Carbasaccharides *via* Ring-Closing Alkene Metathesis. A Synthesis of (+)-Valienamine from D-Glucose

by **Peter Kapferer**, **Francisco Sarabia**[1]), and **Andrea Vasella***

Laboratorium für Organische Chemie, ETH-Zentrum, Universitätstrasse 16, CH-8092 Zürich

(+)-Valienamine (**16**) was prepared in seven steps and in an overall yield of 17% from commercially available 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose. Stereoselective addition of vinylmagnesium bromide to the 1,3,4,5-tetra-*O*-benzyl-6,7-dideoxy-L-*xylo*-hept-6-en-2-ulose (**2**) gave diene **3** (86%). Ring-closing alkene metathesis of **3** in the presence of 0.15 equiv. of *Grubb*'s catalyst **1** gave the cyclohexene **4** (58%), that was converted into (+)-valienamine (**16**) in three steps and in 47% yield. Similarly, ring-closing alkene metathesis of the D-mannose-derived diene **20** gave the cyclohexene **21** (89%).

Introduction. – Glycosylamines and related *N*-glycosyl derivatives are of limited use as glycosidase inhibitors, due to their tendency to anomerise and to undergo hydrolysis. Carbocyclic analogues, such as (+)-valienamine (**16**), are exempt from this disadvantage. Thus, in our search for glycosidase inhibitors with improved characteristics as transition-state analogues [1–7], we became interested in the synthesis of six-membered carbasaccharides. A range of methods lead to monocyclic carbapyranoses [8a–q] (for older reviews on carbasugar synthesis, see [8r–u]). Among the newer methods, ring-closing alkene metathesis (RCM) [9–16] seems to be particularly promising. It has led to pyranoses [17], carbohydrate-derived oxepines [18] and indolizidines [19][20], pyranopyranoses [21], bridged [22][23] and chain-elongated [24][25] carbohydrates, a cyclohexene annulated to a pyranoside [26], a carbafuranose [27], and a couple of carbapyranoses [28][29]. We intended to synthesize carbocyclic glucose and mannose analogues by RCM, to prepare the required diene precursors diastereoselectively, to explore the influence of the configuration and steric hindrance on the RCM, and to apply the method to a synthesis of (+)-valienamine (**16**). (+)-Valienamine is accessible by microbial degradation [30] or NBS-cleavage [31][32] of validoxylamine A. It has been synthesized several times *de novo* [33–37] and from enantiomerically pure precursors [38–46]. The two most efficient routes appear to be the one by *Fukase* and *Horii* [45], who obtained **16** in eight steps and in 12% yield from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose *via* intramolecular *Horner-Emmons* alkenylation and the one by *Nicotra et al.* [44], who obtained **16** in five steps and in 22% yield from a cyclohexenone, that was prepared by a *Ferrier* cyclization from methyl 4,6-*O*-benzylidene-2,3-di-*O*-benzyl-α-D-glucopyranoside in six steps and in 57% yield [40][47].

---

[1]) Current address: Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Málaga, Campus de Teatinos, E-29071 Málaga.

Retrosynthetic analysis revealed the cyclohexene **4** as a key intermediate and the diene **3** as an appropriate starting material. This diene should be readily accessible from the known ketone **2** [48]. The reduction of a similar ketone possessing a nitrile function instead of the ethenyl moiety ($NaBH_4/CeCl_3$) proceeded with a diastereoselectivity of 86% [49][50], auguring well for a diastereoselective addition of vinylmagnesium bromide to **2**. The epimer **8** of **4** has been transformed by *Nicotra et al.* into (+)-valienamine [44] and by *McAuliffe* and *Stick* into a 4-epivalienamine derivative [51]. Several protected derivatives of **4** have been transformed into valiolamine derivatives [52].

Results and Discussion. – The ketone **2** is readily obtained from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose [48]. Addition of vinylmagnesium bromide to **2** in THF at $-78°$ gave the epimeric dienes **3** and **7** in 86 and 1% yield, respectively (*Scheme 1*). The constitution of the products is evidenced by their ^{1}H- and ^{13}C-NMR spectra. The configuration of **3** and **7** was tentatively assigned by analogy to the above mentioned reduction [49][50], where the nucleophile attacked preferentially from the *re* face.

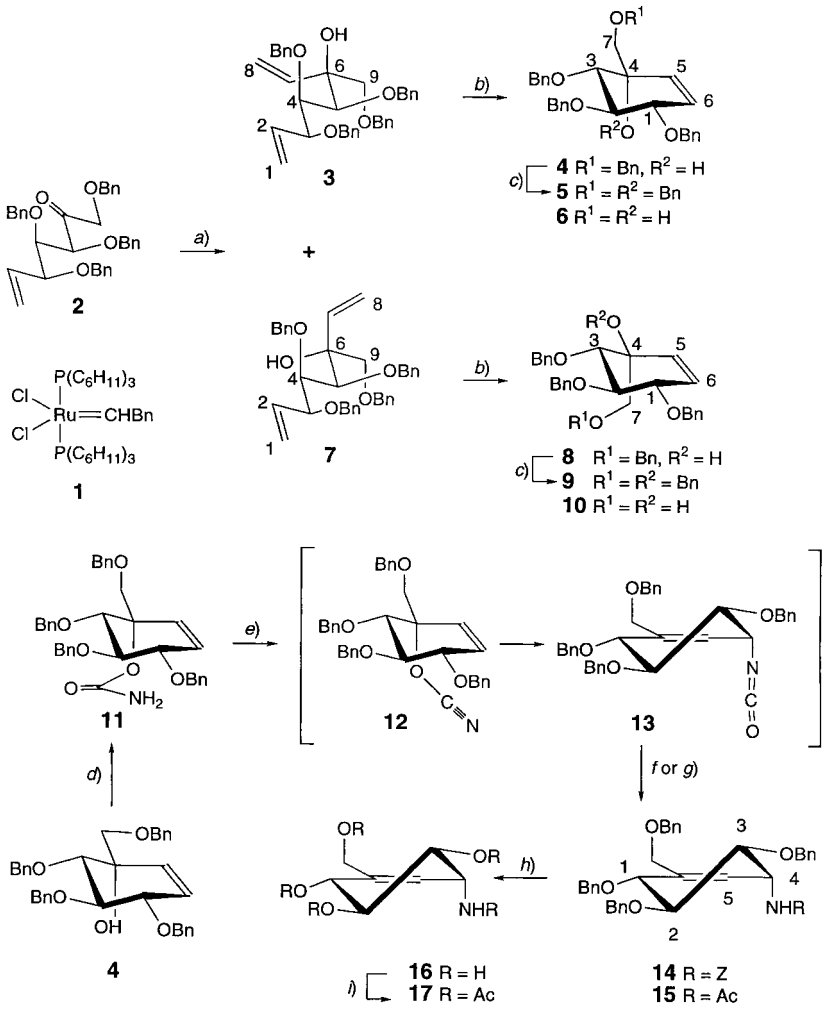
Ring-closing alkene metathesis of the homogeneous dienes **3** and **7** in the presence of *Grubb*'s catalyst **1** [53] (0.15 equiv. for **3**, 0.3 equiv. for **7**) gave the cyclohexenes **4** and **8** [44] in 58 and 66% yield, respectively. While the D-*gluco*-isomer **8** was colourless, the L-*ido*-isomer **4** was isolated as a green oil, contaminated with traces of ruthenium oxides. Benzylation of **4** and **8** gave the fully protected **5** and **9** in 88 and 49% yield, respectively. The optical rotation and ^{1}H-NMR spectrum of **8** matched the data reported by *Nicotra et al.* [44], thus establishing the (6*R*)-configuration of **7**, the (4*R*)-configuration of **8**, and, indirectly, the (6*S*)-configuration of **3** and the (4*S*)-configuration of **4**.

The vicinal coupling constants for the ring H of **4**, **5**, **8**, and **9** indicate a $^3H_2$ conformation[2]) (*Table 1*). The alkenyl H-atoms of **8** appear as a *s* at 5.74 ppm, while those of **4** appear as two *dd*'s at 5.92 (H–C(6)) and 5.69 ppm (H–C(5), $J(5,6) = 10.3$ Hz). The geminal coupling constants for H–C(7) of **4** and **5**, where the benzyloxymethyl ($BnOCH_2$) groups are pseudoequatorial, are smaller than those of the epimers **8** and **9** ($\Delta J = 0.6$ to 1.0 Hz), possessing pseudoaxial $BnOCH_2$ groups. This is rationalised by different rotameric equilibria (*Fig.*). Conformations **I** and **II** should be about equally populated in both epimeric series, while **III** is destabilized for **8** and **9**, but not for **4** and **5**. In conformation **III**, the tertiary OR group is g*auche* to both methylene H-atoms. It is known [54][55] that such an orientation of an electron-withdrawing substituent leads to a decreased (absolute) geminal coupling constant. Such a dependence of the geminal coupling constant on the configuration of the quarternary center of 1-(hydroxymethyl)cyclohex-2-en-1-ol derivatives has been reported by *Ogawa et al.* for **6** ($J(7,7') = 10.8$ Hz) and **10** ($J(7,7') = 11.8$ Hz) [56],

---

[2]) The systematic numbering differs between **4**, **6**, **8**, and **10** on the one hand, and **5** and **9** on the other; the locants of the cyclohexenes in *Scheme 1* used for the discussion of the conformation are those of the unprotected cyclohexenes **6** and **10** with the exception for the locant for the $HOCH_2$ group that is 7. Similarly, the $HOCH_2$ group of the dienes is designated as C(9).

Scheme 1



a) $H_2C{=}CHMgBr$, THF; 86% of **3**, 1% of **7**. *b*) **1**, CH_2Cl_2; 58% of **4**; 66% of **8**. *c*) NaH, DMF, then BnBr; 88% of **5**; 49% of **9**. *d*) CCl_3CONCO, CH_2Cl_2, then K_2CO_3, MeOH/H_2O; 86%. *e*) Ph_3P, Et_3N, CBr_4, CH_2Cl_2. *f*) BnOH; 70% of **14** (from **11**). *g*) Me_3Al; 77% of **15** (from **11**). *h*) **14**, Na, NH_3/THF; 78%. *i*) Ac_2O, pyridine; 86%.

and by *Tagmose* and *Bols* for the 1-deoxy analogues of **4** and **8** ($J(7,7')=8.5$ *vs.* 9.5 Hz)[3]), and for the corresponding acetates ($J(7,7')=8.5$ *vs.* 10 Hz) [57].[4])

[3]) The data for the 1-deoxy analogue of **8** ($J(2,3)=6.5$ Hz) indicate that it does not adopt a $^3H_2$ conformation.

[4]) *Paulsen* and co-workers [52] claimed a synthesis of **5** by benzylation of **6**, which was synthesized by stereoselective addition of a 2-lithio-1,3-dithian to (3*S*,4*R*,5*S*)-4,5,6-tris(benzyloxy)cyclohex-2-en-1-one. *Paulsen*'s data for **6** are at variance with the data reported by *Ogawa et al.* [56] for **6** and for **10**. Similarly, *Paulsen*'s data for **5** differ from our data for **5** and for **9**, the origin for the difference remaining unclear, as the original samples and spectra are no longer available. We thank Prof. Dr. *H. Paulsen* for pertinent discussions.

Table 1. *Selected NMR* ($CDCl_3$) *Chemical Shifts* [ppm], *Coupling Constants* [Hz], *and Optical Rotations* ($CHCl_3$) *of* **4**, **5**, **8**, **9**, *and* **21**[2])

	4	**5**[a])	**8**	**9**[a])	**21**
H–C(1)	4.20	4.19	4.20	4.22	4.16
H–C(2)	4.02	4.49	3.87	4.47–4.38	3.94
H–C(3)	3.76	3.97	3.76	3.97	4.26
H–C(5)	5.69	5.76	5.74	5.67	5.79
H–C(6)	5.92	5.90	5.74	5.84	5.95
H–C(7)	3.38	3.73	3.83	4.14	3.46
H′–C(7)	3.30	3.53	3.63	3.76	3.43
OH	2.80	–	2.74	–	3.10
C(4)	72.97	78.13	75.77	–[b])	73.08
J(1,2)	8.1	7.5	7.2	7.8	3.7
J(1,5)	2.2	1.9	0	2.2	0
J(1,6)	1.9	2.5	0	1.9	5.0
J(2,3)	10.3	10.6	10.3	10.3	9.7
J(5,6)	10.3	10.3	0	10.6	10.0
J(7,7′)	8.7	8.7	9.3	9.7	9.3
$[\alpha]_D^{25}$	70.8	20.1	8.7	26[c])	–35.2

[a]) In C_6D_6. [b]) Not determined. [c]) $[\alpha]_D^{20}$ Value.

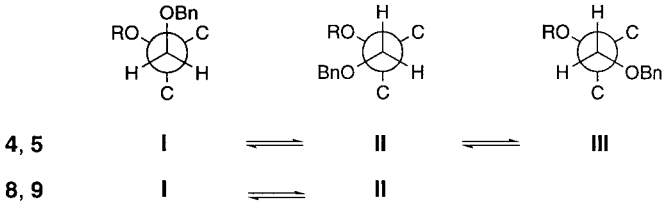


Figure. *Rotational equilibria for the BnOCH₂ group of* **4** *and* **5**, *and* **8** *and* **9**

To transform **4** into (+)-valienamine (**16**), we applied *Ichikawa*'s method for the conversion of allylic alcohols to allylic amines by a [3,3]-sigmatropic rearrangement of allylic cyanates [58–60] that has proven useful in the synthesis of 3-deoxyvalienamine [57].[5]) Thus, treatment of the tertiary allylic alcohol **4** with trichloroacetyl isocyanate in CH_2Cl_2 at 0°, followed by hydrolysis with K_2CO_3 in aqueous MeOH gave 86% of the carbamate **11**. Dehydration of **11** with Ph_3P, Et_3N, and CBr_4 in CH_2Cl_2 at –20° led to the isocyanate **13** by spontaneous rearrangement of the *bona fide* cyanate **12**. The isocyanate **13** was treated *in situ* with $PhCH_2OH$ to yield 70% of the protected (+)-valienamine **14**. Alternatively, *in situ* treatment of **13** with Me_3Al yielded 77% of *N*-acetyl-tetra-*O*-benzylvalienamine **15** [32]. Its ^{1}H- and ^{13}C-NMR spectra were identical to those of an authentic sample[6]), confirming the (4*S*)-configuration of **4** and the (6*S*)-configuration of **3**. The vicinal coupling constants for the ring H-atoms of **14** ($J(1,2) = 4.3$, $J(2,3) = 7.5$, $J(3,4) = 4.7$ Hz) and **15** ($J(1,2) = 4.1$, $J(2,3) = 7.2$, $J(3,4) = 4.7$ Hz) indicate an equilibrium of the $^3H_2$ and $^2H_3$ conformers. The vicinal coupling constants of

---

5) *Overman* rearrangement [61–64] of the trichloroacetimidate derived from **4** proceeded in low yields.

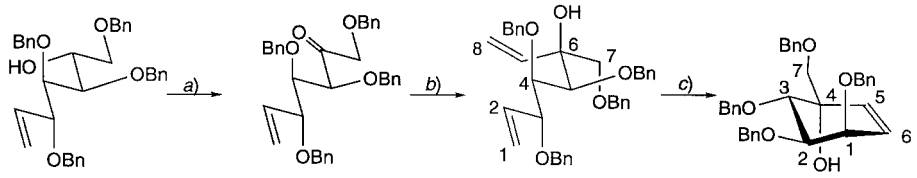
6) The authentic sample was prepared from validoxylamine A following the protocol of *Ogawa et al.* [32]. We thank Dr. *A. G. O'Sullivan, Novartis Agro*, Basel, for a generous gift of validoxylamine A.

the individual conformers ($^3H_2$: $J(1,2) = 2.8$, $J(2,3) = 4.2$, $J(3,4) = 2.8$ Hz; $^2H_3$: $J(1,2) = 7.8$, $J(2,3) = 9.8$, $J(3,4) = 4.3$ Hz) were calculated by gas-phase molecular modelling (Macromodel version 6.0, MM3* force-field [65]).

The benzyl carbamate **14** was readily deprotected under *Birch* conditions [45]. Workup following the procedure of *Paulsen* and *Heiker* [39] gave (+)-valienamine (**16**) in 78% yield as a slightly yellow solid. The optical rotation, and the ^{1}H- and ^{13}C-NMR spectra of **16** and of the pentaacetate **17** were in complete agreement with the published data [30][35][44][45][66].

For the synthesis of the D-mannose-derived L-*gulo*-configured **21**, we subjected *manno*-heptenitol **18** [67] to a *Moffatt* oxidation [68][69], similarly as described for the synthesis of **2** [48]. This gave the ketone **19** (87%; *Scheme 2*). Addition of vinylmagnesium bromide to **19** yielded 95% of the diene **20**. The diastereoselectivity of this addition was higher than that observed for the addition to **2**. Only traces of a by-product were detected on TLC. The configuration of **20** was assigned tentatively by analogy to that of **3**.

Scheme 2



18 **19** **20** **21**

a) DMSO, DCC, pyridine, CF_3CO_2H, toluene; 87%. *b*) $H_2C{=}CHMgBr$, THF; 95%. *c*) **1**, CH_2Cl_2; 89%.

The C(6)–OH signals of **20** and **3** are nearly isochronous. Their chemical shift is larger than that of **7** ($\Delta\delta$ *ca.* 0.65 ppm) (*Table 2*), indicating a stronger intramolecular H-bond. The IR bands (**3**: 3468, **20**: 3462 cm^{-1}) agree well with a six-membered intramolecular H-bond to BnO–C(4), and thus with the conformations depicted in *Schemes 1* and *2*. The chemical shift for C(6)–OH of **7** suggests a five-membered H-bond to BnO–C(9). This implies that H–C(9) of **3** and **20** (but not of **7**) are both g*auche* to the tertiary OH group (as in conformer **III** (*Fig.*) of **4** and **5**). Indeed, smaller (absolute) $J(9,9')$ values are observed for **3** and **20** (8.7 Hz) than for **7** (9.3 Hz). Thus, **20** should possess the same configuration at C(6) as **3**. In keeping with that, the difference between the optical rotation of **20** and **19** ($\Delta([\alpha]_D^{25}) = 40.7$) is very similar to that between **3** and **2** ($\Delta([\alpha]_D^{25}) = 34.5$).

RCM of **20** in the presence of 0.15 equiv. of **1** gave the cyclohexene **21** in 89% yield as a green oil. The vicinal coupling constants for the ring H of **21** indicate a $^3H_2$ conformation as in **4** (*Table 1*). The chemical shifts for H–C(7), H′–C(7), and C(6) of **21** show a stronger similarity to the values for **4** than to those for **8** (*Table 1*). In cyclohexanes, the C-atoms carrying an axial substituent absorb at higher field than those with equatorial substituents, and this effect is larger for oxy substituents than for alkyl substituents [70]. Thus, the upfield shift for C(6) of **4** and **21** as compared to **8** agrees with a pseudoaxial tertiary OH group. The assignment of the configuration of **21** was corroborated by a NOE experiment. Upon irradiation at 3.45 ppm (H–C(7) and

Table 2. *Selected NMR* ($CDCl_3$) *Chemical Shifts* [ppm], *Coupling Constants* [Hz], *and Optical Rotations* ($CHCl_3$) *of* **3**, **7**, *and* **20**[2])

	3	**7**	**20**
H–C(1)	5.30	5.26	5.47–5.42
H′–C(1)	5.20	5.25	5.47–5.42
H–C(2)	5.83	5.94	6.02–5.91
H–C(3)	4.07	4.09	4.05
H–C(4)	3.88–3.84	3.74–3.68	3.90
H–C(5)	3.88–3.84	3.99	4.07
H–C(9)	3.63	3.74–3.68	3.73
H′–C(9)	3.29	3.28	3.28
OH	3.74	3.09	3.75
J(1,2)	10.3	17.1	[a])
J(1′,2)	17.4	10.6	[a])
J(2,3)	7.8	7.5	7.5
J(3,4)	6.5	4.4	7.2
J(4,5)	3.5	5.9	2.5
J(9,9′)	8.7	9.3	8.7
$[\alpha]_D^{25}$	35.2	[a])	−4.5

[a]) Not determined.

H′–C(7) at 3.43 and 3.46 ppm), a NOE of 10% was observed for H–C(3), whereas no effect was observed for H–C(2).

The higher yield for the RCM of **20** as compared to the one of **3** is presumably due to the different conformational strain of the bicyclic intermediate of the cyclization. *Miller* and *Grubbs* have shown that the relative configuration of the centers between the reacting double bonds can have a profound effect on the RCM of a diene [71].

We thank the *Swiss National Science Foundation* and *F. Hoffmann-La Roche AG*, Basel, for generous support and Dr. *B. Bernet* for checking the manuscript.

Experimental Part

General. Solvents were freshly distilled from CaH_2 (CH_2Cl_2, MeOH, DMF) or Na/benzophenone (THF, toluene). All reactions were carried out under Ar, unless stated otherwise. Anal. TLC: *Merck* precoated silica gel *60 F-254* plates; detection by treatment with a soln. of 5% $(NH_4)_6Mo_7O_{26}\cdot 4H_2O$, 0.1% $Ce(SO_4)_2\cdot H_2O$, in 10% H_2SO_4 soln. Flash chromatography (FC): silica gel *60* (40–63 μm). M.p.: uncorrected. Optical rotations: 1-dm cell, 589 nm. FT-IR Spectra: absorption in cm^{-1}. NMR Spectra: chemical shifts in ppm relative to TMS (^1H, ^{13}C); coupling constants in Hz. NOE Experiments allowed unambiguous assignments of all ^1H-NMR signals of **4** and **21**, and HSQC.GRASP spectra unambiguous assignments of the ^{13}C-NMR signals of **4** and **21**. The assignments of the other cyclohexenes are based on comparisons with **4** and **21**. An * indicates that the assignments may be interchanged. MS: FAB in 3-nitrobenzyl alcohol (NOBA) matrix.

3,4,5-Tri-O-*benzyl-6*-C-*[(benzyloxy)methyl]-1,2,7,8-tetradeoxy*-D-gluco-*octa-1,7-dienitol* (**3**) *and 3,4,5-Tri*-O-*benzyl-6*-C-*[(benzyloxy)methyl]-1,2,7,8-tetradeoxy*-L-ido-*octa-1,7-dienitol* (**7**). A cooled (−78°) soln. of **2** (2.32 g, 4.32 mmol) in THF (43 ml) was treated dropwise with 1M vinylmagnesium bromide in THF (6.5 ml, 6.5 mmol), stirred for 45 min at this temp., warmed to 0°, and treated with Et_2O (80 ml) and sat. aq. NH_4Cl soln. (80 ml). The org. phase was separated, washed with brine (50 ml), dried ($MgSO_4$), and evaporated. FC (300 g of silica gel; hexane/AcOEt 6:1) of the oily residue (2.7 g) gave **7** (22 mg, 1%) and **3** (2.11 g, 86%).

Data of **3**: colourless oil. R_f (hexane/AcOEt 3:1) 0.57. $[\alpha]_D^{25} = 35.2$ ($c = 3.3$, $CHCl_3$). FT-IR (3%, $CHCl_3$): 3448*m*, 3089*w*, 3066*w*, 3007*m*, 2911*w*, 2866*m*, 1951*w*, 1873*w*, 1811*w*, 1732*w*, 1639*w*, 1604*w*, 1496*m*, 1454*m*, 1422*w*, 1398*w*, 1351*m*, 1093*s*, 1028*m*, 996*m*, 934*m*, 822*w*, 606*w*, 515*w*. ^1H-NMR (300 MHz, $CDCl_3$): 7.36–7.23 (*m*, 20 arom. H); 5.97 (*dd*, $J = 17.1$, 10.6, H–C(7)); 5.83 (*ddd*, $J = 17.4$, 10.3, 7.8, H–C(2)); 5.47 (*dd*, $J = 17.1$, 1.9,

H–C(8)); 5.30 (br. *dd*, *J* = 10.3, 1.9, H–C(1)); 5.20 (br. *dd*, *J* = 17.4, 1.9, H′–C(1)); 5.19 (*dd*, *J* = 10.6, 1.9, H′–C(8)); 4.84 (*d*, *J* = 11.2, PhC*H*); 4.78 (*d*, *J* = 11.5, PhC*H*); 4.65–4.61 (*m*, 3 PhC*H*); 4.48 (*d*, *J* = 12.1, PhC*H*); 4.43 (*d*, *J* = 11.8, PhC*H*); 4.35 (*d*, *J* = 11.8, PhC*H*); 4.07 (br. *dd*, *J* = 7.8, 6.5, H–C(3)); 3.88–3.84 (*m*, H–C(4), H–C(5)); 3.74 (*s*, OH); 3.63 (*d*, *J* = 8.7, CH–C(6)); 3.29 (*d*, *J* = 8.7, CH′–C(6)). ^{13}C-NMR (75 MHz, $CDCl_3$): 140.32 (*d*, C(7)); 139.05 (*s*); 138.56 (*s*); 138.47 (*s*); 138.34 (*s*); 135.67 (*d*, C(2)); 128.65–127.62 (several *d*); 119.66 (*t*, C(1)); 114.88 (*t*, C(8)); 81.83 (*d*); 81.23 (*d*); 78.35 (*d*); 77.98 (*s*, C(6)); 74.76 (*t*); 74.54 (*t*); 74.49 (*t*); 73.52 (*t*); 70.70 (*t*). FAB-MS (NOBA): 587 (9, $[M+Na]^+$), 565 (53, $[M+1]^+$), 457 (18, $[M-BnO]^+$), 267 (7), 241 (9), 197 (10), 181 (100), 173 (16), 154 (11), 147 (15), 107 (9). Anal. calc. for $C_{37}H_{40}O_5$ (564.72): C 78.70, H 7.14; found: C 78.87, H 7.35.

Data of **7**: colourless oil. R_f (hexane/AcOEt 3 : 1) 0.62. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.36–7.21 (*m*, 20 arom. H); 6.07 (*dd*, *J* = 17.4, 10.9, H–C(7)); 5.94 (*ddd*, *J* = 17.1, 10.6, 7.5, H–C(2)); 5.45 (*dd*, *J* = 17.4, 2.2, H–C(8)); 5.26 (br. *dd*, *J* = 17.1, 1.0, H–C(1)); 5.25 (br. *dd*, *J* = 10.6, 1.0, H′–C(1)); 5.23 (*dd*, *J* = 10.9, 2.2, H′–C(8)); 4.82 (*d*, *J* = 11.5, PhC*H*); 4.68 (*d*, *J* = 11.5, PhC*H*); 4.64 (*d*, *J* = 11.8, PhC*H*); 4.62–4.43 (*m*, 4 PhC*H*); 4.35 (*d*, *J* = 11.8, PhC*H*); 4.09 (br. *dd*, *J* = 7.5, 4.4, H–C(3)); 3.99 (*d*, *J* = 5.9, H–C(5)); 3.74–3.68 (*m*, H–C(4), CH–C(6)); 3.28 (*d*, *J* = 9.3, CH′–C(6)); 3.09 (*s*, OH). ^{13}C-NMR (75 MHz, $CDCl_3$): 139.43; 138.99; 138.52; 138.34; 138.03 (C(7)); 136.09 (C(2)); 128.62–127.45; 118.96 (C(1)); 115.92 (C(8)); 81.67; 80.83; 79.32; 74.78; 74.75; 74.65; 73.52; 70.64; *s* of C(6) hidden by noise or other signals.

*(Iᴅ)-(1,3,4/2)-1,2,3-Tri-*O*-benzyl-4-*C*-[(benzyloxy)methyl]cyclohex-5-ene-1,2,3,4-tetrol* (**4**). A soln. of **3** (2.20 g, 3.89 mmol) in CH_2Cl_2 (200 ml) was degassed by puckering with N_2, treated with **1** (0.48 g, 0.54 mmol), stirred at r.t. for 7 d, and evaporated. FC (300 g of silica gel; hexane/AcOEt 3 : 1) of the residual oil gave **3** (0.5 g, 23%) as a dark green oil and **4** (1.25 g) as a dark-green oil. An additional FC (150 g of silica gel, as above) of the latter gave **4** (1.2 g, 58%). Green oil. R_f (hexane/AcOEt 3 : 1) 0.33. $[\alpha]_D^{25} = 70.8$ ($c = 1.51$, $CHCl_3$). FT-IR (1.5%, $CHCl_3$): 3538*m*, 3089*m*, 3066*m*, 3008*m*, 2863*m*, 1951*w*, 1875*w*, 1811*w*, 1731*w*, 1604*w*, 1496*m*, 1454*m*, 1393*w*, 1361*m*, 1294*w*, 1136*m*, 1064*s*, 1028*m*, 929*w*, 912*w*, 857*w*, 628*w*, 609*w*, 548*w*, 537*w*, 525*w*, 518*w*, 511*w*, 503*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.37–7.16 (*m*, 20 arom. H); 5.92 (*dd*, *J* = 10.3, 1.9, H–C(6)); 5.69 (*dd*, *J* = 10.3, 2.2, H–C(5)); 4.95 (*d*, *J* = 10.9, PhC*H*); 4.93 (*d*, *J* = 10.9, PhC*H*); 4.86 (*d*, *J* = 11.2, PhC*H*); 4.72 (*s*, PhCH_2); 4.48 (*d*, *J* = 12.5, PhC*H*); 4.46 (*d*, *J* = 10.9, PhC*H*); 4.38 (*d*, *J* = 12.1, PhC*H*); 4.20 (*dt*, *J* = 8.1, 2.1, irrad. at 5.92 → NOE of 6%, H–C(1)); 4.02 (*dd*, *J* = 10.3, 8.1, H–C(2)); 3.76 (*d*, *J* = 10.3, H–C(3)); 3.38 (*d*, *J* = 8.7, CH–C(4)); 3.30 (*d*, *J* = 8.7, irrad. at 5.69 → NOE of 3%, CH′–C(4)); 2.80 (*s*, OH). ^{13}C-NMR (75 MHz, $CDCl_3$, assignment based on HSQC.GRASP): 139.09 (*s*); 138.75 (*s*); 138.34 (*s*); 138.03 (*s*); 131.24 (*d*, C(6)); 129.86 (*d*, C(5)); 128.67–127.79 (several *d*); 81.57 (*d*, C(2)); 80.28 (*d*, C(1)); 78.39 (*d*, C(3)); 75.85 (*t*); 75.51 (*t*); 73.53 (*t*, CH_2–C(4)); 73.47 (*t*); 72.97 (*s*, C(4)); 72.01 (*t*). FAB-MS (NOBA): 559 (6, $[M+Na]^+$), 535 (15, $[M-1]^+$), 519 (36, $[M-OH]^+$), 429 (5, $[M-BnO]^+$), 412 (15, $[M-OH-BnO]^+$), 411 (17, $[M-H_2O-BnO]^+$), 321 (26), 297 (17), 291 (11), 271 (15), 213 (17), 197 (12), 181 (100). Anal. calc. for $C_{35}H_{36}O_5$ (536.67): C 78.33, H 6.76; found: C 78.42, H 6.91.

*(Iʟ)-(1,2,4/3)-1,2,3,4-Tetra-*O*-benzyl-1-*C*-[(benzyloxy)methyl]cyclohex-5-ene-1,2,3,4-tetrol* (**5**). A cooled (0°) suspension of oil-free NaH (washed with hexane, 25 mg, 1.04 mmol) in DMF (5 ml) was treated with a soln. of **4** (257 mg, 0.48 mmol) in DMF (6 ml) and stirred for 30 min. After warming to r.t., the mixture was treated with BnBr (85 µl, 0.72 mmol), stirred for 3.5 h, treated carefully with MeOH (0.3 ml), and diluted with AcOEt (40 ml). The org. phase was separated, washed with H_2O (3 × 10 ml), dried (Na_2SO_4), and evaporated. FC (40 g of silica gel; hexane/AcOEt 10 : 1) of the oily residue gave **5** (264 mg, 88%). Colourless oil. R_f (hexane/AcOEt 9 : 1) 0.20. $[\alpha]_D^{20} = 20.1$ ($c = 0.50$, $CHCl_3$). FT-IR (1.5%, $CHCl_3$): 3089*w*, 3066*m*, 3008*m*, 2913*m*, 2865*m*, 1951*w*, 1876*w*, 1811*w*, 1711*w*, 1604*w*, 1496*m*, 1454*m*, 1361*m*, 1309*w*, 1140*m*, 1093*s*, 1067*s*, 1028*m*, 911*w*, 855*w*, 607*w*, 552*w*, 530*w*, 514*w*. ^{1}H-NMR (300 MHz, C_6D_6): 7.42–7.04 (25 arom. H); 5.90 (*dd*, *J* = 10.3, 2.5, H–C(5)); 5.76 (*dd*, *J* = 10.3, 1.9, H–C(6)); 5.07 (*d*, *J* = 11.5, PhC*H*); 4.96 (*d*, *J* = 11.5, PhC*H*); 4.89 (*d*, *J* = 11.5, PhC*H*); 4.76–4.64 (*m*, 3 PhC*H*); 4.61 (*d*, *J* = 12.1, PhC*H*); 4.55 (*d*, *J* = 12.1, PhC*H*); 4.49 (*dd*, *J* = 10.6, 7.5, H–C(3)); 4.23 (*d*, *J* = 12.1, PhC*H*); 4.19 (*dt*, *J* = 7.5, 2.2, H–C(4)); 4.18 (*d*, *J* = 12.1, PhC*H*); 3.97 (*d*, *J* = 10.6, H–C(2)); 3.73 (*d*, *J* = 8.7, CH–C(1)); 3.53 (*d*, *J* = 8.7, CH′–C(1)). ^{13}C-NMR (75 MHz, $CDCl_3$): 140.33 (*s*); 139.91 (*s*); 139.15 (*s*); 138.79 (*s*); 138.16 (*s*); 132.40 (*d*, C(5)); 129.72 (*d*, C(6)); 128.65–127.44 (several *d*); 81.98 (*d*); 80.73 (*d*); 80.00 (*d*); 78.13 (*s*, C(1)); 75.75 (*t*); 75.30 (*t*); 73.40 (*t*); 72.13 (*t*); 71.69 (*t*); 66.84 (*t*). FAB-MS (NOBA): 625 (11, $[M-1]^+$), 519 (18, $[M-BnO]^+$), 412 (25, $[M-BnO-BnO]^+$), 321 (17), 291 (7), 271 (19), 213 (14), 197 (20), 181 (100). Anal. calc. for $C_{42}H_{42}O_5$ (626.79): C 80.48, H 6.75; found: C 80.35, H 6.61.

*(Iᴅ)-(1,3/2,4)-1,2,3-Tri-*O*-benzyl-4-*C*-[(benzyloxy)methyl]cyclohex-5-ene-1,2,3,4-tetrol* (**8**) [44]. A soln. of **7** (22 mg, 0.04 mmol) in CH_2Cl_2 (5 ml) was degassed by puckering with N_2, treated with **1** (10 mg, 0.012 mmol), stirred at r.t. for 5 d, and evaporated. FC (5 g of silica gel; hexane/AcOEt 4 : 1) of the residual oil gave 18 mg of a green oil, which was subjected to an additional FC (as above) yielding **8** (14 mg, 66%). Colourless oil. R_f

(hexane/AcOEt 3:1) 0.31. $[\alpha]_D^{25} = 8.7$ ($c = 1.01$, $CHCl_3$; [44]: $[\alpha]_D = 8.5$ ($c = 1$, $CHCl_3$)). FT-IR (1%, $CHCl_3$): 3553*m*, 3089*w*, 3066*w*, 3007*m*, 2866*m*, 1951*w*, 1811*w*, 1603*w*, 1497*m*, 1454*m*, 1360*m*, 1329*w*, 1090*s*, 1069*s*, 1028*m*, 930*w*, 911*w*, 609*w*, 515*w*, 507*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see [44]. ^{13}C-NMR (75 MHz, $CDCl_3$): 138.79 (*s*); 138.61 (*s*); 138.34 (*s*); 137.93 (*s*); 131.93 (*d*, C(6)*); 128.42–127.60 (several *d*); 126.59 (*d*, C(5)*); 83.97 (*d*); 81.69 (*d*); 79.68 (*d*); 75.77 (*s*, C(4)); 75.69 (*t*); 75.14 (*t*); 73.99 (*t*); 73.78 (*t*); 73.13 (*t*). FAB-MS (NOBA): 756 (7), 663 (11), 559 (15, $[M+Na]^+$), 535 (29, $[M-1]^+$), 519 (100, $[M-OH]^+$), 429 (11, $[M-BnO]^+$), 412 (17, $[M-BnO-OH]^+$), 321 (14), 296 (10), 271 (12), 231 (6), 213 (8), 181 (89).

(1D)-(1,3/2,4)-1,2,3,4-Tetra-O-*benzyl-1*-C-*[(benzyloxy)methyl]cyclohex-5-ene-1,2,3,4-tetrol* (**9**). A cooled (0°) soln. of **8** (7.5 mg, 14 μmol) in DMF (1.5 ml) was treated with NaH (60% suspension in oil, 5 mg, 125 μmol), stirred for 30 min, treated with BnBr (30 μl, 250 μmol), allowed to warm to r.t., and stirred for 4 h. The mixture was treated with MeOH (0.1 ml), diluted with AcOEt (20 ml), washed with H_2O (2 × 5 ml), brine (5 ml), dried (Na_2SO_4), and evaporated. FC (10 g of silica gel, hexane/AcOEt 10:1) gave **9** (4.3 mg, 49%). Colourless oil. R_f (hexane/AcOEt 9:1) 0.24. $[\alpha]_D^{20} = 26$ ($c = 0.2$, $CHCl_3$). ^{1}H-NMR (300 MHz, C_6D_6): 7.42–7.08 (25 arom. H); 5.84 (*dd*, *J* = 10.6, 1.9, H–C(5)); 5.67 (*dd*, *J* = 10.6, 2.2, H–C(6)); 5.04 (*d*, *J* = 11.5, PhC*H*); 4.91 (*d*, *J* = 11.5, PhC*H*); 4.86 (*s*, PhCH_2); 4.65 (*d*, *J* = 12.1, PhC*H*); 4.59 (*d*, *J* = 12.1, PhC*H*); 4.47–4.38 (*m*, 2 PhC*H*, H–C(3)); 4.36 (*d*, *J* = 11.8, PhC*H*); 4.27 (*d*, *J* = 11.8, PhC*H*); 4.22 (*dt*, *J* = 7.8, 2.2, H–C(4)); 4.14 (*d*, *J* = 9.7, CH–C(1)); 3.97 (*d*, *J* = 10.3, H–C(2)); 3.76 (*d*, *J* = 9.7, CH′–(1)).

(1D)-(1,3,4/2)-1,2,3-Tri-O-*benzyl-4*-C-*[(benzyloxy)methyl]-4*-O-*carbamoylcyclohex-5-ene-1,2,3,4-tetrol* (**11**). A cooled (0°) soln. of **4** (300 mg, 0.56 mmol) in CH_2Cl_2 (5 ml) was treated dropwise with CCl_3CONCO (133 μl, 1.12 mmol), stirred for 30 min at this temp., and evaporated. The residue, dissolved in MeOH (10 ml) and H_2O (1 ml), was cooled to 0°, treated with K_2CO_3 (0.24 g, 1.72 mmol), and stirred for 100 min at 0° and 100 min at r.t.. After evaporation of MeOH, the aq. soln. was diluted with H_2O (10 ml) and extracted with CH_2Cl_2 (4 × 15 ml). The combined org. phases were washed with brine (10 ml), dried ($MgSO_4$), and evaporated. FC (30 g of silica gel, hexane/AcOEt 5:2) of the resulting oil (394 mg) gave **11** (281 mg, 86%). Colourless oil. R_f (hexane/AcOEt 2:1) 0.24. $[\alpha]_D^{25} = 36.6$ ($c = 0.50$, $CHCl_3$). FT-IR (0.5%, $CHCl_3$): 3543*m*, 3428*m*, 3089*w*, 3066*w*, 3008*m*, 2939*m*, 2866*m*, 1952*w*, 1810*w*, 1729*s*, 1582*s*, 1497*m*, 1454*m*, 1357*s*, 1281*w*, 1175*w*, 1143*m*, 1091*s*, 1059*s*, 1028*m*, 930*w*, 911*w*, 629*w*, 606*w*, 554*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.38–7.20 (*m*, 20 arom. H); 6.34 (*dd*, *J* = 10.3, 1.9, H–C(6)); 5.95 (*dd*, *J* = 10.3, 2.5, H–C(5)); 4.91 (*s*, PhCH_2); 4.90 (*d*, *J* = 10.9, PhC*H*); 4.70 (*s*, PhCH_2); 4.58 (*d*, *J* = 10.9, PhC*H*); 4.51 (*d*, *J* = 12.1, PhC*H*); 4.40 (*d*, *J* = 12.1, PhC*H*); 4.60–4.49 (br., NH_2); 4.23 (*d*, *J* = 8.1, CH–C(4)); 4.22 (*dt*, *J* = 7.2, 2.2, H–C(1)); 4.16 (*dd*, *J* = 10.0, 7.2, H–C(2)); 3.90 (*d*, *J* = 10.0, H–C(3)); 3.85 (*d*, *J* = 8.1, CH′–C(4)). ^{13}C-NMR (75 MHz, $CDCl_3$): 155.60 (*s*, C=O); 139.12 (*s*); 138.62 (*s*); 138.52 (*s*); 138.02 (*s*); 131.58 (*d*, C(6)); 129.52 (*d*, C(5)); 128.72–127.79 (several *d*); 81.56 (*d*, C(2)); 81.02 (*s*, C(4)); 80.55 (*d*, C(1)); 78.77 (*d*, C(3)); 76.17 (*t*); 75.26 (*t*); 73.61 (*t*); 72.13 (*t*); 69.02 (*t*). FAB-MS (NOBA): 602 (11, $[M+Na]^+$), 580 (7, $[M+1]^+$), 519 (59, $[M-NH_2CO_2]^+$), 472 (95, $[M-BnO]^+$), 411 (66, $[M-BnOH-NH_2CO_2]^+$), 321 (19), 213 (23), 197 (13), 181 (100), 154 (45), 136 (34), 123 (18), 107 (19). Anal. calc. for $C_{36}H_{37}NO_6$ (579.69): C 74.59, H 6.43, N 2.42; found: C 74.52, H 6.49, N 2.41.

(1L)-(1,3,4/2)-1,2,3-Tri-O-*benzyl-4-[(benzyloxycarbonyl)amino]-6-[(benzyloxy)methyl]cyclohex-5-ene-1,2,3-triol* (**14**). A cooled (−20°) soln. of **11** (228 mg, 0.39 mmol), Ph_3P (258 mg, 0.98 mmol) and Et_3N (110 μl, 0.79 mmol) in CH_2Cl_2 (4.5 ml) was treated dropwise with a soln. of CBr_4 (365 mg, 1.10 mmol) in CH_2Cl_2 (2.1 ml), stirred for 1 h at −20°, treated dropwise with BnOH (326 μl, 3.15 mmol), and allowed to warm to r.t. overnight. The mixture was poured into H_2O (10 ml). The org. phase was separated and the aq. phase extracted with CH_2Cl_2 (4 × 10 ml). The combined org. phases were washed with brine (10 ml), dried (Na_2SO_4), and evaporated. FC (35 g of silica gel; hexane/AcOEt 9:2) of the resulting oil (1.4 g) gave a mixture of **14** and BnOH. Removal of BnOH in h.v. at 60° gave pure **14** (184 mg, 70%). Colourless oil. R_f (hexane/AcOEt 3:1) 0.43. $[\alpha]_D^{25} = 30.9$ ($c = 1.51$, $CHCl_3$). FT-IR (1.5%, $CHCl_3$): 3439*m*, 3089*w*, 3067*m*, 3008*m*, 2865*m*, 1952*w*, 1876*w*, 1810*w*, 1717*s*, 1604*w*, 1498*s*, 1454*m*, 1366*w*, 1331*m*, 1294*m*, 1144*m*, 1068*s*, 1028*m*, 911*w*, 604*w*, 544*w*, 536*w*, 520*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.38–7.23 (*m*, 25 arom. H); 5.81 (br. *d*, *J* = 3.1, H–C(5)); 5.11 (*s*, PhCH_2OC=O); 5.07 (*d*, *J* = 9.7, NH); 4.77–4.63 (*m*, 2 PhC*H*, H–C(4)); 4.60 (*s*, PhCH_2); 4.59 (*d*, *J* = 11.2, PhC*H*); 4.57 (*d*, *J* = 11.5, PhC*H*); 4.49 (*d*, *J* = 11.8, PhC*H*); 4.40 (*d*, *J* = 11.8, PhC*H*); 4.24 (*d*, *J* = 12.1, CH–C(6)); 4.05 (br. *d*, *J* = 4.3, H–C(1)); 3.90 (*d*, *J* = 12.1, CH′–C(6)); 3.81 (*dd*, *J* = 7.5, 4.7, H–C(3)); 3.73 (br. *dd*, *J* = 7.5, 4.3, H–C(2)). ^{13}C-NMR (75 MHz, $CDCl_3$): 156.41 (*s*, C=O); 138.50 (*s*); 138.41 (*s*); 138.12 (*s*); 137.35 (*s*); 136.80 (*s*); 1*s* hidden by noise or other signals; 128.76–127.87 (several *d*); 125.40 (*d*, C(5)); 77.26 (*d*); 76.33 (*d*); 75.96 (*d*); 74.42 (*t*); 73.84 (*t*); 72.30 (*t*); 72.13 (*t*); 70.62 (*t*, CH_2–C(6)); 66.92 (*t*, $COOCH_2Ph$); 47.20 (*d*, C(4)). FAB-MS (NOBA): 670 (9, $[M+1]^+$), 562 (100, $[M-BnO]^+$), 534 (6), 518 (7, $[M-BnOCO_2]^+$), 472 (9), 429 (12), 181 (33). Anal. calc. for $C_{43}H_{43}NO_6$ (669.82): C 77.11, H 6.47, N 2.09; found: C 77.10, H 6.25, N 2.09.

*(1L)-(1,3,4/2)-4-Acetamido-1,2,3-tri-*O*-benzyl-6-[(benzyloxy)methyl]cyclohex-5-ene-1,2,3-triol* (**15**) [32]. A cooled (−20°) soln. of **11** (260 mg, 0.45 mmol), Ph_3P (296 mg, 1.13 mmol) and Et_3N (126 µl, 0.90 mmol) in CH_2Cl_2 (5 ml) was treated dropwise with a soln. of CBr_4 (420 mg, 1.27 mmol) in CH_2Cl_2 (2.4 ml), stirred for 1 h at this temp., and treated dropwise with 2.0M Me_3Al in heptane (1.8 ml, 3.62 mmol). After stirring for 1 h at −20°, the mixture was treated carefully with MeOH (2 ml), CH_2Cl_2 (5 ml), and 0.2M HCl (10 ml), and allowed to warm to 0°. The org. phase was separated and the aq. phase extracted with CH_2Cl_2 (6 × 10 ml). The combined organic phases were washed with brine (10 ml), dried ($MgSO_4$), and evaporated. FC (30 g of silica gel; hexane/AcOEt 1:1) of the resulting oil (1.1 g) gave **15** (200 mg, 77%). Colourless oil. R_f (hexane/AcOEt 1:1) 0.21. $[\alpha]_D^{23} = 23.4$ ($c = 1.01$, $CHCl_3$; [32]: $[\alpha]_D^{23} = 22$ ($c = 1$, $CHCl_3$)). FT-IR (0.6%, $CHCl_3$): 3438*m*, 3065*w*, 3008*m*, 2976*m*, 2895*m*, 1667*m*, 1603*w*, 1498*m*, 1454*m*, 1390*m*, 1370*m*, 1297*w*, 1146*w*, 1048*s*, 877*m*, 847*w*, 600*w*, 522*w*, 506*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.36–7.25 (*m*, 20 arom. H); 5.76 (*d*, $J = 3.7$, H−C(5)); 5.69 (*d*, $J = 9.0$, NH); 4.96–4.93 (*m*, H−C(4)); 4.74 (*d*, $J = 11.5$, PhC*H*); 4.70 (*d*, $J = 10.3$, PhC*H*); 4.62 (*d*, $J = 11.2$, PhC*H*); 4.60 (*d*, $J = 12.1$, PhC*H*); 4.58 (*d*, $J = 11.5$, PhC*H*); 4.54 (*d*, $J = 11.5$, PhC*H*); 4.49 (*d*, $J = 12.1$, PhC*H*); 4.40 (*d*, $J = 11.8$, PhC*H*); 4.27 (*d*, $J = 12.1$, CH−C(6)); 4.07 (br. *d*, $J = 4.1$, H−C(1)); 3.90 (*d*, $J = 12.1$, CH′−C(6)); 3.82 (*dd*, $J = 7.2$, 4.1, H−C(2)); 3.73 (*dd*, $J = 7.2$, 4.7, H−C(3)); 1.93 (*s*, Ac). ^{13}C-NMR (75 MHz, $CDCl_3$): 169.92 (*s*, C=O); 138.49 (*s*); 138.45 (*s*); 138.41 (*s*); 138.07 (*s*); 137.01 (*s*, C(6)); 128.73–127.86 (several *d*); 125.61 (*d*, C(5)); 76.91 (*d*); 75.94 (*d*), 75.62 (*d*); 74.50 (*t*); 73.65 (*t*); 72.16 (*t*); 72.04 (*t*); 70.67 (*t*, CH_2−C(6)); 45.19 (*d*, C(4)); 23.49 (*q*, Me). FAB-MS (NOBA): 1155 (8, $[2M+1]^+$), 600 (11, $[M+Na]^+$), 578 (98, $[M+1]^+$), 471 (100, $[M+1-BnO]^+$), 380 (46), 363 (20), 337 (20), 272 (16), 254 (41), 242 (11), 228 (19), 212 (32), 181 (87), 164 (61), 154 (75), 150 (42), 138 (58), 136 (74), 107 (23).

(1L)-(1,3,4/2)-4-Amino-6-(hydroxymethyl)cyclohex-5-ene-1,2,3-triol (*(+)-Valienamine*, **16**) [39][45][66] *and (1L)-(1,3,4/2)-4-Acetamido-1,2,3-tri-*O*-acetyl-6-[(acetyloxy)methyl]cyclohex-5-ene-1,2,3-triol* (**17**) [35][37][44]. At −78°, NH_3 (20 ml) was condensed into a soln. of **14** (145 mg, 0.22 mmol) in THF (5 ml). The soln. was treated with Na in small pieces (*ca.* 30 mg), until the blue colour of the soln. persisted. After stirring for 2 h at −78°, the mixture was treated with NH_4Cl (220 mg), stirred at r.t. overnight, and evaporated. The residue was dried in h.v., extracted with abs. MeOH, filtered, and evaporated. The resulting residue was extracted with EtOH, filtered, and evaporated. The residue (66 mg) was adsorbed on 3 ml of neutral *Dowex 50-WX-8* (washed with H_2O). After washing with H_2O (30 ml), elution with 2% aq. NH_3 gave **16** (30 mg, 78%). Slightly yellow solid. $[\alpha]_D^{25} = 79.3$ ($c = 1.5$, H_2O; [66]: $[\alpha]_D^{25} = 81.6$ (H_2O)). ^{1}H-NMR (300 MHz, D_2O): see [45]. ^{13}C-NMR (75 MHz, D_2O): see [66]. Conventional acetylation of **16** gave, after FC, **17** (55 mg, 86%). Colourless crystals (Et_2O). R_f (toluene/acetone 7:2) 0.08. M.p. 94–95° ([35]: 92.5–95° (EtOH/toluene)). $[\alpha]_D^{25} = 26.3$ ($c = 1.02$, $CHCl_3$; [44]: $[\alpha]_D = 24$ ($c = 1$, $CHCl_3$)). ^{1}H-(300 MHz, $CDCl_3$) and ^{13}C-NMR (75 MHz, $CDCl_3$): see [37]. FAB-MS (NOBA): 771 (21, $[2M+1]^+$), 386 (41, $[M+1]^+$), 326 (100, $[M-AcO]^+$), 284 (7), 206 (7), 164 (12), 122 (12).

*1,3,4,5-Tetra-*O*-benzyl-6,7-dideoxy-*D-arabino*-hept-6-en-2-ulose* (**19**). A soln. of **18** [67] (1.86 g, 3.45 mmol) in toluene (6.7 ml) was treated with dicyclohexyl carbodiimide (1.67 g, 8.09 mmol), DMSO (0.93 ml, 17.60 mmol), and pyridine (0.37 ml, 4.58 mmol), and then dropwise with CF_3COOH (0.37 ml, 3.32 mmol), and stirred for 4 h. The mixture was treated with H_2O (2 ml), Et_2O (9.5 ml), and filtered through *Celite*. The filter residue was washed with Et_2O (25 ml). The filtrate was washed with 1M HCl (2 × 10 ml), sat. aq. $NaHCO_3$ soln. (20 ml), and brine (20 ml), dried (Na_2SO_4), and evaporated. FC (110 g of silica gel; hexane/AcOEt 6:1) of the residue (2.6 g) gave **19** (1.58 g, 87%). Colourless oil. R_f (hexane/AcOEt 3:1) 0.59. $[\alpha]_D^{25} = -39.8$ ($c = 1.52$, $CHCl_3$). FT-IR (1.5%, $CHCl_3$): 3089*m*, 3067*m*, 3008*m*, 2868*m*, 1952*w*, 1874*w*, 1811*w*, 1728*s*, 1604*w*, 1497*m*, 1454*m*, 1422*w*, 1391*w*, 1336*w*, 1306*w*, 1171*w*, 1072*s*, 1028*m*, 996*m*, 936*m*, 908*w*, 818*w*, 651*w*, 601*w*, 538*w*, 520*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.35–7.16 (20 arom. H); 5.89 (*ddd*, $J = 17.4$, 10.3, 7.8, H−C(6)); 5.50–5.41 (*m*, 2 H−C(7)); 4.61–4.55 (*m*, 2 H); 4.48–4.29 (*m*, 7 H); 4.23–4.17 (*m*, 2 H); 4.08 (br. *t*, $J = 8.1$, H−C(5)); 3.92 (*dd*, $J = 8.4$, 3.4, H−C(4)). ^{13}C-NMR (75 MHz, $CDCl_3$): 209.33 (*s*, C(2)); 138.34 (*s*); 137.82 (*s*); 137.63 (*s*); 137.29 (*s*); 136.17 (*d*, C(6)); 128.75–127.84 (several *d*); 120.69 (*t*, C(7)); 84.37 (*d*); 82.56 (*d*); 79.60 (*d*); 75.09 (*t*); 74.71 (*t*); 74.55 (*t*); 73.37 (*t*); 70.17 (*t*). FAB-MS (NOBA): 559 (86, $[M+Na]^+$), 537 (43, $[M+1]^+$), 536 (36, $[M]^+$), 535 (26, $[M-1]^+$), 429 (96, $[M-BnO]^+$), 271 (31), 181 (100). Anal. calc. for $C_{35}H_{36}O_5$ (536.67): C 78.33, H 6.76; found: C 78.29, H 6.75.

*3,4,5-Tri-*O*-benzyl-6-*C*-[(benzyloxy)methyl]-1,2,7,8-tetradeoxy-*D-manno*-octa-1,7-dienitol* (**20**). A cooled (−78°) soln. of **19** (1.49 g, 2.77 mmol) in THF (31 ml) was treated dropwise with 1M vinylmagnesium bromide in THF (4.15 ml, 4.15 mmol), stirred for 85 min, treated with Et_2O (40 ml), warmed to 0°, and treated with sat. aq. NH_4Cl soln. (40 ml). The org. phase was separated and the aq. phase extracted with Et_2O (2 × 20 ml). The combined org. phases were washed with brine (30 ml), dried (Na_2SO_4), and evaporated. FC (110 g of silica gel; hexane/AcOEt 6.5:1) of the oily residue (1.85 g) gave **20** (1.49 g, 95%). Colourless oil. R_f (hexane/AcOEt 3:1) 0.64. $[\alpha]_D^{25} = -4.5$ ($c = 1.5$, $CHCl_3$). FT-IR (1.5%, $CHCl_3$): 3462*m*, 3089*m*, 3066*m*, 3008*m*, 2909*m*, 1951*w*, 1870*w*,

1810*w*, 1749*w*, 1700*w*, 1637*w*, 1605*w*, 1558*w*, 1497*m*, 1454*m*, 1420*w*, 1397*m*, 1348*m*, 1307*w*, 1091*s*, 1028*s*, 1000*m*, 934*m*, 634*w*, 602*w*, 580*w*, 564*w*, 550*w*, 544*w*, 534*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.36–7.22 (20 arom. H); 6.18 (*dd*, *J* = 17.4, 10.9, H–C(7)); 6.02–5.91 (*m*, H–C(2)); 5.56 (*dd*, *J* = 17.4, 1.9, H–C(8)); 5.47–5.42 (*m*, 2 H–C(1)); 5.26 (*dd*, *J* = 10.9, 1.9, H′–C(8)); 4.71 (*d*, *J* = 10.6, PhC*H*); 4.72–4.52 (*m*, 4 PhC*H*); 4.49 (*d*, *J* = 11.8, PhC*H*); 4.43 (*d*, *J* = 12.1, PhC*H*); 4.24 (*d*, *J* = 11.8, PhC*H*); 4.07 (*d*, *J* = 2.5, H–C(5)); 4.05 (br. *t*, *J* = 7.5, H–C(3)); 3.90 (*dd*, *J* = 7.2, 2.5, H–C(4)); 3.75 (*s*, OH); 3.73 (*d*, *J* = 8.7, CH–C(6)); 3.28 (*d*, *J* = 8.7, CH′–C(6)). ^{13}C-NMR (75 MHz, $CDCl_3$): 140.72 (*d*, C(7)); 138.97 (*s*); 138.55 (*s*); 138.49 (*s*); 138.34 (*s*); 136.35 (*d*, C(2)); 128.63–127.63 (several *d*); 120.22 (*t*, C(1)); 114.87 (*t*, C(8)); 81.46 (*d*); 81.04 (*d*); 78.56 (*d*); 78.05 (*s*, C(6)); 75.09 (*t*); 74.97 (*t*); 73.61 (*t*); 73.37 (*t*); 70.05 (*t*). FAB-MS (NOBA): 1129 (3, $[2M+1]^+$), 587 (8, $[M+Na]^+$), 565 (100, $[M+1]^+$), 457 (27, $[M-BnO]^+$), 181 (15). Anal. calc. for $C_{37}H_{40}O_5$ (564.72): C 78.70, H 7.14; found: C 78.60, H 7.12.

(1L)-(1,2/3,4)-1,2,3-Tri-O-*benzyl-4*-C-*[(benzyloxy)methyl]cyclohex-5-ene-1,2,3,4-tetrol* (**21**). A soln. of **20** (2.20 g, 3.89 mmol) in CH_2Cl_2 (200 ml, degassed by puckering with N_2) was treated with **1** (480 mg, 0.58 mmol), stirred for 4 d under N_2, and concentrated. FC (250 g of silica gel; hexane/AcOEt 4 : 1) of the oily residue gave **21** (1.85 g, 89%). Green oil. R_f (cyclohexane/AcOEt 3:1) 0.44. $[\alpha]_D^{25} = -35.2$ (*c* = 1.5, $CHCl_3$). FT-IR (1.5%, $CHCl_3$): 3532*m*, 3089*m*, 3066*m*, 3008*m*, 2864*m*, 1951*w*, 1877*w*, 1811*w*, 1737*w*, 1604*w*, 1496*m*, 1454*m*, 1368*m*, 1306*m*, 1098*s*, 1028*m*, 913*w*, 855*w*, 636*w*, 601*w*, 563*w*, 536*w*, 524*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.41–7.22 (20 arom. H); 5.95 (*dd*, *J* = 10.0, 5.0, H–C(6)); 5.79 (*d*, *J* = 10.0, irrad. at 3.45 → NOE of 5%, H–C(5)); 4.97 (*d*, *J* = 10.9, PhC*H*); 4.77 (*d*, *J* = 12.1, PhC*H*); 4.75–4.67 (*m*, 3 PhC*H*); 4.59 (*d*, *J* = 10.9, PhC*H*); 4.57 (*d*, *J* = 12.1, PhC*H*); 4.46 (*d*, *J* = 12.1, PhC*H*); 4.26 (*d*, *J* = 9.7, irrad. at 3.45 → NOE of 10%, H–C(3)); 4.16 (*dd*, *J* = 5.0, 3.7, irrad. at 5.95 → NOE of 15%, H–C(1)); 3.94 (*dd*, *J* = 9.7, 3.7, H–(2)); 3.46 (*d*, *J* = 9.3, CH–C(4)); 3.43 (*d*, *J* = 9.3, CH′–C(4)); 3.10 (*s*, OH). ^{13}C-NMR (75 MHz, $CDCl_3$): 139.10 (*s*); 138.88 (*s*); 138.52 (*s*); 138.39 (*s*); 132.84 (br. *d*, C(5)); 128.59–127.81 (several *d*, incl. C(6)); 78.16 (*d*, C(2)); 75.98 (*d*, C(3)); 75.57 (*t*); 74.55 (*t*, CH_2–C(4)); 73.58 (*t*); 73.08 (*s*, C(4)); 72.87 (*t*); 71.88 (*t*); 71.69 (*d*, C(1)). Anal. calc. for $C_{35}H_{36}O_5$ (536.67): C 78.33, H 6.76; found: C 78.42, H 6.87.

REFERENCES

[1] T. D. Heightman, A. Vasella, *Angew. Chem.* **1999**, *111*, 795.

[2] P. Ermert, A. Vasella, M. Weber, K. Rupitz, S. G. Withers, *Carbohydr. Res.* **1993**, *250*, 113.

[3] S. Vonhoff, T. D. Heightman, A. Vasella, *Helv. Chim. Acta* **1998**, *81*, 1710.

[4] T. Storz, A. Vasella, *Helv. Chim. Acta* **1998**, *81*, 1896.

[5] N. Panday, T. Granier, A. Vasella, *Helv. Chim. Acta* **1998**, *81*, 475.

[6] S. Vorwerk, A. Vasella, *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1732.

[7] T. D. Heightman, A. Vasella, K. E. Tsitsanou, S. E. Zographos, V. T. Skamnaki, N. G. Oikonomakos, *Helv. Chim. Acta* **1998**, *81*, 853.

[8] a) A. Martinez-Grau, J. Marco-Contelles, *Chem. Soc. Rev.* **1998**, *27*, 155; b) I. S. de Gracia, H. Dietrich, S. Bobo, J. L. Chiara, *J. Org. Chem.* **1998**, *63*, 5883; c) A. Kornienko, D. I. Turner, C. H. Jaworek, M. d'Alarcao, *Tetrahedron: Asymmetry* **1998**, *9*, 2783; d) A. M. Gómez, G. O. Danelón, S. Valverde, J. C. López, *J. Org. Chem.* **1998**, *63*, 9626; e) E. Maudru, G. Singh, R. H. Wightman, *J. Chem. Soc., Chem. Commun.* **1998**, 1505; f) J. Desire, J. Prandi, *Tetrahedron Lett.* **1997**, *38*, 6189; g) S. K. Das, J. M. Mallet, P. Sinay, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 493; h) A. M. Gómez, S. Mantecon, S. Valverde, J. C. Lopez, *J. Org. Chem.* **1997**, *62*, 6612; i) A. Sudha, M. Nagarajan, *J. Chem. Soc., Chem. Commun.* **1998**, 925; j) C. H. Tran, D. H. G. Crout, W. Errington, G. M. Whited, *Tetrahedron: Asymmetry* **1996**, *7*, 691; k) C. H. Tran, D. H. G. Crout, *Tetrahedron: Asymmetry* **1996**, *7*, 2403; l) G. Mehta, N. Mohal, *Tetrahedron Lett.* **1998**, *39*, 3285; m) Y. Landais, *Chimia* **1998**, *52*, 104; n) S. Moutel, M. Shipman, *Synlett* **1998**, 1333; o) D. L. J. Clive, X. He, M. H. D. Postema, M. J. Mashimbye, *Tetrahedron Lett.* **1998**, *39*, 4231; p) B. M. Trost, E. J. Hembre, *Tetrahedron Lett.* **1999**, *40*, 219; q) D. Tanner, *Tetrahedron* **1999**, *55*, 1427; r) T. Suami, S. Ogawa, *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 21; s) R. J. Ferrier, S. Middleton, *Chem. Rev.* **1993**, *93*, 2779; t) T. V. RajanBabu, in 'Preparative Carbohydrate Chemistry', Ed. S. Hanessian, Marcel Dekker, Inc., New York, 1997, p. 545. u) R. J. Ferrier, in 'Preparative Carbohydrate Chemistry', Ed. S. Hanessian, Marcel Dekker, Inc., New York, 1997, p. 569.

[9] R. H. Grubbs, S. J. Miller, G. C. Fu, *J. Am. Chem. Soc.* **1995**, *117*, 446.

[10] H.-G. Schmalz, *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1833.

[11] U. Koert, *Nachr. Chem. Tech. Lab.* **1995**, *43*, 809.

[12] M. Schuster, S. Blechert, *Angew. Chem.* **1997**, *109*, 2124.
[13] A. Fürstner, *Top. Catal.* **1997**, *4*, 285.
[14] R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413.
[15] S. E. Armstrong, *J. Chem. Soc., Perkin Trans. 1* **1998**, 371.
[16] K. J. Ivin, *J. Mol. Catal. A* **1998**, *133*, 1.
[17] K. C. Nicolaou, R. M. Rodriguez, H. J. Mitchell, F. L. van Delft, *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1874.
[18] H. Ovaa, M. A. Leeuwenburgh, H. S. Overkleeft, G. A. van der Marel, J. H. van Boom, *Tetrahedron Lett.* **1998**, *39*, 3025.
[19] H. S. Overkleeft, U. K. Pandit, *Tetrahedron Lett.* **1996**, *37*, 547.
[20] C. Paolucci, L. Musiano, F. Venturelli, A. Fava, *Synthesis* **1997**, *12*, 1415.
[21] M. A. Leeuwenburgh, H. S. Overkleeft, G. A. van der Marel, J. H. van Boom, *Synlett* **1997**, 1263.
[22] A. Fürstner, T. Müller, *J. Org. Chem.* **1998**, *63*, 424.
[23] G. Descotes, J. Ramza, J.-M. Basset, S. Pagano, E. Gentil, J. Banoub, *Tetrahedron* **1996**, *52*, 10903.
[24] H. El Sukkari, J.-P. Gesson, B. Renoux, *Tetrahedron Lett.* **1998**, *39*, 4043.
[25] P. A. V. van Hooft, M. A. Leeuwenburgh, H. S. Overkleeft, G. A. van der Marel, C. A. A. van Boeckel, J. H. van Boom, *Tetrahedron Lett.* **1998**, *39*, 6061.
[26] D. J. Holt, W. D. Barker, P. R. Jenkins, D. L. Davies, S. Garratt, J. Fawcett, D. R. Russell, S. Gosh, *Angew. Chem.* **1998**, *110*, 3486.
[27] H. Ovaa, J. D. C. Codee, B. Lastdrager, H. S. Overkleeft, G. A. van der Marel, J. H. van Boom, *Tetrahedron Lett.* **1998**, *39*, 7987.
[28] F. E. Ziegler, Y. Wang, *J. Org. Chem.* **1998**, *63*, 7920.
[29] O. Sellier, P. Van de Weghe, D. Le Nouen, C. Strehler, J. Eustache, *Tetrahedron Lett.* **1999**, *40*, 853.
[30] Y. Kameda, S. Horii, *J. Chem. Soc., Chem. Commun.* **1972**, 746.
[31] S. Ogawa, Y. Miyamoto, A. Nakajima, *Chem. Lett.* **1989**, 725.
[32] S. Ogawa, A. Nakajima, Y. Miyamoto, *J. Chem. Soc., Perkin Trans. 1* **1991**, 3287.
[33] S. Ogawa, T. Toyokuni, N. Chida, T. Suami, *Kenkyu Hokoku – Asahi Garasu Kogyo Gijutsu Shoreikai* **1983**, *43*, 127.
[34] S. Ogawa, Y. Iwasawa, T. Nose, T. Suami, S. Ohba, M. Ito, Y. Saito, *J. Chem. Soc., Perkin Trans. 1* **1985**, 903.
[35] S. Ogawa, Y. Shibata, T. Nose, T. Suami, *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3387.
[36] S. Knapp, A. B. J. Naughton, T. G. M. Dhar, *Tetrahedron Lett.* **1992**, *33*, 1025.
[37] B. M. Trost, L. S. Chupak, T. Lübbers, *J. Am. Chem. Soc.* **1998**, *120*, 1732.
[38] H. Paulsen, F. R. Heiker, *Angew. Chem.* **1980**, *92*, 930.
[39] H. Paulsen, F. R. Heiker, *Liebigs Ann. Chem.* **1981**, 2180.
[40] N. Sakairi, H. Kuzuhara, *Tetrahedron Lett.* **1982**, *23*, 5327.
[41] R. R. Schmidt, A. Köhn, *Angew. Chem.* **1987**, *99*, 490.
[42] M. Yoshikawa, B. C. Cha, T. Nakae, I. Kitagawa, *Chem. Pharm. Bull.* **1988**, *36*, 3714.
[43] M. Yoshikawa, B. C. Cha, Y. Okaichi, Y. Takinami, Y. Yokokawa, I. Kitagawa, *Chem. Pharm. Bull.* **1988**, *36*, 4236.
[44] F. Nicotra, L. Panza, F. Ronchetti, G. Russo, *Gazz. Chim. Ital.* **1989**, *119*, 577.
[45] H. Fukase, S. Horii, *J. Org. Chem.* **1992**, *57*, 3651.
[46] T. K. Park, S. J. Danishefsky, *Tetrahedron Lett.* **1994**, *35*, 2667.
[47] A. Lipták, I. Jodál, P. Nánási, *Carbohydr. Res.* **1975**, *44*, 1.
[48] P. S. Liu, *J. Org. Chem.* **1987**, *52*, 4717.
[49] P. Ermert, A. Vasella, *Helv. Chim. Acta* **1991**, *74*, 2043.
[50] T. D. Heightman, Ph. D. Thesis, ETH-Zürich, No. 12696, 1998.
[51] J. C. McAuliffe, R. V. Stick, *Aust. J. Chem.* **1997**, *50*, 193.
[52] H. Paulsen, B. Mielke, W. von Deyn, *Liebigs Ann. Chem.* **1987**, 439.
[53] P. Schwab, A. B. France, J. W. Ziller, R. H. Grubbs, *Angew. Chem.* **1995**, *107*, 2179.
[54] R. Davies, *J. Chem. Soc., Perkin Trans. 2* **1975**, 1400.
[55] D. Höfner, S. A. Lesko, G. Binsch, *Org. Magn. Reson.* **1978**, *11*, 179.
[56] S. Ogawa, K. Sato, Y. Miyamato, *J. Chem. Soc., Perkin Trans. 1* **1993**, 691.
[57] T. M. Tagmose, M. Bols, *Chem. Eur. J.* **1997**, *3*, 453.
[58] Y. Ichikawa, *Synlett* **1991**, 238.
[59] Y. Ichikawa, M. Yamazaki, M. Isobe, *J. Chem. Soc., Perkin Trans. 1* **1993**, 2429.
[60] Y. Ichikawa, K. Tsuboi, M. Isobe, *J. Chem. Soc., Perkin Trans. 1* **1994**, 2791.

[61] L. E. Overman, *J. Am. Chem. Soc.* **1974**, *96*, 597.
[62] L. E. Overman, *J. Am. Chem. Soc.* **1976**, *98*, 2901.
[63] L. E. Overman, *Acc. Chem. Res.* **1980**, *13*, 218.
[64] K. Ritter, in 'Houben-Weyl's Stereoselective Synthesis', Vol. E 21, Eds. G. Helmchen, R. W. Hoffmann, J. Mulzer and E. Schaumann, Thieme, Stuttgart, 1996, 9, p. 5677.
[65] F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, C. Caufield, M. Lipton, G. Chang, T. Hendrickson, W. C. Still, *J. Comput. Chem.* **1990**, *11*, 440.
[66] T. Furumoto, Y. Kameda, K. Matsui, *Chem. Pharm. Bull.* **1992**, *40*, 1871.
[67] T. Oshitari, M. Shibasaki, T. Yoshizawa, M. Tomita, K.-I. Takao, S. Kobayashi, *Tetrahedron* **1997**, *53*, 10993.
[68] K. E. Pfitzner, J. G. Moffatt, *J. Am. Chem. Soc.* **1965**, *87*, 5661.
[69] K. E. Pfitzner, J. G. Moffatt, *J. Am. Chem. Soc.* **1965**, *87*, 5670.
[70] H. Günther, 'NMR-Spektroskopie', Georg Thieme Verlag, Stuttgart, 1992.
[71] S. J. Miller, R. H. Grubbs, *J. Org. Chem.* **1995**, *117*, 5855.

Received March 13, 1999