Hz, H2′); 4.40–4.20 (m, H4′

and H5′); 4.20–4.00 (m, H6′); 1.60 (s, CH_3); 1.46 (s, CH_3); 1.37 (s, 2 CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): 165.0 (s, C1); 132.4 (t, C3); 128.1 (d, C2); 112.7 and 109.7 (s, C7′and C8′); 105.5 (d, C1′); 83.8 (d, C4′); 80.2 (d, C2′); 76.7 (d, C3′); 72.9 (d, C5′); 67.6 (t, C6′); 27.4 (q, CH_3); 27.3 (q, CH_3); 26.8 (q, CH_3); 25.8 (q, CH_3). LREIMS (70 eV, m/z): 299 (31); 101 (59); 55 (100). HREIMS calcd for $C_{14}H_{19}O_7$ (M^+-43): 299.1131. Found: 299.1128.

Compound **6d** was obtained as a colorless oil (4.42 g; 88%). $[\alpha]_D^{25}$ −54 (c 2; $CHCl_3$). IR (neat, cm^{-1}): 2920; 2844; 1725; 1625; 1440; 1361; 1251; 1162; 1023; 922; 845. ^1H NMR ($CDCl_3$, 200 MHz, ppm): 6.47 (dd, 16.2 Hz, 1.4 Hz, H3); 6.15 (dd, 16.2 Hz, 10.8 Hz, H2); 5.92 (d, 4.1 Hz, H1′); 5.90 (dd, 10.8 Hz, 1.4 Hz, H3); 5.41 (d, 2.7 Hz, H3′); 4.54 (d, 4.1 Hz, H2′); 4.32–4.16 (m, H4′and H5′); 4.16–3.96 (m, H6′); 1.80–1.20 (m, CH_2). ^{13}C NMR ($CDCl_3$, 50 MHz, ppm): 164.4 (s, C1); 131.6 (t, C3); 127.6 (d, C2); 112.8 and 109.6 (s, C7′ and C13′); 104.6 (d, C1′); 82.7 (d, C3′); 79.9 (d, C4′); 76.1 (d, C2′); 71.9 (d, C5′); 66.8 (t, C6′); 36.3, 36.2, 35.5, 34.5, 24.9, 24.7, 23.8, 23.7, 23.5 and 23.3 (t, C8′–C12′ and C14′–C18′). LREIMS (70 eV, m/z): 394 (M^+, 24); 351 (50); 141 (30); 55 (100). HREIMS calcd for $C_{21}H_{23}O_7$ (M^+-43): 351.1444. Found: 351.1448.

Compound **6e** was obtained as a colorless oil (2.56 g; 74%). $[\alpha]_D^{25}$ −76 (c 2; $CHCl_3$). IR (neat, cm^{-1}): 2981; 2930; 2883; 1730; 1627; 1623; 1448; 1381; 1222; 1172; 1071; 912; 855. ^1H NMR ($CDCl_3$, 200 MHz, ppm): 6.49 (dd, 17.8 Hz, 1.5 Hz, H3); 6.17 (dd, 17.8 Hz, 10.0 Hz, H2); 5.92 (dd, 10.0 Hz, 1.5 Hz, H3); 5.20 (d, 7.7 Hz, H3′); 4.34 (dd, 7.7 Hz, 5.4 Hz, H4′); 4.30–4.03 (m, H5′ and H6′); 3.97 (d, 9.3 Hz, H1′); 3.84 (d, 9.3 Hz, H1′); 1.58 (s, CH_3); 1.50 (s, CH_3); 1.38 (s, CH_3); 1.36 (s, CH_3). ^{13}C NMR ($CDCl_3$, 50 MHz, ppm): 165.4 (s, C1); 131.6 (t, C3); 127.8 (d, C2); 111.9 and 109.5 (s, C7′ and C8′); 103.6 (s, C2′); 74.8 (d, C5′); 73.6 (d, C3′); 71.6 (d, C4′); 70.2 (t, C1′); 60.3 (t, C6′); 27.6 (q, CH_3); 26.3 (q, CH_3); 26.2 (q, CH_3); 25.9 (q, CH_3). LREIMS (70 eV, m/z): 314 (M^+, 9); 299 (100); 257 (44); 241 (25); 181 (50); 169 (56); 143 (62); 126 (96); 113 (62); 97 (65); 85 (95); 72 (55); 69 (54). HREIMS calcd for $C_{14}H_{19}O_7$ (M^+-15): 299.1131. Found: 299.1117.

3.4. Cycloadducts (R)-7a–e and (S)-8a–e: general procedure

To a −78°C cooled solution of the acrylate **6** (0.5 mmol) in dry dichloromethane or toluene (10 ml) under a nitrogen atmosphere was added dropwise a solution of the appropriate Lewis acid in hexanes (0.6 or 0.75 mmol, as indicated in Table 1) and the mixture was stirred for 45 min. Freshly distilled cyclopentadiene (0.4 ml, 5 mmol) was added dropwise and the mixture was stirred at this temperature for between 1 and 2 h and allowed to reach room temperature. The reaction was quenched with $CaCO_3$ (0.2 g), stirred for an additional 15 min and dried over anhydrous Na_2SO_4. Solvent removal under vacuum was followed by flash chromatrography on silica gel using a 30% solution of ethyl acetate in n-hexane as eluant to give the mixtures of cycloadducts **7a–e** and **8a–e** along with the respective *exo* adducts as colorless oils in the yields shown in Table 1.

Adducts **7a** and **8a** (*endo*+*exo*). ^1H NMR ($CDCl_3$, 300 MHz, ppm): 6.19–6.11 (m, H5 of **7a**+**8a** and H5+H6 of *exo*-**9a**); 6.06 (dd, 5.7 Hz, 3.0 Hz, H6 of **7a**); 5.99 (dd, 5.7 Hz, 3.0 Hz, H6 of **8a**); 5.56 (d, 5.1 Hz, H1′ of **7a**); 5.54 (d, 4.8 Hz, H1′ of **8a**); 4.62–4.59 (m, H3′); 4.44–4.37 (m, H6′); 4.34–4.30 (m, H2′); 4.26–4.18 (m, H4′ and H6′); 4.18–3.95 (m, H5′); 3.21 (sl, H1 of **7a**); 3.19 (sl, H1 of **8a**); 3.08 (sl, H1 of *exo*-**9a**); 3.06 (sl, H1 of *exo*-**9a**); 2.98 (dt, 9.3 Hz, 3.4 Hz, H2); 2.90 (sl, H4); 2.31–2.26 (m, H3 of *exo*-**9a**); 1.98–1.94 (m, H3 of **7a**); 1.54 (d, 3.9 Hz, H7); 1.50 (s, CH_3); 1.45 (s, CH_3); 1.43–1.36 (m, H3 of **8a**); 1.33 (s, 2 CH_3); 1.26 (d, 7.5 Hz, H7). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): 175.9 (s, C=O of *exo*-**9a**); 174.4 (s, C=O of **7a**+**8a**); 137.9 and 137.8 (d, C5 of *exo*-**9a**); 137.4 (d, C5 of **8a**); 137.3 (d, C5 of **7a**); 135.6 and 135.5 (d, C6 of *exo*-**9a**); 132.6 (d, C6 of **7a**); 132.4 (d, C6 of **8a**); 109.4 (s, C7′ of **7a**+**8a**); 109.3 (s, C7′ of *exo*-**9a**); 108.5 (s, C8′ of **7a**+**8a**); 108.4 (s, C8′ of *exo*-**9a**); 96.2 (d, C1′ of **7a**+**8a**); 96.1

(d, C1′ of *exo*-**9a**); 70.9 (d, C4′); 70.5 (d, C3′); 70.2 (d, C2′ of **7a+8a**); 70.1 (d, C2′ of *exo*-**9a**); 66.0 (d, C5′ of *exo*-**9a**); 65.9 (d, C5′ of **7a+8a**); 63.1 (t, C6′ of *exo*-**9a**); 63.0 (t, C6′ of **7a**); 62.9 (t, C6′ of **8a**); 49.3 (t, C7); 46.2 and 45.9 (d, C4 of *exo*-**9a**); 45.4 (d, C4 of **8a**); 45.2 (d, C4 of **7a**); 43.1 (d, C2 of **7a**); 43.0 (d, C2 of **8a**); 42.9 and 42.8 (d, C2 of *exo*-**9a**); 42.3 (d, C1 of **7a+8a**); 41.5 (d, C1 of *exo*-**9a**); 30.2 and 29.9 (t, C3 of *exo*-**9a**); 29.1 (t, C3 of **8a**); 28.9 (t, C3 of **7a**); 25.8 (q, CH_3); 25.7 (q, CH_3); 24.7 (q, CH_3); 24.2 (q, CH_3).

Adducts **7b** and **8b** (*endo*+*exo*). ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): 6.28–6.22 (m, H5 of **7b+8b**); 6.11–6.08 (m, H5+H6 of *exo*-**9b**); 5.88–5.82 (m, H6 of **7b+8b**); 5.48 (d, 1.5 Hz, H1′ of *exo*-**9b**); 5.46 (d, 1.5 Hz, H1′ of *exo*-**9b**); 5.45 (d, 1.5 Hz, H1′ of **8b**); 5.43 (d, 1.5 Hz, H1′ of **7b**); 5.00–4.96 (m, H3′ of *exo*-**9b**); 4.87 (dd, 8.7 Hz, 2.1 Hz, H3′ of **7b**); 4.86 (dd, 8.7 Hz, 1.8 Hz, H3′ of **8b**); 4.61–4.51 (m, H2′); 4.32–4.27 (m, H4′); 4.15–4.07 (m, H5′); 3.92–3.75 (m, H6′); 3.20 (sl, H1 of **7b**); 3.16 (sl, H1 of **8b**); 2.86–2.78 (m, H2); 2.59 (sl, H4); 2.30–2.27 (m, H3 of *exo*-**9b**); 2.18–2.06 (m, H3 of **7b+8b**); 1.58 (d, 3.3 Hz, H7); 1.48 (s, CH_3); 1.44 (s, CH_3); 1.34–1.27 (m, H3 of **7b+8b**+*exo*-**9b**); 1.23 (d, 5.7 Hz, H7); 1.07 (s, CH_3); 1.06 (s, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): 173.6 (s, C=O); 138.1 and 138.0 (d, C5 of *exo*-**9b**); 137.7 (d, C5 of **8b**); 137.3 (d, C5 of **7b**); 135.5 and 135.4 (d, C6 of *exo*-**9b**); 132.5 (d, C6 of **7b**); 131.8 (d, C6 of **8b**); 112.7 and 109.8 (s, C7′ and C8′); 104.0 (d, C1′); 76.8 (d, C2′); 76.4 (d, C4′); 74.9 (d, C5′); 72.5 (d, C3′); 65.5 (t, C6′); 49.3 (t, C7); 45.9 (d, C4); 42.6 (d, C2); 41.5 (d, C1); 29.2 (t, C3 of **7b+8b**); 28.9 (t, C3 of *exo*-**9b**); 26.6 (q, CH_3); 26.5 (q, CH_3); 26.1 (q, CH_3); 24.9 (q, CH_3).

Adducts **7c** and **8c** (*endo*+*exo*). IR (neat, cm^{-1}): 3040; 2970; 2860; 1735; 1445; 1380; 1245; 1155; 1070; 880. ^{1}H NMR ($CDCl_3$, 200 MHz, ppm): 6.24–6.19 (m, H5 of **7c+8c**); 6.17–6.06 (m, H5+H6 of *exo*-**9c**); 5.98 (dd, 8.3 Hz, 5.0 Hz, H6 of **7c**); 5.91 (dd, 8.3 Hz, 5.0 Hz, H6 of **8c**); 5.88 (d, 5.3 Hz, H1′ of **8c**); 5.85 (d, 5.3 Hz, H1′ of **7c**); 5.30 (bd, 3.7 Hz, H3′ of *exo*-**9c**); 5.16 (bd, 3.7 Hz, H3′ of **7c+8c**); 4.50–3.95 (m, H2′, H4′– H6′); 3.23 (sl, H4 of **7c+8c**); 3.10–2.90 (m, H1, H4 of *exo*-**9c** and H2 of **7c+8c**); 2.28–2.20 (m, H2 of *exo*-**9c**); 2.00–1.80 (m, H3); 1.68 (sl, H7 of *exo*-**9c**); 1.60–1.20 (m, H7 of **7c+8c**, H3 and 4CH_3). ^{13}C NMR ($CDCl_3$, 50 MHz, ppm): 174.5 (s, C=O of *exo*-**9c**); 173.0 (s, C=O of **7c+8c**); 138.1 (d, C5 of *exo*-**9c**); 137.9 (d, C5 of **8c**); 137.6 (d, C5 of **7c**); 135.4 (d, C6 of *exo*-**9c**); 132.0 (d, C6 of **7c**); 131.9 (d, C6 of **8c**); 112.1 (s, C8′ of **7c+8c**); 112.0 (s, C8′ of *exo*-**9c**); 109.2 (s, C7′); 105.0 (d, C1′ of **7c+8c**); 104.9 (d, C1′ of *exo*-**9c**); 83.2 (d, C2′ of *exo*-**9c**); 83.1 (d, C2′ of **7c+8c**); 80.0 (d, C4′ of **7c+8c**); 79.7 (d, C4′ of *exo*-**9c**); 75.7 (d, C3′ of *exo*-**9c**); 75.6 (d, C3′ of **7c+8c**); 72.3 (d, C5′ of *exo*-**9c**); 72.2 (d, C5′ of **7c+8c**); 67.5 (t, C6′ of **7c+8c**); 67.1 (t, C6′ of *exo*-**9c**); 49.4 (t, C7); 46.0 (d, C2 of **7c**); 45.5 (d, C2 of **8c**); 43.3 (d, C1 of **8c**); 43.1 (d, C1 of **7c**); 42.4 (d, C1 of *exo*-**9c**); 42.3 (d, C4 of **7c+8c**); 41.8 (d, C4 of *exo*-**9c**); 30.0 (t, C3 of *exo*-**9c**); 29.1 (t, C3 of **8c**); 28.6 (t, C3 of **7c**); 26.6 (q, CH_3); 26.1 (q, CH_3); 26.0 (q, CH_3); 25.1 (q, CH_3). LREIMS (70 eV, m/z): 380 (M^+, 2); 101 (92); 66 (63); 55 (100). HREIMS calcd for $C_{19}H_{25}O_7$ (M^+-15): 365.1601. Found: 365.1597.

Adducts **7d** and **8d** (*endo*+*exo*). IR (neat, cm^{-1}): 3066; 2940; 2866; 1742; 1445; 1366; 1236; 1166; 1087; 929. ^{1}H NMR ($CDCl_3$, 200 MHz, ppm): 6.21 (dd, 6.0 Hz, 3.0 Hz, H5 of **7d+8d**); 6.12–6.06 (m, H5+H6 of *exo*-**9d**); 6.02 (dd, 6.0 Hz, 3.0 Hz, H6 of **7d**); 5.93 (dd, 6.0 Hz, 3.0 Hz, H6 of **8d**); 5.88 (d, 4 Hz, H1′ of **7d**); 5.86 (d, 4 Hz, H1′ of **8d**); 5.40–5.10 (m, H3′); 4.50–3.90 (m, H2′, H4′– H6′); 3.23 (sl, H4 of **7d+8d**); 3.15–2.90 (m, H4 of *exo*-**9d**, H2 of **7d+8d** and H1); 2.28–2.20 (m, H2 of *exo*-**9d**); 2.05–1.82 (m, H3); 1.80–1.20 (m, H3, H7 and CH_2). ^{13}C NMR ($CDCl_3$, 50 MHz, ppm): 174.2 (s, C=O of *exo*-**9d**); 173.1 (s, C=O of **7d+8d**); 138.0 (d, C5 of *exo*-**9d**); 137.8 (d, C5 of **8d**); 137.5 (d, C5 of **7d**); 135.3 (d, C6 of *exo*-**9d**); 131.9 (d, C6 of **7d+8d**); 112.7 (s, C13′ of **7d+8d**); 112.6 (s, C13′ of *exo*-**9d**); 109.8 (s, C7′ of **8d**); 109.6 (s, C7′ of **7d**); 109.5 (s, C7′ of *exo*-**9d**); 104.6 (d, C1′ of *exo*-**9d**); 104.5 (d, C1′ of **7d+8d**); 82.7 (d, C2′ of *exo*-**9d**); 82.6 (d, C2′ of **7d+8d**); 80.2 (d, C4′ of *exo*-**9d**); 80.0 (d, C4′ of **8d**); 79.8 (d, C4′ of **7d**); 75.7 (d, C3′); 72.0 (d, C5′ of **7d**); 71.9 (d, C5′ of **8d**); 71.8 (d, C5′ of *exo*-**9d**); 67.1 (t, C6′ of **7d+8d**); 66.8 (t, C6′ of *exo*-**9d**); 49.3 (t, C7); 45.9 (d, C2 of **7d**); 45.4 (d, C2 of **8d**); 43.2

(d, C1 of **8d**); 43.1 (d, C1 of **7d**); 42.3 (d, C4 of *exo*-**9d**); 42.2 (d, C4 of **7d+8d**); 36.3, 36.2, 35.4 and 34.6 (t, C8′, C12′, C14′ and C18′); 29.1 (t, C3 of **8d**); 28.5 (t, C3 of **7d**); 24.9, 24.6, 23.8, 23.6, 23.5 and 23.3 (t, C9′– C12′ and C15′– C17′). LREIMS (70 eV, m/z): 460 (M^+, 15); 85 (64); 84 (52); 83 (100).

Adducts **7e** and **8e** (*endo*+*exo*). IR (neat, cm^{-1}): 3067; 2988; 1746; 1462; 1373; 1217; 1083; 976. ^1H NMR ($CDCl_3$, 200 MHz, ppm): 6.25–6.14 (m, H5 of **7e+8e**); 6.12–6.06 (m, H5+H6 of *exo*-**9e**); 6.01 (dd, 6 Hz, 3 Hz, H6 of **7e**); 5.96 (dd, 6 Hz, 3 Hz, H6 of **8e**); 5.13 (d, 8 Hz, H3′ of *exo*-**9e**); 5.07 (d, 8 Hz, H3′ of **8e**); 5.03 (d, 8 Hz, H3′ of **7e**); 4.35–3.70 (m, H1′, H4′–H6′); 3.25 (sl, H4 of **7e+8e**); 3.20–2.95 (m, H4 of *exo*-**9e**, H2 of **7e+8e**); 2.91 (sl, H1); 2.37–2.26 (m, H2 of *exo*-**9e**); 2.10–1.70 (m, H7 of *exo*-**9e**, H3); 1.60–1.20 (m, H3, H7 of **7e+8e**, $4CH_3$). ^{13}C NMR ($CDCl_3$, 50 MHz, ppm): 175.2 (s, C=O of *exo*-**9e**); 174.0 (s, C=O of **7e+8e**); 138.0 and 137.3 (d, C5 of **7e+8e**); 137.7 (d, C5 of *exo*-**9e**); 135.5 and 135.3 (d, C6 of *exo*-**9e**); 132.7 and 131.4 (d, C6 of **7e+8e**); 111.7 (s, C8′); 109.3 (s, C7′); 103.0 (s, C2′); 74.8 and 74.7 (d, C5′ of **7e+8e**); 73.5 and 73.4 (d, C4′ of **7e+8e**); 71.7 and 71.6 (t, C1′ of **7e+8e**); 71.5 (t, C1′ of *exo*-**9e**); 70.0 and 69.7 (d, C3′ of *exo*-**9e**); 69.9 and 69.8 (d, C3′ of **7e+8e**); 60.4 and 60.3 (t, C6′ of **7e+8e**); 60.2 (t, C6′ of *exo*-**9e**); 49.8 and 49.1 (t, C7 of **7e+8e**); 46.4 and 46.0 (t, C7 of *exo*-**9e**); 45.9 and 45.5 (d, C2 of **7e+8e**); 43.3 and 43.0 (d, C1 of **7e+8e**); 42.4 (d, C1 of *exo*-**9e**); 42.3 (d, C4′ of **7e+8e**); 41.4 (d, C4′ of *exo*-**9e**); 30.8 and 30.0 (t, C3 of *exo*-**9e**); 29.0 and 28.6 (t, C3 of **7e+8e**); 27.6 (s, CH_3); 27.5 (s, CH_3); 26.3 (s, CH_3); 26.2 (s, CH_3). LREIMS (70 eV, m/z): 380 (M^+, 20); 121 (62); 66 (45); 55 (100).

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