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Ruthenium Carbene Complexes with Imidazol-2-ylidene Ligands: Syntheses of Conduritol Derivatives Reveals Superior RCM Activity

Lutz Ackermann, David El Tom and Alois Fürstner*

Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, D-45470 Mülheim/Ruhr, Germany

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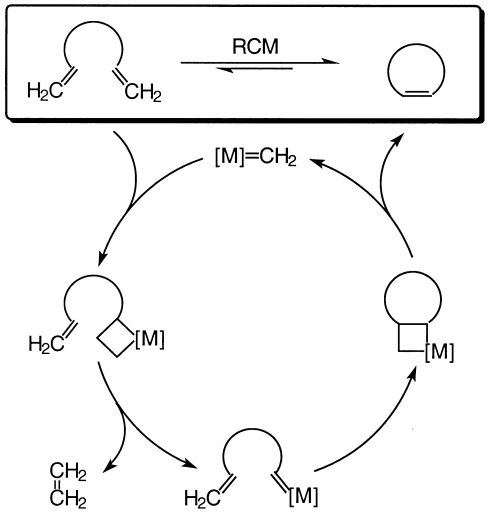
Abstract—Syntheses of conduritol A, E and F derivatives are described using galactitol, D-mannitol and D-glucitol, respectively, as the starting materials. The key steps of this approach comprise a Tebbe olefination reaction for the preparation of dienes **15**, **21** and **27** followed by ring closing metathesis (RCM) for the formation of the polyhydroxylated cyclohexene rings of the targets. A comparative study shows that the latter transformation is best achieved with catalytic amounts of ruthenium carbene complex **3a** bearing one PCy_3 and one 2,3-dihydro-1*H*-imidazol-2-ylidene ligand in its coordination sphere.

Introduction

Ring closing metathesis (RCM) is a very powerful method for the formation of unsaturated cyclic systems from acyclic dienes.[1] According to the generally accepted mechanism,[2] the reaction proceeds via a sequence of formal [2+2] cycloadditions/cycloreversions and is mainly driven by entropy gained by release of ethylene or other volatile side products (Scheme 1). Among the plethora of metathesis pre-catalysts described in the literature, the molybdenum alkylidene species **1**[3] developed by Schrock and the ruthenium carbene complex **2**[4] introduced by Grubbs play a most prominent role and set the standards in the field (Scheme 2).

Whereas the former is distinguished by its superior reactivity even toward highly substituted alkenes, the latter turned out to be somewhat less active but significantly more stable, is easy to handle, shows an excellent compatibility with functional groups, and has therefore gained great popularity over the last few years.[1] This analysis makes clear that a reagent combining the positive features of either system into a single RCM catalyst is highly desirable and will strongly impact further advancements in this timely field of research.

A promising development in this direction has recently been triggered by the advent of complexes of the general type **3** containing a mixed ligand sphere with *one* phosphine and *one* bulky *N*,*N*′-disubstituted 2,3-dihydro-1*H*-imidazol-2-ylidene substituent (R=mesityl, cyclohexyl, isopropyl etc.)[5,6] at the ruthenium carbene center. As has been independently reported by three different research groups,[7–9] these new reagents allow the formation of tri- and tetra-substituted cycloalkenes which are beyond the scope of **2** and have so far been a domain of the molybdenum complex **1**. In terms of stability, however, compounds **3** turned out to be even more robust than the original Grubbs carbene **2** in solution as well as in the solid state. These favorable properties in combination with the user-friendly character of **3** and its excellent tolerance toward an array of polar groups sum up to a very attractive overall application profile. The synthesis of three members of the conduritol family of natural products summarized



Scheme 1.

Keywords: ruthenium carbene complex; olefination; metathesis.

* Corresponding author. E-mail: fuerstner@mpi-muelheim.mpg.de

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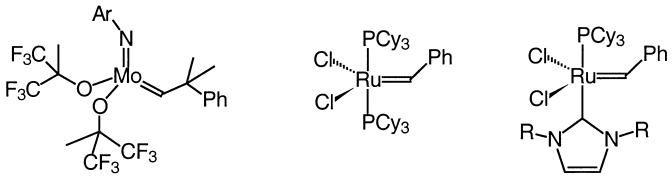


1 2 3

Scheme 2.

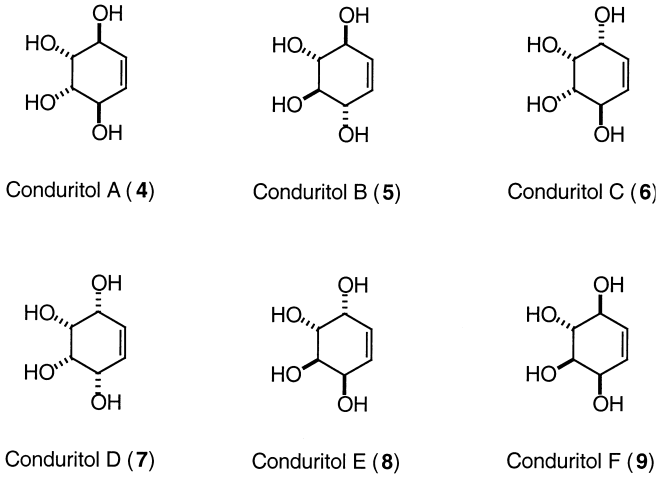
below provided an unexpected but excellent opportunity to substantiate this preliminary assessment.

Results and Discussion

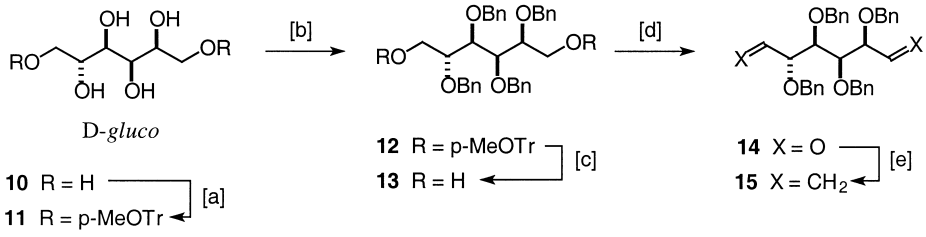
Preparation of the diene substrates

Polyhydroxylated cyclohexene derivatives in general exhibit diverse biological effects and have repeatedly been used as starting materials for advanced organic synthesis.[10] As a result, conduritols A–F (**4**–**9**) and derivatives thereof have attracted considerable attention and were frequently targeted in recent years. Despite the fact that various successful approaches to products of this type have already been reported in the literature,[10] RCM constitutes an obvious tool for their synthesis since the required diene substrates can be easily traced back to cheap monosaccharide building blocks. Prompted by a recent publication of d'Alarcao et al. describing the conversion of D-xylose into protected conduritol B and F via RCM as one of the key steps,[11] we now wish to disclose our complementary approach to conduritols A, E and F which exemplifies the superb activity of the new ruthenium based metathesis catalyst **3a** (R=2,4,6-trimethylphenyl) (Scheme 3).

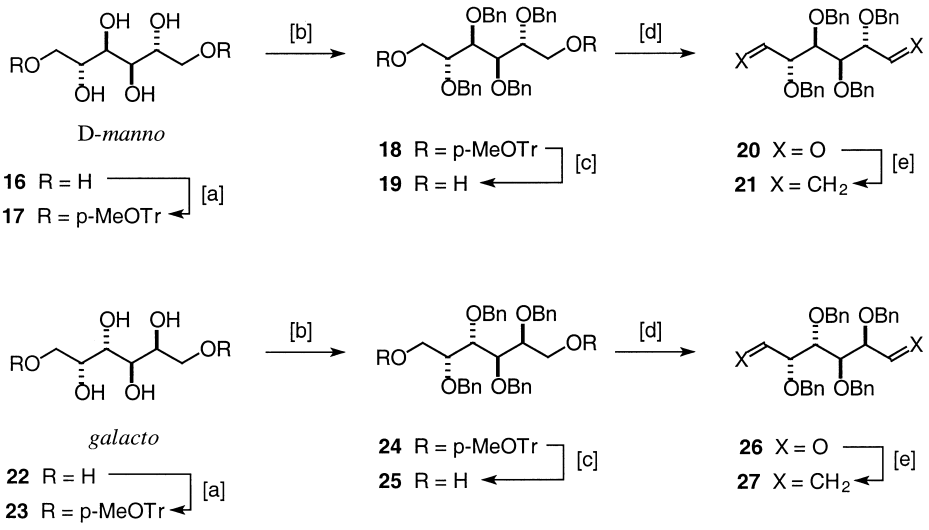
Retrosynthetic analysis of the targets shows that (−)-conduritol F (**9**) exhibits the same stereochemistry as D-glucose, (−)-conduritol E (**8**) shows the pattern of D-mannose, whereas conduritol A (**4**) as a *meso* compound can be matched by galactose. For a matter of convenience, our synthesis of compound **9** starts from cheap and commercially available D-glucitol **10** (Scheme 4). Reaction with *p*-methoxyphenyldiphenylmethyl chloride (*p*-methoxytrityl chloride, *p*-MeOTrCl)[12] in the presence of pyridine and DMAP results in the protection of both primary hydroxyl groups in good yield. Benzylation of the remaining secondary alcohol functions of **11** thus obtained followed by cleavage of the pMeOTr ethers in the resulting product **12** with H_2SO_4 cat. in $MeOH/CH_2Cl_2$ readily delivers the corresponding diol **13**. Swern oxidation was found to be the



Scheme 3.



Scheme 4. [a] *p*-methoxytrityl chloride, DMAP, pyridine, rt, 85%; [b] BnBr, NaH, THF, rt, 96%; [c] H_2SO_4 cat., $MeOH/CH_2Cl_2$, 0°C, 87%; [d] DMSO, oxalyl chloride, NEt_3, CH_2Cl_2, −78°C→rt, quant.; [e] $Cp_2Ti(\mu\text{-}Cl)(\mu\text{-}CH_2)AlMe_2$, THF/pyridine, −40°C→rt, 42%.



Scheme 5. [a] *p*-methoxytrityl chloride, DMAP, pyridine, 78% (**16**→**17**), 74% (**22**→**23**); [b] BnBr, NaH, THF, rt, 92% (**17**→**18**); 91% (**23**→**24**); [c] H_2SO_4 cat., $MeOH/CH_2Cl_2$, 0°C, 94% (**18**→**19**); 89% (**24**→**25**); [d] DMSO, oxalyl chloride, NEt_3, CH_2Cl_2, −78°C→rt, quant.; [e] $Cp_2Ti(\mu\text{-}Cl)(\mu\text{-}CH_2)AlMe_2$, THF/pyridine, −40°C→rt, 47% (**20**→**21**), 42% (**26**→**27**).

method of choice for the preparation of dialdehyde **14**,[13] whereas attempted oxidation of **13** with Pr_4NRuO_4[14] or by means of the Dess–Martin periodinane[15] failed to afford this rather labile product which must be processed without delay. Unfortunately, however, the sensitivity of **14** turned out to be a major obstacle for the envisaged conversion into diene **15**. Despite considerable experimentation with Wittig olefinations (in the presence/absence of crown ethers),[16] alkene syntheses using CH_2Br_2/Zn in the presence of different Lewis acids,[17] Cr(II)-induced Takai–Utimoto olefination,[18] and the Peterson reaction,[19] the overall yield remained low. Best results were obtained with the Tebbe reagent[20] by slowly adding a solution of $Cp_2Ti(\mu\text{-}Cl)(\mu\text{-}CH_2)AlMe_2$ in toluene to a solution of the dialdehyde in THF/pyridine. Under these conditions, the desired diene **15** was obtained in 42% yield.

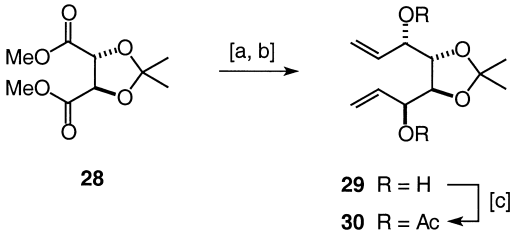
Although this outcome for the seemingly trivial alkene formation is far from optimal, the small number of steps and the ready accessibility of all precursors in large quantity from inexpensive starting materials encouraged us to extend this approach to D-mannitol **16** and the *meso* compound **22** (galactitol) as well. Scheme 5 summarizes our results: in analogy to the glucitol case described above, all transformations proceed smoothly except for the olefination; the yields obtained in this difficult transformation are again in the 40–50% range.

We have also briefly pursued an alternative synthesis of a suitable diene precursor for the preparation of conduritol E. As can be seen from Scheme 6, reduction of (*R*,*R*)-dimethyl tartrate **28** with Dibal-H followed by addition of vinylmagnesium bromide to the aldehyde formed in situ affords the C_2-symmetric diol **29** as the major isomer which can be converted into diacetate **30** under standard conditions.

Comparative investigation of the reactivity of metathesis catalysts 1–3

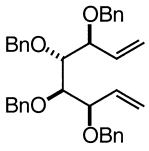
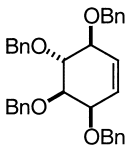
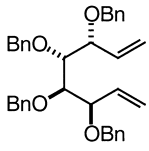
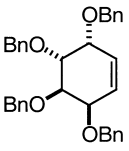
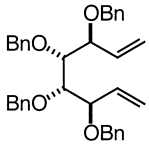
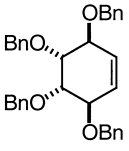
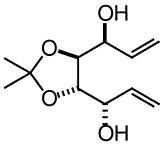
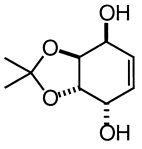
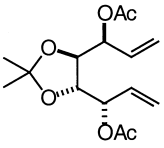
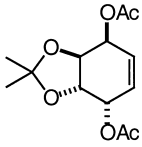
The envisaged key step of our approach to the conduritols, i.e. the conversion of dienes **15**, **21**, **27**, **29** and **30** into the protected conduritol derivatives **31**–**35** by means of RCM, turned out to be significantly more challenging than anticipated. The high reactivity of the Grubbs benzylidenecarbene **2** toward terminal alkenes in general,[1] the kinetically favorable formation of a six-membered ring, and ample precedence for the successful application of **2** in the carbohydrate series[21–23] suggested that the fully protected terminal diene **15** would react without incident with this particular catalyst. In contrast to our expectations, however, this substrate cyclizes very reluctantly on exposure to catalytic amounts of **2** (5 mol%) in refluxing CH_2Cl_2 solution.[24] As little as 32% conversion (GC) into cycloalkene **31** was noticed after 60 h (!) reaction time; complete conversion can only be reached with unduly high catalyst loadings (≥30%). This poor result is in stark contrast to the smooth cyclization of **15** using Schrock's molybdenum complex **1** as pre-catalyst, which depletes the starting material within 1 h and delivers compound **31** in excellent yield.

In view of the preliminary results summarized in the Introduction indicating that the new ruthenium carbene species **3** bearing one imidazol-2-ylidene ligand rival the reactivity of **1**,[7–9] we were prompted to probe their performance in this particular application as well. In fact, the reaction rate for the cyclization of diene **15** on exposure to **3a** (R=mesityl, 5 mol%)[7] is in the same range as that observed with



Scheme 6. [a] Dibal-H, toluene, −78°C; [b] vinylmagnesium bromide, −78°C; 41% (over both steps) (+ca. 20% of isomers); [c] Ac_2O, CH_2Cl_2, pyridine, reflux, 83%.

Table 1. Comparative investigation of the reactivity of different metathesis pre-catalysts

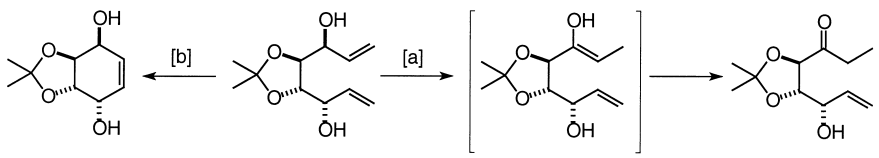
Entry	Substrate	Catalyst	Mol%	*t* (h)	Product	Yield (%)[a]
1	 **15**	**2**	5	60	 **31**	32[b]
2		**1**	5	1		92
3		**3a**	5	2		89
4	 **21**	**1**	5	1	 **32**	95
5		**3a**	5	1		90
6	 **27**	**1**	5	1	 **33**	91
7		**3a**	5	3		85
8	 **29**	**1**	5	2	 **34**	0
9		**2**	20	20		0[c]
10		**3a**	1.5	2		69
11	 **30**	**2**	20	120	 **35**	77
12		**3a**	1	5		71

[a] Isolated yield unless stated otherwise.
[b] GC yield.
[c] Cyclohexene **34** was not obtained; the catalyst delivers only hydroxyketone **36** in 29% yield, cf. Scheme 7.

Schrock's catalyst, and the isolated yield of **31** is also virtually identical in both cases. In view of the significantly higher stability of **3a** toward air and moisture, however, this reagent has a clear-cut advantage in practical terms over the very sensitive molybdenum alkylidene **1** which can only be handled using rigorous Schlenk techniques.

The other data summarized in Table 1 concerning the cyclization of the *manno*-configurated dienes **21**, **29** and **30** as well as the *meso*-diene **27** into the conduritol E and A derivatives **32**, **34**, **35** and **33**, respectively, fully support this notion. Again, the reactivity of ruthenium carbene **2** was found to be significantly lower than that of carbene **3a** in all cases investigated. Particularly revealing is a comparison of entries 11 and 12: Whereas substrate **30** cyclizes smoothly in the presence of as little as 1 mol% of complex **3a** in less than 5 h, the reaction mediated by **2** takes 120 h to go to completion despite of the high catalyst loading (20%). An additional illustration of the superior activity of **3a** was encountered when applied to the diol derivative **29**. It is the only catalyst which allows the transformation of this particular substrate into the cyclohexene derivative **34**, since the molybdenum species **1** is incompatible with the unprotected –OH groups, whereas catalyst **2** effects a slow isomerization of one of the double bonds rather than RCM and thereby delivers hydroxyketone **36** as the only product (Scheme 7).

It may therefore be concluded that the newly discovered ruthenium species **3** bearing one imidazol-2-ylidene ligand constitute excellent tools for RCM by combining the activity of the classical molybdenum systems with the stability and tolerance of ruthenium based catalysts. Further studies corroborating this aspect are underway and will be reported in due course.[25]



34 **29** **36**

Scheme 7. [a] **2** (20 mol%), CH_2Cl_2, reflux, 20 h, 29%; [b] **3a** (1.5 mol%), CH_2Cl_2, reflux, 69%.

Experimental

General

All reactions were carried out under Ar in pre-dried glassware using Schlenk techniques. The solvents were dried by distillation over the drying agents indicated and were stored and transferred under Ar: CH_2Cl_2 (P_4O_{10}), toluene (Na/K), THF (magnesium/anthracene), pyridine (KOH), EtOH (Mg), MeOH (Mg). Flash chromatography: Merck silica gel (230–400 mesh) using hexane/EtOAc in various proportions as eluent. Mp: Gallenkamp apparatus (uncorrected). NMR: Spectra were recorded on a Bruker DPX 300 spectrometer in the solvent indicated. Chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. The multiplicity in the ^{13}C NMR spectra refers to the geminal protons (DEPT). IR: Nicolet FT-7199, wavenumbers in cm^{-1}. MS: Finnigan MAT 8200 (70 eV); HRMS: Finnigan MAT SSQ 7000 (70 eV). Elemental analyses: Dornis & Kolbe, Mülheim. Commercially available reagents (Aldrich, Fluka) were used as received. The solution of the Tebbe reagent was purchased from Fluka.

1,6-Bis[(*p*-methoxyphenyl)(diphenyl)methyl]-D-glucitol (11). *p*-Methoxytrityl chloride (17.50 g, 56.7 mmol) is added in portions to a cooled solution (0°C) of D-(−)-glucitol **10** (5.00 g, 27.4 mmol) and DMAP (1.60 g, 13.1 mmol) in pyridine (100 mL) over a period of 2 h. The mixture is stirred for 48 h at room temperature. After addition of EtOAc (100 mL), the reaction mixture is washed with sat. aq. NH_4Cl (2×50 mL), water (50 mL) and brine (2×50 mL), the combined organic layers are dried (Na_2SO_4) and concentrated. Flash chromatography (hexane/EtOAc, 10:1→2:1) gives the title compound as a colorless syrup (17.0 g, 85%). ^1H NMR (300 MHz, CD_2Cl_2) δ 2.75 (1H, d, J=5.8 Hz), 2.94 (2H, m), 3.07 (1H, d, J=5.5 Hz), 3.16 (1H, dd, J=6.2, 9.6 Hz), 3.28 (3H, m), 3.61 (1H, t, J=5.9 Hz), 3.82 (9H, m), 6.80 (4H, d, J=8.8 Hz), 7.25 (16H, m), 7.43 (8H, m); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 55.6, 65.2, 65.3, 70.2, 71.9, 73.5, 73.9, 87.0, 113.5, 127.4, 128.3, 128.6, 130.7, 135.6, 135.6, 144.6, 144.7, 144.8, 159.2; IR: 3440, 3057, 3032, 3001, 2932, 2836, 1608, 1583, 1510, 1491, 1463, 1447, 1413, 1300, 1251, 1223, 1180, 1154, 1076, 1033, 1001, 989, 950, 902, 832, 796, 766, 755, 727, 707, 632, 590, 548; MS (EI) *m/z* (rel. intensity): 726 ([M^+], 2), 273 (100), 165 (7), 44 (7); HRMS $C_{46}H_{46}O_8$ calcd 726.3193, found 726.3204.

1,6-Bis[(*p*-methoxyphenyl)(diphenyl)methyl]-D-mannitol (17). Prepared as described above from D-mannitol **16** (2.00 g, 10.98 mmol). Colorless syrup (6.25 g, 78%). ^1H NMR (300 MHz, CD_2Cl_2) δ 2.72 (2H, d, J=5.3 Hz), 2.91 (2H, d, J=6.2 Hz), 3.28 (4H, m), 3.75 (8H, m), 3.87 (2H, quint., J=5.6 Hz), 6.82 (4H, dt, J=8.9, 2.5 Hz), 7.28 (16H, m), 7.43 (8H, m); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 55.6, 65.3, 71.1, 72.3, 87.1, 113.6, 127.4, 128.3, 128.6, 130.7, 135.6, 144.7, 144.7, 159.2; IR: 3432, 3057, 3032, 3001, 2931, 2836, 1608, 1583, 1510, 1491, 1463, 1447, 1414, 1300, 1251, 1223, 1180, 1155, 1070, 1033, 985, 902, 832, 796, 766, 755, 727, 708, 632, 590; MS (EI) *m/z* (rel. intensity): 726 ([M^+], 1), 273 (100), 213 (8), 165 (9).

1,6-Bis[(*p*-methoxyphenyl)(diphenyl)methyl]-galactitol (23). Prepared as described above from galactitol **22** (1.00 g, 5.49 mmol). Colorless syrup (2.96 g, 74%). ^1H NMR (300 MHz, CD_2Cl_2) δ 2.64 (2H, d, J=5.7 Hz), 2.72 (2H, m), 3.22 (2H, dd, J=6.2, 9.7 Hz), 3.33 (2H, dd, J=4.5, 9.6 Hz), 3.55 (2H, m), 3.78 (6H, s), 3.99 (2H, q, J=5.1 Hz), 6.84 (4H, dt, J=8.9, 2.6 Hz), 7.28 (16H, m), 7.43 (8H, m); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 55.6, 66.5, 69.7, 72.2, 87.2, 113.6, 127.4, 128.3, 128.6, 130.7, 135.5, 144.6, 144.7, 159.2; IR: 3447, 3057, 3033, 3002, 2932, 2836, 1608, 1584, 1510, 1491, 1463, 1447, 1413, 1385, 1300, 1251, 1224, 1180, 1155, 1115, 1074, 1033, 1001, 902, 832, 796, 766, 727, 707, 633, 587; MS (EI) *m/z* (rel. intensity) 726 ([M^+], 2), 273 (100), 165 (7), 44 (7).

2,3,4,5-Tetra-*O*-benzyl-1,6-bis[(*p*-methoxyphenyl)(diphenyl)methyl]-D-glucitol (12). Compound **11** (3.00 g, 4.13 mmol) is added in portions to a cooled (0°C) suspension of sodium hydride (1.58 g, 66.0 mmol) in THF (50 mL). After the evolution of gas has ceased, benzyl bromide (7.85 mL, 66.0 mmol) is added dropwise during 1 h at the same temperature. After stirring for 16 h at room temperature, the reaction is quenched by carefully adding sat. aq. NH_4Cl (50 mL) at 0°C. The organic layer is washed with water (2×30 mL) and brine (2×30 mL), dried (Na_2SO_4) and concentrated. Flash chromatography (hexane/EtOAc, 1:0→10:1) affords product **12** as a colorless syrup (4.30 g, 96%). ^1H NMR (300 MHz, CD_2Cl_2) δ 3.28 (2H, dt, J=5.5, 10.1 Hz), 3.42 (1H, dd, J=2.8, 10.2 Hz), 3.56 (1H, dd, J=2.1, 10.3 Hz), 3.70 (3H, s), 3.71 (3H, s), 3.90 (3H, m), 4.06 (2H, m), 4.29 (1H, d, J=11.1 Hz), 4.47 (1H, d, J=11.9 Hz), 4.51 (1H, d, J=12.6 Hz) 4.60 (2H, d, J=11.3 Hz), 4.73 (1H, d, J=11.5 Hz), 4.76 (1H, d, J=11.7 Hz), 6.70 (4H, dd, J=2.2, 8.9 Hz), 6.76 (2H, m), 7.28 (42H, m); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 55.5, 55.6, 63.3, 63.9, 72.5, 73.4, 73.9, 74.8, 78.7, 79.4, 79.8, 80.3, 86.6, 86.7, 113.3, 113.4, 127.1, 127.2, 127.5, 127.6, 127.8, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 128.9, 130.8, 135.8, 135.9, 138.8, 139.2, 139.3, 139.4, 145.1, 145.2, 158.9, 159.0; IR: 3086, 3060, 3030, 3002, 2931, 2876, 2835, 1607, 1584, 1510, 1495, 1448, 1393, 1350, 1301, 1252, 1218, 1180, 1154, 1087, 1070, 1031, 1002, 901, 832, 796, 735, 698, 631, 589; MS (EI) *m/z* (rel. intensity) 1086 ([M^+], <0.1), 363 (8), 273 (100), 91 (40).

2,3,4,5-Tetra-*O*-benzyl-1,6-bis[(*p*-methoxyphenyl)(diphenyl)methyl]-D-mannitol (18). Prepared as described above from substrate **17** (6.00 g, 8.25 mmol). Colorless syrup (8.23 g, 92%). ^1H NMR (300 MHz, CD_2Cl_2) δ 3.29 (2H, dd, J=4.2, 10.5 Hz), 3.70 (8H, m), 3.86 (2H, m), 4.25–4.45 (8H, m), 4.79 (2H, d, J=11.7 Hz), 6.69 (4H, dt, J=8.9, 2.5 Hz), 6.91 (4H, m), 7.18 (18H, m), 7.35 (10H, m), 7.47 (12H, m); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 55.5, 62.4, 71.9, 74.0, 77.9, 79.0, 86.7, 113.4, 127.2, 127.5, 127.6, 127.7, 127.9, 128.1, 128.2, 128.4, 128.7, 128.8, 128.9, 130.8, 135.9, 139.1, 139.2, 145.1, 145.2, 159.0; IR: 3060, 3031, 3004, 2931, 2878, 2835, 1607, 1584, 1510, 1496, 1448, 1392, 1325, 1302, 1252, 1219, 1180, 1092, 1071, 1031, 1002, 985, 901, 832, 735, 698, 632, 589; MS (EI) *m/z* (rel. intensity) 1086 ([M^+], <0.1), 363 (14), 273 (100), 91 (61).

2,3,4,5-Tetra-*O*-benzyl-1,6-bis[(*p*-methoxyphenyl)(diphenyl)methyl]-galactitol (24). Prepared as described above

starting from substrate **23** (4.95 g, 6.81 mmol). Colorless crystals (6.71 g, 91%). mp=142–143°C ^{1}H NMR (300 MHz, CD_2Cl_2) δ 3.43 (4H, d, J=5.3 Hz), 3.76 (6H, s), 3.98 (2H, m), 4.06 (2H, m), 4.40–4.65 (8H, m), 6.78 (4H, dt, J=8.9, 2.5 Hz), 7.11 (4H, m), 7.29 (32H, m), 7.46 (8H, m); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 55.5, 63.8, 72.9, 74.1, 78.8, 79.3, 86.9, 113.4, 127.1, 127.2, 127.6, 127.7, 127.9, 128.0, 128.2, 128.5, 128.6, 128.7, 128.8, 130.7, 135.9, 139.2, 139.3, 145.1, 159.0; IR: 3086, 3058, 3032, 2933, 2888, 2861, 2836, 1607, 1584, 1510, 1496, 1448, 1393, 1334, 1301, 1252, 1217, 1177, 1155, 1126, 1091, 1068, 1030, 1002, 987, 946, 901, 828, 797, 765, 736, 697, 632, 584; MS (EI) *m/z* (rel. intensity) 1086 ([M^+], <0.1), 363 (9), 273 (100), 91 (55).

2,3,4,5-Tetra-*O*-benzyl-D-glucitol (13). H_2SO_4 conc. (0.2 mL) is added to a cooled solution (0°C) of substrate **12** (10.0 g, 9.2 mmol) in MeOH/CH_2Cl_2 (10:3, 150 mL). After stirring for 1 h, the reaction is quenched by addition of $NaHCO_3$ (ca. 5 g) and the resulting slurry is stirred for 30 min. Filtration affords a clear solution which is dried (Na_2SO_4) and concentrated. Flash chromatography (hexane/EtOAc, 2:1) provides product **13** as a colorless syrup (4.32 g, 87%). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 2.09 (1H, t, J=5.5 Hz), 2.22 (1H, t, J=5.6 Hz), 3.65 (1H, m), 3.75–3.90 (6H, m), 3.97 (1H, t, J=4.7 Hz), 4.43–4.82 (m, 8H), 7.33 (20H, m); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 60.9, 62.0, 72.0, 73.1, 74.5, 75.0, 78.8, 79.7, 80.1, 80.3, 128.0, 128.0, 128.1, 128.3, 128.4, 128.5, 128.7, 128.8, 128.9, 138.7, 138.8 (2x), 138.9; IR: 3442, 3088, 3063, 3030, 3007, 2929, 2876, 1606, 1586, 1496, 1454, 1396, 1352, 1308, 1250, 1209, 1091, 1066, 1028, 913 877, 735, 697, 602; MS (EI) *m/z* (rel. intensity) 451 ([$(M-Bn)^+$], 2), 345 (8), 253 (6), 181 (29), 91 (100).

2,3,4,5-Tetra-*O*-benzyl-D-mannitol (19). Deprotection of compound **18** (8.00 g, 7.36 mmol) was carried out as described above providing diol **19** as a colorless syrup (3.78 g, 94%). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 2.14 (2H, dd, J=4.6, 7.6 Hz), 3.77 (4H, m), 3.90–4.00 (4H, m), 4.47 (2H, d, J=11.5 Hz), 4.59 (2H, d, J=10.7 Hz), 4.63 (2H, d, J=11.1 Hz), 4.77 (2H, d, J=11.2 Hz), 7.34 (20H, m); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 60.3, 71.7, 74.8, 78.8, 80.0, 128.0, 128.1, 128.2, 128.7, 128.8, 138.6; IR: 3448, 3088, 3063, 3030, 2930, 2879, 1605, 1586, 1496, 1454, 1394, 1350, 1326, 1248, 1209, 1095, 1066, 1028, 913, 876, 848, 736, 698, 604; MS (EI) *m/z* (rel. intensity) 451 ([$(M-Bn)^+$], 1), 181 (23), 91 (100).

2,3,4,5-Tetra-*O*-benzyl-galactitol (25). Substrate **24** (6.31 g, 5.80 mmol) was deprotected as described above affording product **25** as a colorless solid (2.80 g, 89%). mp=114–115°C; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 2.41 (2H, dt, J=1.6, 6.3 Hz), 3.71–3.85 (6H, m), 3.97 (2H, d, J=5.4 Hz), 4.62 and 4.67 (4H, AB, J=11.5 Hz), 4.72 (4H, s), 7.32 (20H, m); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 61.5, 72.9, 74.6, 80.2, 80.4, 127.9, 128.0, 128.2, 128.3, 128.6, 128.7, 138.8, 139.0; IR: 3475, 3087, 3063, 3030, 2926, 2875, 1509, 1497, 1453, 1397, 1334, 1250, 1216, 1109, 1068, 1028, 1004, 751, 697; MS (EI) *m/z* (rel. intensity) 451 ([$(M-Bn)^+$], 0.3), 91 (100).

(3*R*,4*R*,5*R*,6*S*)-3,4,5,6-Tetra(benzyloxy)-1,7-octadiene (15). DMSO (540 μl, 7.6 mmol) in CH_2Cl_2 (2 mL) is added dropwise (5 min) to a solution of oxalyl chloride (360 μl, 3.8 mmol) in CH_2Cl_2 (4 mL) at −60°C. The solution is stirred for 2 min before diol **13** (500 mg, 0.92 mmol) dissolved in CH_2Cl_2 (4 mL) is introduced during 5 min at the same temperature. After stirring the resulting mixture for an additional 10 min, Et_3N (2.4 mL, 17.2 mmol) is added at −60°C. The reaction mixture is kept at −60°C for 15 min and is then allowed to warm to ambient temperature. The reaction is diluted with CH_2Cl_2 (100 mL), the organic phase is successively washed with aq. HCl (0.05 M, 2×20 mL), water (20 mL) and brine (2×20 mL), dried (Na_2SO_4) and evaporated. Crude dialdehyde **14** thus obtained is used in the next step without further purification.

The commercially available Tebbe reagent (~0.5 M in toluene, 0.4 mmol, 0.8 mL) is diluted with THF (5 mL) and the resulting solution is added dropwise over a period of 2 h to a cooled solution (−40°C) of the crude dialdehyde **14** (100 mg, 0.185 mmol) and pyridine (0.1 mL) in THF (10 mL). The reaction mixture is slowly warmed to ambient temperature and stirred for 30 min. The reaction is quenched by addition of a few drops of aq. NaOH (2N) at −10°C, the mixture is stirred for 20 min, insoluble residues are filtered off through a pad of celite and the filtrate is concentrated. Flash chromatography of the residue (hexane/EtOAc, 50:1) affords diene **15** as a colorless syrup (39.1 mg, 42%). $[\alpha]_D^{20}$=+14.9° (c=1.5, $CHCl_3$); ^{1}H NMR (300 MHz, CD_2Cl_2) δ 3.80 (2H, m), 4.07 (1H, dd, J=5.7, 7.9 Hz), 4.14 (1H, dd, J=6.1, 7.7 Hz), 4.27 (1H, d, J=11.6 Hz), 4.39 (1H, d, J=11.6 Hz), 4.56–4.63 (4H, m), 4.80 (1H, d, J=10.9 Hz), 4.81 (1H, d, J=11.0 Hz), 5.25–5.43 (4H, m), 5.94 (1H, ddd, J=7.8, 10.4, 17.2 Hz), 6.02 (1H, ddd, J=8.0, 10.4, 17.1 Hz), 7.32 (20H, m); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 70.4, 70.9, 74.4, 75.6, 81.0, 81.7, 82.0, 82.1, 119.3, 119.7, 127.6, 127.7, 127.8, 127.85, 128.0, 128.1, 128.2, 128.3, 128.36, 128.4 (2×) 128.5, 128.6, 136.2, 136.6, 139.0, 139.2, 139.5, 139.6; IR: 3087, 3064, 3030, 2979, 2866, 1673, 1640, 1606, 1585, 1497, 1454, 1422, 1391, 1349, 1305, 1243, 1208, 1089, 1068, 1028, 997, 930, 734, 697, 599; MS (EI) *m/z* (rel. intensity) 443 ([$(M-Bn)^+$], <0.1), 181 (10), 147 (5), 91 (100); HRMS $C_{36}H_{38}O_4$ calcd 535.2848, found 535.2840.

(3*R*,4*R*,5*R*,6*R*)-3,4,5,6-Tetra(benzyloxy)-1,7-octadiene (21). Diol **19** (205 mg, 0.377 mmol) was processed as described above affording diene **21** as a colorless solid (94.7 mg, 47%). mp=66–67°C; $[\alpha]_D^{20}$=−20.7° (c=1.9, $CHCl_3$); ^{1}H NMR (300 MHz, CD_2Cl_2) δ 3.82 (2H, d, J=6.7 Hz), 4.06 (2H, t, J=7.2 Hz), 4.27 (2H, d, J=11.5 Hz), 4.45 (2H, d, J=10.9 Hz), 4.61 (2H, d, J=11.6 Hz), 4.66 (2H, d, J=10.9 Hz), 5.38 (2H, d, J=2.0 Hz), 5.43 (2H, d, J=1.9 Hz), 5.98 (2H, m), 7.28 (20H, m); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 70.3, 74.9, 80.7, 81.2, 119.9, 127.7, 127.8, 128.2, 128.2, 128.5, 128.7, 136.9, 139.0, 139.3; IR: 3088, 3062, 2978, 2919, 2874, 2846, 2825, 1642, 1606, 1585, 1497, 1452, 1420, 1389, 1342, 1325, 1302, 1281, 1206, 1173, 1142, e1114, 1095, 1069, 1027, 1042, 996, 949, 936, 903, 772, 734, 696, 600, 505; MS (EI) *m/z* (rel. intensity) 443 ([$(M-Bn)^+$], <0.2), 279 (6), 189 (5), 181 (24), 147 (8), 91 (100). HRMS $C_{36}H_{38}O_4$ calcd 535.2848, found 535.2839.

(3*R,4*S**,5*R**,6*S**)-3,4,5,6-Tetra(benzyloxy)-1,7-octadiene (27).** Obtained as a colorless solid (41.9 mg, 42%) from diol

25 (100 mg, 0.185 mmol) according to the procedure outlined above. mp=84–85°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (2H, s), 4.20 (2H, d, J=7.8 Hz), 4.30 (2H, d, J=11.8 Hz), 4.47 (2H, d, J=11.4 Hz), 4.61 (2H, d, J=11.3 Hz), 4.62 (2H, d, J=12.3 Hz), 5.25 (2H, d, J=10.6 Hz), 5.34 (2H, d, J=17.3 Hz), 5.94 (2H, m), 7.26 (20H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.2, 74.4, 80.3, 81.5, 118.5, 127.3, 127.4, 127.6, 128.0, 128.1, 128.2, 136.6, 138.5, 138.7; IR: 3086, 3061, 3030, 3008, 2979, 2931, 2866, 1638, 1604, 1586, 1496, 1453, 1421, 1393, 1333, 1214, 1147, 1097, 1063, 1028, 1005, 937, 909, 760, 751, 738, 697, 591; MS (EI) *m*/*z* (rel. intensity) 443 ([M−Bn)$^+$], <0.2), 189 (5), 181 (21), 147 (10), 91 (100).

(3*S*,4*S*,5*S*,6*S*)-3,6-Dihydroxy-4,5-(isopropylidenedioxy)-1,7-octadiene (29). A solution of Dibal-H (1 M in toluene, 28.9 mL, 28.9 mmol) is added dropwise to a solution of (2*R*,3*R*)-2,3-*O*-isopropylidene tartrate **28** (3.0 g, 13.8 mmol) in toluene (50 mL) at −78°C. The resulting mixture is stirred at that temperature for 2.5 h prior to the addition of vinylmagnesium bromide (1 M in THF, 41.3 mL, 41.3 mmol). Stirring at −78°C is continued for another 2 h before the mixture is allowed to reach ambient temperature. For work-up, the reaction is carefully quenched with sat. aq. NH_4Cl (100 mL), the aqueous layer is repeatedly extracted with EtOAc, the combined organic layers are washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the crude product with hexane/EtOAc (3/1) allows to separate the individual isomers affording diol **29** as the major product in form of a colorless syrup (1.23 g, 41%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.93 (2H, ddd, J=16.5, 10.4, 6.0 Hz), 5.35 (2H, ddd, J=16.5, 1.5, 1.0 Hz), 5.24 (2H, ddd, J=10.4, 1.5, 1.0 Hz), 4.09–4.22 (2H, m), 3.82–4.01 (2H, m), 2.82 (2H, bs, –OH), 1.37 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.5 (d), 117.5 (t), 109.8 (s), 82.1 (d), 74.0 (d), 27.3 (q). IR: 3382, 3086, 2987, 2935, 2893, 1645, 1457, 1429, 1381, 1373, 1244, 1217, 1166, 1078, 1055, 996, 927, 879. MS (EI) *m*/*z* (rel. intensity): 199 (7), 157 (8), 101 (37), 59 (100).

(3*S*,4*S*,5*S*,6*S*)-3,6-Diacetoxy-4,5-(isopropylidenedioxy)-1,7-octadiene (30). A solution of diol **29** (0.40 g, 1.87 mmol) and Ac_2O (0.39 g, 3.8 mmol) in CH_2Cl_2 (10 mL) and pyridine (10 mL) is refluxed for 3 h. Standard extractive work-up followed by flash chromatography (hexane/EtOAc, 10/1) affords the title compound as a colorless syrup (0.46 g, 83%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.87 (2H, ddd, J=6.1, 7.2, 14.3 Hz), 5.29–5.36 (6H, m), 3.96 (2H, m), 2.09 (6H, s), 1.37 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 131.8, 120.0, 110.7, 78.9, 74.5, 26.9, 21.0. IR: 3086, 2989, 2937, 1747, 1646, 1455, 1430, 1373, 1233, 1169, 1107, 1072, 1025, 996, 937, 869, 611, 463 cm^{-1}. MS (EI) *m*/*z* (rel. intensity): 283 (11), 199 (14), 141 (29), 81 (10), 43 (100).

Representative procedure for RCM catalyzed by complex 3a: (3*S*,4*S*,5*S*,6*S*)-3,6-diacetoxy-4,5-(isopropylidenedioxy)-cyclohexene (35). A solution of diene **30** (193.4 mg, 0.64 mmol) and complex **3a** (5.3 mg, 0.0064 mmol, 1 mol%) in CH_2Cl_2 (150 mL) is refluxed for 5 h until TLC shows complete conversion of the substrate. Evaporation of the solvent followed by flash chromatography (hexane/EtOAc, 10/1) provides cyclohexene **35** as a colorless syrup (123 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.02 (2H, dd, J=1.5, 3.2 Hz), 5.62 (2H, m), 3.99 (2H, dd, J=1.2, 2.0 Hz), 2.05 (6H, s), 1.40 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6 (s), 129.8 (d), 111.2 (s), 72.0 (d), 65.6 (d), 26.5 (q), 20.7 (q). IR: 3043, 2986, 2936, 2902, 1746, 1457, 1435, 1372, 1228, 1174, 1149, 1113, 1097, 1053, 1025, 941, 851, 824, 794. MS (EI) *m*/*z* (rel. intensity): 255 (32), 153 (19), 111 (47), 43 (100). The following compounds have been obtained analogously:

(3*R*,4*R*,5*R*,6*S*)-3,4,5,6-Tetra(benzyloxy)-cyclohexene (31). $[\alpha]_D^{20}$=−17.8° (c=1.05, $CHCl_3$); ^{1}H NMR (300 MHz, CD_2Cl_2) δ 3.57 (1H, dd, J=3.5, 9.5 Hz), 4.04–4.16 (3H, m), 4.65–5.00 (8H, m), 5.88 (2H, m), 7.35 (20H, m); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 72.1, 72.4, 72.5, 72.9, 75.2, 80.2, 80.3, 80.5, 126.6, 127.7, 127.8, 127.9, 128.1, 128.2, 128.3, 128.5, 128.6, 131.1, 139.2, 139.4, 139.6; IR: 3087, 3062, 3031, 2917, 2865, 1604, 1585, 1496, 1453, 1388, 1365, 1338, 1308, 1261, 1207, 1163, 1123, 1091, 1073, 1027, 911, 734, 697; MS (EI) *m*/*z* (rel. intensity) 415 ([(M−Bn)$^+$], 2), 292 (11), 266 (9), 201 (7), 91 (100). HRMS $C_{34}H_{34}O_4$ calcd 507.2535, found 507.2540.

(3*R*,4*R*,5*R*,6*R*)-3,4,5,6-Tetra(benzyloxy)-cyclohexene (32). $[\alpha]_D^{20}$=−111.5° (c=1.2, $CHCl_3$); ^{1}H-NMR (300 MHz, CD_2Cl_2) δ 4.06 (2H, d, J=2.5 Hz), 4.29 (2H, m), 4.58–4.75 (8H, m), 5.84 (2H, s), 7.31 (20H, m); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 72.0, 73.6, 74.1, 76.7, 127.8, 127.9, 128.1, 128.2, 128.3, 128.6, 139.3, 139.4; IR: 3087, 3062, 3030, 2864, 1469, 1453, 1202, 1088, 1073, 1027, 952, 910, 735, 697; MS (EI) *m*/*z* (rel. intensity) 415 ([(M−Bn)$^+$], 1), 266 (16), 91 (100). HRMS $C_{34}H_{34}O_4$ calcd 507.2535, found 507.2537.

(3*S,4*R**,5*S**,6*R**)-3,4,5,6-Tetra(benzyloxy)-cyclohexene (33).** ^{1}H NMR (300 MHz, CD_2Cl_2) δ 3.91 (2H, d, J=5.1 Hz), 4.17 (2H, d, J=5.1 Hz), 4.61 (4H, s), 4.67 (4H, s), 5.86 (2H, d, J=1.4 Hz), 7.33 (20H, m); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 72.2, 73.0, 75.9, 77.8, 127.8, 127.9, 128.0, 128.2, 128.6, 128.7, 139.2; IR: 3086, 3062, 3030, 2867, 1605, 1585, 1469, 1453, 1385, 1329, 1304, 1247, 1206, 1117, 1132, 1097, 1061, 1040, 1027, 911, 863, 805, 736, 696, 604; MS (EI) *m*/*z* (rel. intensity) 415 ([(M−Bn)$^+$], 1), 266 (18), 91 (100). HRMS $C_{34}H_{34}O_4$ calcd 507.2535, found 507.2539.

(3*S*,4*S*,5*S*,6*S*)-3,6-Dihydroxy-4,5-(isopropylidenedioxy)-cyclohexene (34). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.98 (2H, dd, J=3.2, 1.5 Hz), 4.49 (bd, 2H), 3.94 (2H, dd, J=1.9, 1.3 Hz), 2.63 (2H, bs, –OH), 1.48 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 129.4 (d), 109.5 (s), 72.4 (d), 63.7 (d), 25.9 (q). IR: 3344, 3042, 2988, 2932, 2903, 1449, 1371, 1336, 1279, 1231, 1170, 1149, 1130, 1093, 1066, 1019, 969, 933, 842, 818, 706, 609, 552, 508. MS (EI) *m*/*z* (rel. intensity): 171 (75), 111 (100), 99 (52), 83 (44), 59 (31), 43 (78).

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