Available online at www.sciencedirect.com
SCIENCE DIRECT®
Carbohydrate Research 338 (2003) 293–298
CARBOHYDRATE RESEARCH
www.elsevier.com/locate/carres

Note

Synthesis of anellated carbasugars from (−)-quinic acid

Lidcay Herrera,[a] Holger Feist,[a] Manfred Michalik,[b] José Quincoces,[c] Klaus Peseke[a,*]

[a]*Fachbereich Chemie, Universität Rostock, D-18051 Rostock, Germany*
[b]*Institut für Organische Katalyseforschung, Buchbinderstraße 5–6, D-18055 Rostock, Germany*
[c]*Universidade Bandeirante de São Paulo, Rua Maria Candida, 1813, Vila Guilherme, Sao Paulo, CEP: 02071-013, Brazil*

Received 6 June 2002; received in revised form 30 September 2002; accepted 13 October 2002

Dedicated to Professor Dr. Rainer Radeglia on the occasion of his 65th birthday

Abstract

(3*R*,4*R*,5*R*)-3-[(*tert*-Butyl-dimethylsilyl)oxy]-4,5-(isopropylidenedioxy)-1-cyclohexanone (**2**) reacted with carbon disulfide and methyl iodide in the presence of sodium hydride to furnish (3*R*,4*R*,5*R*)-5-[(*tert*-butyl-dimethylsilyl)oxy]-3,4-(isopropylidenedioxy)-2-[bis(methylthio)methylene]-1-cyclohexanone (**3**). **2** and *N*,*N*-dimethylformamide dimethyl acetal afforded (2*E*,3*R*,4*R*,5*R*)-5-[(*tert*-butyl-dimethylsilyl)oxy]-2-(dimethylaminomethylene)-3,4-(isopropylidenedioxy)-1-cyclohexanone (**4**). These push–pull activated methylenecyclohexanones **3** and **4** underwent a ring closure reaction with hydrazine hydrate and methylhydrazine, respectively, to give pyrazoloanellated carbasugars. Treatment of **3** with formamidinium, acetamidinium and benzamidinium salts, respectively, in the presence of sodium methanolate yielded three (5*R*,6*R*,7*R*)-7-[(*tert*-butyl-dimethylsilyl)oxy]-5,6,7,8-tetrahydro-5,6-(isopropylidenedioxy)benzo[d]pyrimidines. © 2002 Published by Elsevier Science Ltd.

Keywords: (−)-Quinic acid; Benzo[c]pyrazoles; Benzo[d]pyrimidines, α-Oxoketene-*S*,*S*-acetals; Push–pull alkenes

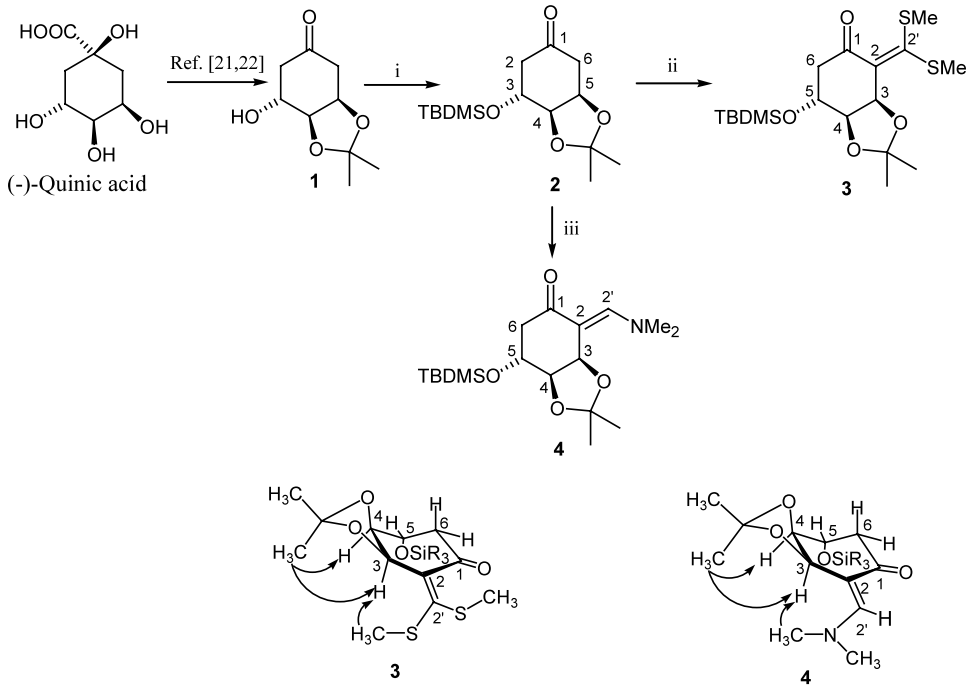
Modifications of monosaccharides to increase their stability towards enzymes and yet retain their biological properties have led to the development of carbohydrate mimics. Replacement of the ring oxygen by a carbon atom creates a carbasugar (pseudosugar) species. The synthesis of carbasugars is a topic of interest in relation to elucidation of the biological role of carbohydrates and their use as drugs.[1–10] Furthermore, anellated cyclic monosaccharide derivatives have attracted great interest in organic synthesis[11–15] because of their biological importance, for example as antibiotics, cancerostatics[16–18] or as inhibitors of different glycosidases.[19,20] Here we report the preparation of carbasugars with a push–pull substituted exocyclic C–C double bond from a cyclohexanone derivative having α-methylene groups activated by the adjacent carbonyl function. These push–pull activated carbasugars could be used as precursors for syntheses of pyrazolo- and pyrimidoanellated carbasugars.

(−)-Quinic acid, a widespread natural compound, was reacted in three steps to furnish (3*R*,4*S*,5*R*)-3-hydroxy-4,5-(isopropylidenedioxy)-1-cyclohexanone (**1**).[21,22] Silylation of this β-hydroxy ketone with *tert*-butyl-chlorodimethylsilane (TBDMSCl) in the presence of imidazole yielded the (3*R*,4*R*,5*R*)-3-[(*tert*-butyl-dimethylsilyl)oxy]-4,5-(isopropylidenedioxy)-1-cyclohexanone (**2**) in 80% yield [cf. Ref. 23]. For structure elucidation of the following compounds it was necessary to assign the signal at $\delta = 4.68$ (dt) in the ^{1}H NMR spectrum to H-3 or H-5. The correlations in a NOESY spectrum for H-4 and H-5 gave the H-5 assignment.

As described earlier,[24–26] treatment of deoxysuguloses with carbon disulfide and alkyl halide in the presence of bases afforded the corresponding monosaccharidic α-oxo ketene dithioacetals. Similarly, the carbasugar **2** reacted with sodium hydride, carbon disulfide and methyl iodide in *N*,*N*-dimethylformamide to give the corresponding push–pull functionalized carbasugar **3** in 79% yield as a yellow syrup. In accordance with the push–pull effect, in the IR spectrum of this α-oxo ketene dithioacetal **3** the carbonyl band appeared at a higher wavelength (1676 cm^{-1}) compared with the

* Corresponding author. Fax: +49-381-4986412
E-mail address: klaus.peseke@chemie.uni-rostock.de (K. Peseke).

0008-6215/03/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0008-6215(02)00411-1

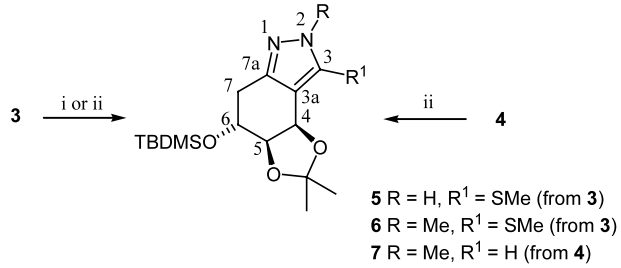


Scheme 1. Syntheses and NOE's of **3** and **4**. Reagents (i) (a) TBDMSC1, imidazole (b) $NaHSO_4/H_2O$; (ii) (a) NaH, CS_2, Mel, DMF, (b) H_2O; (iii) $HC(Ome)_2Nme_2$, toluene.

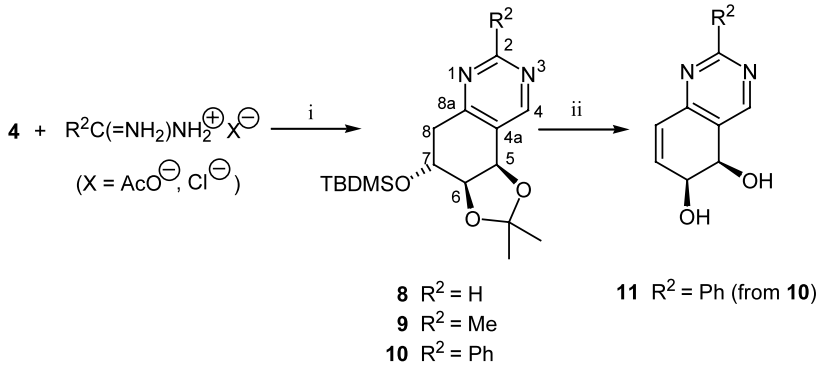
CO band in the starting compound **2** (1724 cm^{-1}).[24] In the ^1H and ^{13}C NMR spectra the signals for both methylthio groups were found at $\delta = 2.49–2.37$ and $\delta = 19.9, 18.6$, respectively. The ^{13}C NMR spectrum of compound **3** showed an upfield shift for the signal of C-2 ($\delta = 131.0$) whereas the signal of C-2′ was shifted downfield ($\delta = 157.9$) which is typically for push–pull alkenes.[27,28] The alternative attack of carbon disulfide on C-2 of carbasugar **2** could be excluded by the comparison of the corresponding signals for H-3 in compound **3** with the corresponding H-5 signals in compound **2** (double triplett at $\delta = 4.68$ for **2** and only a doublet at $\delta = 5.92$ for **3**). Furthermore, a NOESY experiment showed a relation between one methylthio group and H-3 (Scheme 1).

Bredereck et al. reported the reaction of acidic methylene compounds with acetals of amides to furnish push–pull substituted alkenes as well.[29] In this way compound **2** was reacted with *N*,*N*-dimethylformamide dimethyl acetal in boiling toluene to afford (2*E*,3*R*,4*R*,5*R*)-5-[(*tert*-butyl-dimethylsilyl)oxy]-2-(dimethylaminomethylene)-3,4-(isopropylidenedioxy)-1-cyclohexanone (**4**) as a light yellow solid in 58% yield. In the ^1H NMR spectrum signals appeared for a dimethylamino group and H-2′ at $\delta = 3.19$ and $\delta = 7.68$, respectively. Furthermore, in the ^{13}C NMR spectrum the shifts of signals for C-2 ($\delta = 99.3$) and C-2′ ($\delta = 152.9$) were in accordance with the expected one for such push–pull substituted carbon atoms. In a similar fashion to compound **3**, a doublet for H-3 at $\delta = 5.27$ in the ^1H NMR spectrum and the NOE correlation of the dimethylamino group with H-3 proved reaction of the 6-methylene group in compound **2** with the *N*,*N*-dimethylformamide dimethyl acetal, as well as the *E*-configuration of the final product.

In analogy to simple push–pull activated α-oxo ketene dithioacetals[30–32] compound **3** was reacted with hydrazine hydrate to yield (4*R*,5*R*,6*R*)-6-[(*tert*-butyl-dimethylsilyl)oxy]-4,5,6,7-tetrahydro-4,5-(isopropylidenedioxy)-3-methylthio-2*H*(1*H*)-benzo[*c*]pyrazole (**5**) as a colourless solid (Scheme 2). The spectroscopic data clearly verify the formation of compound **5**. The mass spectrum contained a signal for $[M + 1]^+$ at m/z 371. The signals for only one methylthio group at $\delta = 2.50$ and $\delta = 17.1$ were found in the ^1H and ^{13}C NMR spectra, respectively. On the other hand, in the ^{13}C NMR spectrum no signal for a carbonyl group was present. Due to the fast proton exchange between the



Scheme 2. Syntheses of **5**–**7**. Reagents (i) NH_2NH_2/H_2O/MeOH, reflux; (ii) $MeNHNH_2$/MeOH, reflux.



Scheme 3. Syntheses of **8**–**11**. Reagents (i) MeONa/MeOH, 50 °C; (ii) CF_3COOH/H_2O.

nitrogen atoms an NH signal was not identified and in the ^{13}C NMR spectrum the C-7a appeared as broad signal at $\delta = 142.7$. The C-3 signal was not displayed due to exchange broadening.

The α-oxoketene-S,S-acetal **3** and methylhydrazine afforded the (4*R*,5*R*,6*R*)-6-[(*tert*-butyl-dimethylsilyl)oxy]-4,5,6,7-tetrahydro-4,5-(isopropylidenedioxy)-2-methyl-3-methylthio-2*H*-benzo[*c*]pyrazole (**6**) in 52% yield as colourless crystals. In the ^1H and ^{13}C NMR spectra only one methylthio signal at $\delta = 2.36$ and 19.2, respectively, and one *N*-methyl signal at $\delta = 3.88$ and $\delta = 36.4$, respectively, were found. The stereochemistry of this *N*-methyl group was proved by the NOE with the neighbouring methylthio group.

Furthermore, the dimethylaminoenone **4** was reacted with methylhydrazine to furnish the (4*R*,5*R*,6*R*)-6-[(*tert*-butyl-dimethylsilyl)oxy]-4,5,6,7-tetrahydro-4,5-(isopropylidenedioxy)-2-methyl-2*H*-benzo[*c*]pyrazole (**7**) in 69% yield. Similarly to compound **6**, the 3-methyl signal was found at $\delta = 3.84$ and $\delta = 38.9$ in the ^1H and ^{13}C NMR spectra and the position of the methyl group with respect to the N atoms was determined by the NOE with H-3.

Treatment of the dimethylaminoenone **4** with formamidinium, acetamidinium, and benzamidinium salts, respectively, in the presence of sodium methanolate in methanol at 50 °C afforded the corresponding pyrimidoanellated carbasugars **8**–**10** in 30–49% yield (Scheme 3). In the ^1H and ^{13}C NMR spectra of compound **8** the signals at $\delta = 8.97$ for H-2 and $\delta = 158.8$ for C-2 confirmed the successful anellation. Similarly, the corresponding signals for C-2 in the ^{13}C NMR spectra of **9** and **10** were found at $\delta = 168.0$ and $\delta = 165.1(164.2)$.

For compound **10** we examined the deprotection with a 60% aqueous solution of trifluoroacetic acid at 22 °C, which afforded, accompanied by elimination, the (5*R*,6*S*)-5,6-dihydro-5,6-dihydroxy-2-phenyl-benzo[*d*]-pyrimidine (**11**) in 55% yield.

In summary, we have described routes for the synthesis of pyrazolo- and pyrimidoanellated carbasugars with defined stereochemistry on the basis of push–pull activated methylenecyclohexanone.

1. Experimental

1.1. General methods

Melting points were determined with a Boëtius melting point apparatus and are corrected. Optical rotations were measured with a Polar LμP (IBZ Meßtechnik) polarimeter. IR spectra were recorded with a Nicolet 205 FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded with a Bruker AC 250 (250.13 MHz and 62.9 MHz, resp.) and a Bruker ARX 300 (300.13 MHz and 75.5 MHz, resp.). The calibration of spectra was carried out by means of solvent peaks ($CDCl_3$: δ ^1H 7.25; δ ^{13}C 77.0; acetone-D_6: δ ^1H 2.04; δ ^{13}C 29.7; DMSO-D_6: δ ^1H 2.50; δ ^{13}C 39.7). The ^{13}C NMR signals were assigned by DEPT and/or ^1H,^{13}C correlation spectra. Mass spectra were obtained with an AMD 402/3 spectrometer (AMD Intectra GmbH). Elemental analyses were performed with a Leco CHNS-932. Column chromatography was carried out on Silica gel 60 (230–400 μm, Merck). Thin-layer chromatography (TLC) was performed on Silica gel 60 GF_{254} foils (Merck) with detection by UV-light and by charring with sulphuric acid. Solvents and liquid reagents were purified and dried according to recommended procedures.

1.2. (3*R*,4*R*,5*R*)-3-[(*tert*-Butyl-dimethylsilyl)oxy]-4,5-(isopropylidenedioxy)-1-cyclohexanone (2) [cf. Ref. 23]

Imidazole (1.70 g, 25 mmol) and TBDMSCl (2.26 g, 15 mmol) were added to a solution of (*3R*,*4R*,*5R*)-5-hydroxy-3,4-(isopropylidenedioxy)-1-cyclohexanone[21,22] (**1**, 1.86 g, 10 mmol), in DMF (25 mL). The reaction mixture was stirred for 12 h at 22 °C, then diluted with chloroform (100 mL), washed with 3% aqueous $NaHSO_4$ (50 mL) and three times with water (100 mL), dried with Na_2SO_4 and evaporated. The residue was purified by column chromatography (toluene/ethyl acetate 10:1) to yield 2.40 g (80%) of **2** as a colourless solid; TLC: toluene/ethyl acetate 2:1 R_f: 0.75; mp 34–36 °C; $[\alpha]_D^{21}$: +100.1 (*c* 1.0, $CHCl_3$); IR (capillary):

1724 cm^{-1} (CO); ^1H NMR (250.1 MHz, $CDCl_3$): δ 4.68 (dt, 1H, $^3J_{4,5} \sim 7.1$ Hz, $^3J_{5,6} \sim {}^3J_{5,6'} \sim 3.5$ Hz, H-5); 4.23–4.12 (m, 2H, H-4, H-3); 2.73 (dd, 1H, $^2J_{6,6'} \sim 17.5$ Hz, $^3J_{5,6} \sim 3.5$ Hz, H-6); 2.63 (dd, 2H, H-2a, H-6′); 2.35 (ddd, 1H, $^2J_{2,2'} \sim 17.5$ Hz, $^3J_{2',3} \sim 3.7$ Hz, $^4J_{2',4} \sim 2.0$ Hz, H-2′); 1.42, 1.35 (2s, $2 \times 3H$, CMe_2); 0.84 (s, 9H, CMe_3); 0.07, 0.04 (2s, $2 \times 3H$, $SiMe_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 207.6 (C-1); 108.7 (CMe_2); 75.2 (C-4); 72.4 (C-5); 68.8 (C-3); 41.9 (C-2); 40.2 (C-6); 26.3 ($1 \times CMe_2$); 25.6 (CMe_3); 23.9 ($1 \times CMe_2$); 17.9 (CMe_3); −5.0 ($2 \times SiMe_2$); MS, CI (m/z): 301 $[M+1]^+$; Anal. Calcd for $C_{15}H_{28}O_4Si$: C 59.96; H 9.39. Found: C 60.20; H 9.30.

1.3. (3*R*,4*R*,5*R*)-5-[(*tert*-Butyl-dimethylsilyl)oxy]-3,4-(isopropylidenedioxy)-2-[bis(methylthio)methylene]-1-cyclohexanone (3)

A solution of **2** (0.30 g, 1.0 mmol), carbon disulfide (0.18 mL, 3.0 mmol) and methyl iodide (0.25 mL, 4.0 mmol) in anhyd DMF (10 mL) was cooled to 0 °C. Then sodium hydride (0.08 g, 2.0 mmol, 60%) was added. The mixture was stirred for 1 h at 0 °C, then poored onto ice water and extracted three times with $CHCl_3$ (50 mL). The combined organic layers were washed with water, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (toluene/ethyl acetate 15:1) to yield 0.32 g (79%) of **3** as a yellow syrup; TLC: toluene/ethyl acetate 10:1 R_f: 0.53; $[\alpha]_D^{21}$: −75.5 (*c* 1.0, $CHCl_3$); IR (capillary): 1676 cm^{-1} (CO); ^1H NMR (250.1 MHz, $CDCl_3$): δ 5.92 (d, 1H, $^3J_{3,4} \sim 7.5$ Hz, H-3); 4.24 (dt, 1H, $^3J_{3,4} \sim 7.5$ Hz, $^3J_{4,5} \sim {}^4J_{4,6'} \sim 2.5$ Hz, H-4); 4.05 (m, 1H, H-5); 2.81 (dd, 1H, $^2J_{6,6'} \sim 16.8$ Hz, $^3J_{5,6} \sim 2.2$ Hz, H-6); 2.49–2.37 (m, 7H, H-6′, $2 \times$ SMe); 1.43, 1.41 (2s, $2 \times 3H$, CMe_2); 0.78 (s, 9H, CMe_3); 0.03, 0.01 (2s, $2 \times 3H$, $SiMe_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 195.0 (C-1); 157.9 (C-2′); 131.0 (C-2); 108.7 (CMe_2); 77.3 (C-4); 75.5 (C-3); 68.6 (C-5); 42.6 (C-6); 26.4 ($1 \times CMe_2$); 25.6 (CMe_3); 24.2 ($1 \times CMe_2$); 19.9, 18.6 ($2 \times$ SMe); 17.8 (CMe_3); −4.9, −5.0 ($SiMe_2$); MS, CI (m/z): 405 $[M+1]^+$; Anal. Calcd for $C_{18}H_{32}O_4S_2Si$: C 53.46; H 7.92; S 15.84. Found: C 53.63; H 8.07; S 15.92.

1.4. (2*E*,3*R*,4*R*,5*R*)-5-[(*tert*-Butyl-dimethylsilyl)oxy]-2-(dimethylaminomethylene)-3,4-(isopropylidenedioxy)-1-cyclohexanone (4)

To a solution of **2** (0.6 g, 2.0 mmol) in anhyd toluene (20 mL) was added *N*,*N*-dimethylformamide dimethylacetal (1.33 ml, 10 mmol). After 5 h under reflux the mixture was allowed to cool to 20 °C and after that the solvent was evaporated under vacuum. The residue was purified by column chromatography (toluene/ethyl acetate 1:1) to yield 0.41 g (58%) of **4** as a light yellow solid. TLC: toluene/ethyl acetate 1:1; R_f: 0.17; mp 81–83 °C; $[\alpha]_D^{21}$: +266.3 (*c* 1.0, $CHCl_3$); IR (KBr): 1651 cm^{-1} (CO); ^1H NMR (300.1 MHz, $CDCl_3$): δ 7.68 (s, 1H, H-2′); 5.27 (d, 1H, $^3J_{3,4} \sim 6.0$ Hz, H-3); 4.09–4.03 (m, 2H, H-4, H-5); 3.19 (s, 6H, NMe_2); 2.62 (dd, 1H, $^2J_{6,6'} \sim 16.2$ Hz, $^3J_{5,6} \sim 3.3$ Hz, H-6); 2.29 (m, 1H, H-6′); 1.47, 1.38 (2s, $2 \times 3H$, CMe_2); 0.85 (s, 9H, CMe_3); 0.07, 0.05 (2s, $2 \times 3H$, $SiMe_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 193.9 (C-1); 152.9 (C-2′); 107.6 (CMe_2); 99.3 (C-2); 78.3 (C-4); 71.5 (C-3); 69.3 (C-5); 43.4 (NMe_2); 43.2 (C-6); 27.8 ($1 \times CMe_2$); 25.5 (CMe_3); 24.9 ($1 \times CMe_2$); 18.0 (CMe_3); −4.7, −4.8 ($SiMe_2$); MS, EI (m/z): 355 $[M]^+$; Anal. Calcd for $C_{18}H_{33}NO_4Si$: C 60.75; H 9.28; N 3.94. Found: C 61.03; H 9.42; N 4.12.

1.5. (4*R*,5*R*,6*R*)-6-[(*tert*-Butyl-dimethylsilyl)oxy]-4,5,6,7-tetrahydro-4,5-(isopropylidenedioxy)-3-methylthio-2*H*(1*H*)-benzo[*c*]pyrazole (5)

A mixture of **3** (0.40 g, 1.0 mmol) and hydrazine hydrate (0.15 mL, 3.0 mmol) in anhyd methanol (10 mL) was heated at reflux for 30 min., the reaction mixture was cooled and the solvent was evaporated under vacuum. The residue was purified by column chromatography (toluene/ethyl acetate 1:2) to yield 0.11 g (30%) of **5** as colourless solid; TLC: toluene/ethyl acetate 3:1 R_f: 0.36; mp 127–129 °C; $[\alpha]_D^{21}$: +30.5 (*c* 1.0, $CHCl_3$); IR (KBr): 3195 cm^{-1} (NH); ^1H NMR (250.1 MHz, $CDCl_3$): δ 5.17 (d, 1H, $^3J_{4,5} \sim 5.5$ Hz, H-4); 4.30–4.18 (m, 2H, H-5, H-6); 2.95 (dd, 1H, $^2J_{7,7'} \sim 16.0$ Hz, $^3J_{6,7} \sim 4.0$ Hz, H-7); 2.61 (dd, 1H, $^2J_{7,7'} \sim 16.0$ Hz, $^3J_{6,7'} \sim 5.8$ Hz, H-7′); 2.50 (s, 3H, SMe); 1.44, 1.32 (2s, $2 \times 3H$, CMe_2); 0.82 (s, 9H, CMe_3); 0.09, 0.05 (2s, $2 \times 3H$, $SiMe_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 142.7 (br, C-7a); 114.9 (C-3a); 109.5 (CMe_2); 78.2 (C-5); 69.5, 68.7 (C-4, C-6); 27.9 ($1 \times CMe_2$); 27.8 (C-7); 26.1 ($1 \times CMe_2$); 25.5 (CMe_3); 17.8 (CMe_3); 17.1 (SMe); −4.4, −4.6 ($SiMe_2$); C-3 not displayed due to exchange broadening; MS, CI (m/z): 371 $[M+1]^+$; Anal. Calcd for $C_{17}H_{30}N_2O_3SSi$: C 55.14; H 8.11; N 7.57; S 8.64. Found: C 55.08; H 8.30; N 7.49; S 8.50.

1.6. (4*R*,5*R*,6*R*)-6-[(*tert*-Butyl-dimethylsilyl)oxy]-4,5,6,7-tetrahydro-4,5-(isopropylidenedioxy)-2-methyl-3-methylthio-2*H*-benzo[*c*]pyrazole (6)

A mixture of **3** (0.404 g, 1.0 mmol) and methylhydrazine (0.16 mL, 3.0 mmol) was reacted as described before. The residue was purified by column chromatography (toluene/ethyl acetate 3:1) to yield 0.20 g (52%) of **6** as colourless crystals; TLC: toluene/ethyl acetate 3:1 R_f: 0.57; mp 47–49 °C; $[\alpha]_D^{21}$: +57.1 (c 1.0, $CHCl_3$); IR (KBr): 1549 cm^{-1} (C=C); ^1H NMR (250.1 MHz, $CDCl_3$): δ 5.19 (d, 1H, $^3J_{4,5} \sim 5.3$ Hz, H-4); 4.27–4.16 (m, 2H, H-5, H-6); 3.88 (s, 3H, NMe); 2.92 (dd, 1H, $^2J_{7,7'} \sim 15.8$ Hz, $^3J_{6,7} \sim 3.8$ Hz, H-7); 2.58 (dd, 1H, $^2J_{7,7'} \sim 15.8$ Hz, $^3J_{6,7'} \sim 6.1$ Hz, H-7′); 2.36 (s, 3H, SMe);

1.44, 1.32 (2s, 2 × 3H, CMe_2); 0.82 (s, 9H, CMe_3); 0.08, 0.04 (2s, 2 × 3H, $SiMe_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 146.3 (C-7a); 134.2 (C-3); 117.9 (C-3a); 109.4 (CMe_2); 78.6 (C-5); 70.1 (C-6); 69.6 (C-4); 36.4 (NMe); 29.0 (C-7); 28.2, 26.3 (CMe_2); 25.7 (CMe_3); 19.2 (SMe); 18.0 (CMe_3); −4.7, −4.8 ($SiMe_2$); MS, CI (m/z): 385 $[M+1]^+$; Anal. Calcd for $C_{18}H_{32}N_2O_3SSi$: C 56.21; H 8.39; N 7.28; S 8.34. Found: C 56.08; H 8.52; N 7.12; S 8.22.

1.7. (4*R*,5*R*,6*R*)-6-[(*tert*-Butyl-dimethylsilyl)oxy]-4,5,6,7-tetrahydro-4,5-(isopropylidenedioxy)-2-methyl-2*H*-benzo[*c*]pyrazole (7)

A mixture of **4** (0.355 g, 1.0 mmol) and methylhydrazine (0.16 mL, 3.0 mmol) was reacted as described for preparation of **5**. The residue was purified by column chromatography (toluene/ethyl acetate 2:1) to yield 0.23 g (69%) of **7** as colourless solid; TLC: toluene/ethyl acetate 2:1 R_f: 0.27; mp 81–83 °C; $[\alpha]_D^{21}$: +18.6 (*c* 1.0, $CHCl_3$); IR (KBr): 1564 cm^{-1} (C=C); ^1H NMR (300.1 MHz, $CDCl_3$): δ 7.35 (s, 1H, H-3); 5.18 (d, 1H, $^3J_{4,5} \sim 5.5$ Hz, H-4); 4.20–4.12 (m, 2H, H-5, H-6); 3.84 (s, 3H, NMe); 2.93 (dd, 1H, $^2J_{7,7'} \sim 16.0$ Hz, $^3J_{6,7} \sim 3.8$ Hz, H-7); 2.58 (dd, 1H, $^2J_{7,7'} \sim 16.0$ Hz, $^3J_{6,7'} \sim 7.5$ Hz, H-7′); 1.41, 1.36 (2s, 2 × 3H, CMe_2); 0.85 (s, 9H, CMe_3); 0.09, 0.06 (2s, 2 × 3H, $SiMe_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 146.9 (C-7a); 129.3 (C-3); 113.7 (C-3a); 109.4 (CMe_2); 79.3 (C-5); 70.5 (C-6); 69.3 (C-4); 38.9 (NMe); 29.2 (C-7); 28.2, 26.1 (CMe_2); 25.7 (CMe_3); 18.0 (CMe_3); −4.6, −4.7 ($SiMe_2$); MS, CI (m/z): 339 $[M+1]^+$; Anal. Calcd for $C_{17}H_{30}N_2O_3Si$: C 60.32; H 8.93; N 8.28. Found: C 60.18; H 8.82; N 8.12.

1.8. (5*R*,6*R*,7*R*)-7-[(*tert*-Butyl-dimethylsilyl)oxy]-5,6,7,8-tetrahydro-5,6-(isopropylidenedioxy)-benzo[*d*]-pyrimidine (8)

To a solution of sodium (7 mg, 0.3 mmol) in methanol (2 mL) was added formamidinium acetate (31 mg, 0.3 mmol). After stirring for 20 min. at 22 °C this mixture was dropwise added to another stirred solution of **4** (53 mg, 0.15 mmol) in methanol (2 mL). The resulting mixture was stirred at 50 °C for 1.5 h (TLC control). The mixture was cooled to 20 °C, and a saturated solution of NH_4Cl (10 mL) was added. The mixture was extracted three times with $CHCl_3$ (25 mL). The combined organic layers were washed with water, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (toluene/ethyl acetate 2:1) to yield 15 mg (30%) of **8** as colourless syrup; TLC: toluene/ethyl acetate 2:1 R_f: 0.38; $[\alpha]_D^{21}$: +20.5 (*c* 1.0, $CHCl_3$); ^1H NMR (300.1 MHz, acetone-D_6): δ 8.97 (s, 1H, H-2); 8.64 (s, 1H, H-4); 5.36 (d, 1H, $^3J_{5,6} \sim 6.5$ Hz, H-5); 4.44 (ddd, 1H, $^3J_{5,6} \sim 6.5$ Hz, $^3J_{6,7} \sim 4.0$ Hz, $^4J_{6,8'} \sim 1.5$ Hz, H-6); 4.39 (ddd, 1H, $^3J_{7,8'} \sim 4.8$ Hz, $^3J_{6,7} \sim 4.0$ Hz, $^3J_{7,8} \sim 2.8$ Hz, H-7); 3.11 (dd, 1H, $^2J_{8,8'} \sim 16.5$ Hz, $^3J_{7,8} \sim 2.8$ Hz, H-8); 2.84 (ddd, 1H, $^2J_{8,8'} \sim 16.5$ Hz, $^3J_{7,8'} \sim 4.8$ Hz, $^4J_{6,8'} \sim 1.5$ Hz, H-8′); 1.42 (t, 3H, $^4J_{Me,Me} \sim 0.6$ Hz, CMe_2); 1.27 (t, 3H, $^4J_{Me,Me} \sim 0.6$ Hz, CMe_2); 0.73 (s, 9H, CMe_3); 0.1, 0.06 (2s, 2 × 3H, $SiMe_2$); ^{13}C NMR (75.5 MHz, acetone-D_6): δ 164.6 (C-8a); 158.8 (C-2); 157.4 (C-4); 129.0 (C-4a); 110.0 (CMe_2); 77.8 (C-6); 72.7 (C-5); 70.1 (C-7); 36.6 (C-8); 27.3 (1 × CMe_2); 25.9 (CMe_3); 25.0 (1 × CMe_2); 18.4 (CMe_3); −4.8 (2 × $SiMe_2$); MS, CI (m/z): 337 $[M+1]^+$; Anal. Calcd for $C_{17}H_{28}N_2O_3Si$: C 60.68; H 8.39; N 8.32. Found: C 60.54; H 8.58; N 8.23.

1.9. (5*R*,6*R*,7*R*)-7-[(*tert*-Butyl-dimethylsilyl)oxy]-5,6,7,8-tetrahydro-5,6-(isopropylidenedioxy)-2-methyl-benzo[*d*]pyrimidine (9)

Compound **4** (53 mg, 0.15 mmol) and acetamidinium hydrochloride (28 mg, 0.3 mmol) was reacted as described for preparation of **8**. The residue was purified by column chromatography (toluene/ethyl acetate 1:1) to yield 17 mg (33%) of **9** as colourless solid; TLC: toluene/ethyl acetate 1:1 R_f: 0.44; mp 60–62 °C; $[\alpha]_D^{21}$: +33.5 (*c* 1.0, $CHCl_3$); ^1H NMR (300.1 MHz, acetone-D_6): δ 8.51 (s, 1H, H-4); 5.31 (d, 1H, $^3J_{5,6} \sim 6.5$ Hz, H-5); 4.40 (ddd, 1H, $^3J_{5,6} \sim 6.5$ Hz, $^3J_{6,7} \sim 4.1$ Hz, $^4J_{6,8'} \sim 1.3$ Hz, H-6); 4.34 (ddd, 1H, $^3J_{7,8'} \sim 5.0$ Hz, $^3J_{6,7} \sim 4.1$ Hz, $^3J_{7,8} \sim 3.0$ Hz, H-7); 3.05 (dd, 1H, $^2J_{8,8'} \sim 16.4$ Hz, $^3J_{7,8} \sim 3.0$ Hz, H-8); 2.77 (ddd, 1H, $^2J_{8,8'} \sim 16.4$ Hz, $^3J_{7,8'} \sim 5.0$ Hz, $^4J_{6,8'} \sim 1.3$ Hz, H-8′); 2.57 (s, 3H, 2-Me); 1.40 (t, 3H, $^4J_{Me,Me} \sim 0.6$ Hz, CMe_2); 1.27 (t, 3H, $^4J_{Me,Me} \sim 0.6$ Hz, CMe_2); 0.74 (s, 9H, CMe_3); 0.1, 0.06 (2s, 2 × 3H, $SiMe_2$); ^{13}C NMR (75.5 MHz, acetone-D_6): δ 168.0 (C-2); 164.5 (C-8a); 157.6 (C-4); 125.5 (C-4a); 109.8 (CMe_2); 78.0 (C-6); 72.6 (C-5); 70.2 (C-7); 36.8 (C-8); 27.3 (1 × CMe_2); 25.9 (CMe_3); 25.8 (2-Me); 25.1 (1 × CMe_2); 18.4 (CMe_3); −4.7, −4.8 ($SiMe_2$); MS, CI (m/z): 351 $[M+1]^+$; Anal. Calcd for $C_{18}H_{30}N_2O_3Si$: C 61.68; H 8.63; N 7.99. Found: C 61.49; H 8.54; N 7.75.

1.10. (5*R*,6*R*,7*R*)-7-[(*tert*-Butyl-dimethylsilyl)oxy]-5,6,7,8-tetrahydro-5,6-(isopropylidenedioxy)-2-phenyl-benzo[*d*]pyrimidine (10)

Compound **4** (53 mg, 0.15 mmol) and benzamidinium hydrochloride (47 mg, 0.3 mmol) was reacted as described for preparation of **8**. The residue was purified by column chromatography (toluene/ethyl acetate 10:1) to yield 30 mg (49%) of **10** as colourless solid; TLC: toluene/ethyl acetate 10:1 R_f: 0.48; mp 67–69 °C; $[\alpha]_D^{21}$: +57.9 (*c* 1.0, $CHCl_3$); ^1H NMR (300.1 MHz, acetone-D_6): δ 8.74 (s, 1H, H-4); 8.49 (m, 2H, *o*-Ph); 7.50 (m, 3H, *m*-, *p*-Ph); 5.40 (d, 1H, $^3J_{5,6} \sim 6.5$ Hz, H-5); 4.50–4.40 (m, 2H, H-6, H-7); 3.20 (dd, 1H, $^2J_{8,8'} \sim 16.3$ Hz, $^3J_{7,8} \sim 2.8$ Hz, H-8); 2.94 (ddd, 1H, $^2J_{8,8'} \sim 16.3$ Hz,

$^3J_{7,8'} \sim 4.8$ Hz, $^4J_{6,8'} \sim 1.4$ Hz, H-8'); 1.44, 1.31 (2s, 2×3H, CMe_2), 0.74 (s, 9H, CMe_3); 0.12, 0.08 (2s, 2×3H, $SiMe_2$); ^{13}C NMR (75.5 MHz, acetone-D_6): δ 165.1, 164.2 (C-2, C-8a); 158.0 (C-4); 138.6 (*i*-Ph); 131.4 (*p*-Ph); 129.3, 128.8 (*o*-, *m*-Ph); 126.8 (C-4a); 110.0 (CMe_2); 78.0 (C-6); 72.6 (C-5); 70.3 (C-7); 37.0 (C-8); 27.4 ($1 \times CMe_2$); 25.9 (CMe_3); 25.1 ($1 \times CMe_2$); 18.4 (CMe_3); -4.7 ($2 \times SiMe_2$); MS, CI (*m*/*z*): 413 $[M+1]^+$; Anal. Calcd for $C_{23}H_{32}N_2O_3Si$: C 66.95; H 7.82; N 6.79. Found: C 66.89; H 7.87; N 7.03.

1.11. (5*R*,6*S*)-5,6-Dihydro-5,6-dihydroxy-2-phenylbenzo[*d*]pyrimidine (11)

Compound **10** (124 mg, 0.3 mmol) was added to an 60% aq solution of CF_3COOH (5 mL). The mixture was stirred at 22 °C for 12 h, then extracted with ethyl acetate (3×25 ml), and the organic phases were washed with a saturated aq solution of $NaHCO_3$ (2×50 mL) and water (2×50 mL), dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (ethyl acetate/methanol 10:1) to yield 40 mg (55%) of **11** as white crystals; TLC: ethyl acetate/methanol 10:1 R_f: 0.57; mp 180–182 °C; $[\alpha]_D^{21}$: $+85.7$ (*c* 0.5, MeOH); ^{1}H NMR (250.1 MHz, DMSO-D_6): δ 8.76 (s, 1H, H-4); 8.37 (m, 2H, *o*-Ph); 7.50 (m, 3H, *m*-, *p*-Ph); 6.66–6.57 (m, 2H, H-7, H-8); 5.47 (d, 1H, $^3J_{5,OH} \sim 6.0$ Hz, OH-5); 5.19 (d, 1H, $^3J_{6,OH} \sim 6.0$ Hz, OH-6); 4.67 (t, 1H, $^3J_{5,6} \sim 5.2$ Hz, H-5); 4.29 (m, 1H, H-6). ^{13}C NMR (62.9 MHz, DMSO-D_6): δ 162.9, 158.7 (C-2, C-8a); 155.2 (C-4); 142.0 (C-7); 137.5 (*i*-Ph); 130.8 (*p*-Ph); 128.8 (*m*-Ph); 128.0 (C-4a); 127.8 (*o*-Ph); 127.3 (C-8); 67.2 (C-5); 66.3 (C-6). MS, EI (*m*/*z*): 240 $[M]^+$; Anal. Calcd for $C_{14}H_{12}N_2O_2$: C 69.99; H 5.03; N 11.66. Found: C 69.69; H 5.19; N 11.64.

Acknowledgements

Support of this work by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged. J. Q. is grateful to the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP, Brasil) and the Deutscher Akademischer Austauschdienst for financial support. L. H. would like to thank the Deutscher Akademischer Austauschdienst for a scholarship.

References

1. Suami, T. *Topics in Current Chemistry* **1990**, *154*, 257–283.
2. Suami, T.; Ogawa, S. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 22–90.
3. Ferrier, R. J. *J. Chem. Soc. Perkin Trans. 1* **1979**, 1455–1458.
4. Blattner, R.; Ferrier, R. J. *Carbohydr. Res.* **1986**, *150*, 151–162.
5. Ogawa, S.; Iwasawa, Y.; Suami, T. *Chem. Lett.* **1984**, 355–356.
6. Ogawa, S.; Ara, M.; Kondoh, T.; Asitoh, M.; Masuda, R.; Toyokuni, T.; Suami, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1121–1126.
7. Suami, T.; Tadano, K.-I.; Kameda, Y.; Iimura, Y. *Chem. Lett.* **1984**, 1919–1922.
8. Paulsen, H.; von Deyn, W. V.; Röben, W. *Liebigs Ann. Chem.* **1984**, 433–449.
9. Chrétien, F.; Khaldi, M.; Chapleur, Y. *Tetrahedron Lett.* **1997**, *38*, 5977–5980.
10. Chrétien, F.; Khaldi, M.; Chapleur, Y. In *Carbohydrate Mimics*; Chapleur, Y., Ed.; Wiley-VCH: Weinheim, 1998; pp 143–155.
11. Dötz, K. H.; Ehlenz, R.; Paetsch, D. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2376–2378.
12. Piao, M. Z.; Imafuku, K. *Tetrahedron Lett.* **1997**, *38*, 5301–5302.
13. Paton, R. M. In *Levoglucosenone and Levoglucosans Chemistry and Applications*; Witczak, Z. J., Ed.; ATL Press Inc. Science Publishers: Mount Prospect, Illinois, 1994; pp 29–42.
14. Peseke, K.; Thiele, G.; Michalik, M.; Powell, D. R. *Liebigs Ann.* **1997**, 1019–1022.
15. Methling, K.; Aldinger, S.; Peseke, K.; Michalik, M. *J. Carbohydr. Chem.* **1999**, *18*, 429–439.
16. Booma, C.; Balasubramanian, K. K. *Tetrahedron Lett.* **1993**, *34*, 6757–6760.
17. Al-Abed, Y.; Al-Tel, T. H.; Voelter, W. *Tetrahedron* **1993**, *49*, 9295–9306.
18. Mohammad-Ali, A. K.; Chan, T. H.; Thomas, A. W.; Jewett, B.; Strunz, G. M. *Can. J. Chem.* **1994**, *72*, 2137–2143.
19. Deloisy, S.; Ton Thang, T.; Olesker, A.; Lukacs, G. *Tetrahedron Lett.* **1994**, *35*, 4783–4786.
20. Kanno, K.-I.; Hatanaka, K.; Nishimura, S.-I. *Carbohydr. Lett.* **1994**, *1*, 9–12.
21. Grewe, R.; Nolte, E. *Ann. Chem.* **1952**, *575*, 1–17.
22. Barros, M. T.; Maycock, C. D.; Ventura, M. R. *J. Org. Chem.* **1997**, *62*, 3984–3988.
23. Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Chem. Eur. J.* **2000**, 3991–3996.
24. Peseke, K.; Feist, H.; Cuny, E. *Carbohydr. Res.* **1992**, *230*, 319–325.
25. Peseke, K.; Thiele, G.; Michalik, M. *Liebigs Ann.* **1995**, 1633–1636.
26. Gomez, M.; Quincoces, J.; Kuhla, B.; Peseke, K.; Reinke, H. *Carbohydr. Chem.* **1998**, *17*, 57–68.
27. Michalik, M.; Peseke, K.; Radeglia, R. *J. Prakt. Chem.* **1981**, *323*, 506–510.
28. Michalik, M.; Peseke, K. *J. Prakt. Chem.* **1987**, *329*, 705–719.
29. Bredereck, H.; Effenberger, F.; Botsch, H. *Chem. Ber.* **1964**, *97*, 3397–3406.
30. Dieter, R. K. *Tetrahedron* **1986**, *42*, 3029–3096.
31. D. Borrmann, in: E. Müller (Ed.), Houben-Weyl, Methoden der Organischen Chemie, Thieme, Stuttgart 1969; Band VII/4, pp. 404–420.
32. E. Schaumann, in: D. Klamann (Ed.), Houben-Weyl, Methoden der Organischen Chemie, Thieme, Stuttgart, New York 1985; Band E 11, pp. 232–340.