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Synthesis of complex carbobicyclic compounds from sugar allyltins: functionalization of the allylic position in bicyclo[4.3.0]nonene derivatives

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Abstract—Two approaches for the functionalization of the allylic position in 7,8,9-tri-*O*-benzyl-5-substituted bicyclo[4.3.0]non-2-ene derivative **12** were examined. The first method, which involves an epoxidation of the C2–C3 double bond followed by a base induced isomerization, was found to be inappropriate. Although the epoxides were formed in good yields, the base-induced isomerization of the latter performed under the harsh conditions (LDA, HMPA, 80 °C) did not lead to the desired allylic alcohol **13**, but to the tricyclic derivative **15** resulting from the opening of the oxirane ring by the anion generated from the benzyl group at the C9-position. The other, more promising approach, consisted of the *cis*-hydroxylation of the C2–C3 double bond followed by selective protection of one of the hydroxyl groups (at the C2-position) using the dibutyltin methodology. The free hydroxyl group located at the C3 position can be eventually eliminated to give the desired olefin with the double bond between the C3 and C4 carbon atoms of the bicyclic system.

1. Introduction

Highly oxygenated mono-carbocyclic analogues of sugars such as cyclitols,[1] and pseudosugars[2] play an important role in biological processes. Much less is known about the synthesis and biological activity of the bicyclic systems. It has, however, been reported that highly oxygenated—although racemic—bicyclo[4.4.0]decanes **5** and bicyclo[4.3.0]nonanes **6** show potent and selective inhibition at micromolar concentrations against the α- and β-glucosidases.[3]

The most convenient route to such derivatives in enantiomerically pure form, is undoubtedly the chiron approach;[4] the best starting materials appeared to be simple sugars. Recently we proposed a useful route to enantiomerically pure carbobicyclic derivatives from sugar allyltins **1** (Fig. 1), which are readily prepared from the corresponding allylic alcohols in a 3-step sequence.[5] The most striking feature of this methodology

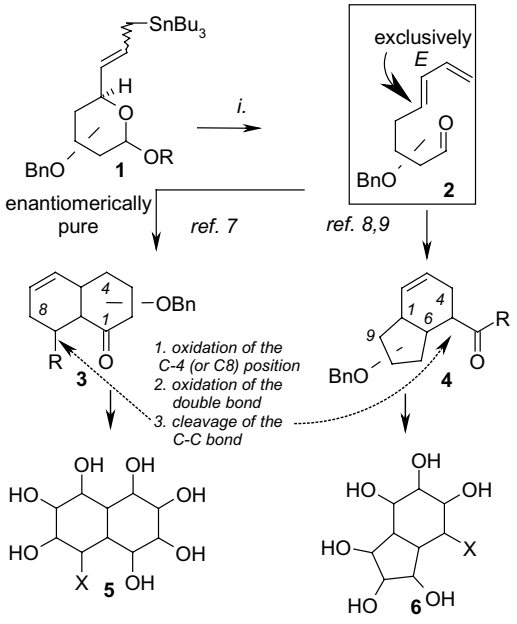

Figure 1. Strategy to fully hydroxylated bicyclic derivatives from sugar allyltins.

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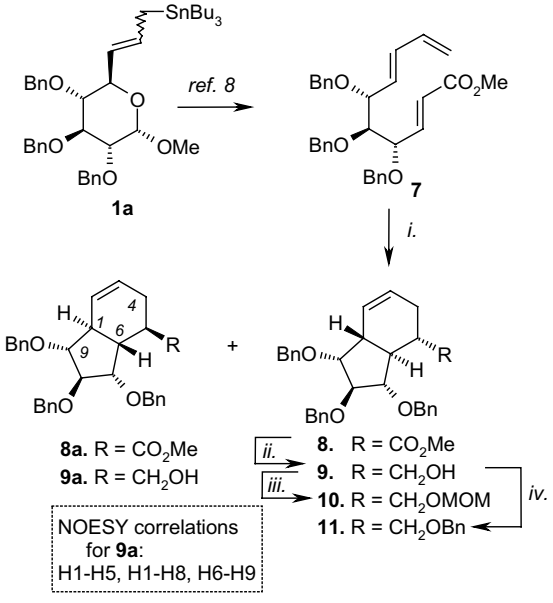
was highly stereoselective fragmentation of compounds **1** induced by Lewis acids, providing dieno-aldehydes **2** with an *E*-configuration across the internal double bond regardless of the geometry of the starting allyltin **1**.[6] Enantiomerically pure bicyclo[4.4.0]decenes **3**[7] and bicyclo[4.3.0]nonenes[8,9] **4** prepared easily from this diene are potential convenient precursors of highly oxidized, enantiomerically pure carbobicyclic derivatives **5** or **6**. Such a transformation requires, among others presented in Figure 1, the oxidation of the allylic methylene function.

Herein we report a model study on the functionalization of the allylic position in such bicyclic precursors.

2. Results and discussion

2.1. Synthesis of the starting material

Compound **8** was selected as a model for the elaboration of the methodology leading to fully oxygenated carbobicyclic derivatives. It was prepared easily from sugar allyltin **1a** via its transformation into triene **7** and subsequent intramolecular Diels–Alder cyclization. The latter process can be catalyzed either with a Lewis acid or performed under high pressure. We reported, that the latter process (Δp), conducted in a 10 mg scale, was highly stereoselective and afforded stereoisomer **8** as the only product.[8] However, when this reaction was performed on a preparative scale, significant amounts of the other stereoisomer **8a** were formed; after reduction of the ester group in the post-reaction mixture **8** and **8a** with diisobutyl aluminum hydride, alcohol **9a** was easily separated from the major product **9** (Scheme 1).

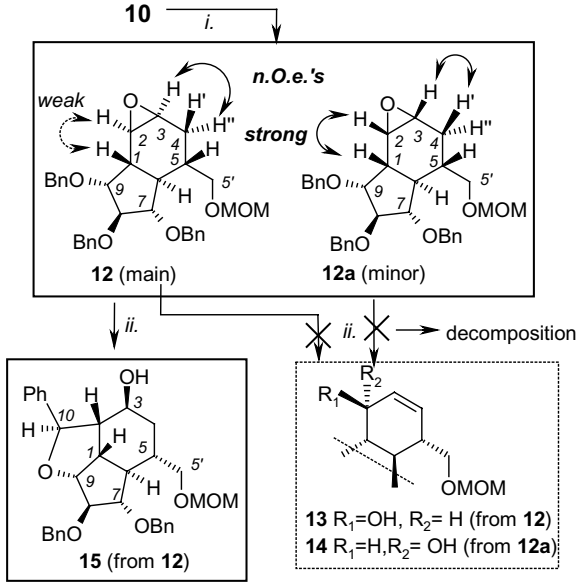


Scheme 1. Reagents and conditions: (i) 10 kbar, toluene–benzene, 4:1; (ii) DIBAL, CH_2Cl_2; (iii) NaH, DMF, MOMCl; (iv) NaH, DMF, BnBr.

The *trans* junction between both rings in **9a** (predicted from the *endo* transition state of this IMDA reaction[8]) was fully confirmed by advanced NMR experiments (NOESY correlations Scheme 1). Protected derivatives of alcohol **9**, compounds **10** and **11**, rather than the primary Diels–Alder adduct **8** should be used in the model studies of funtionalization of the C2–C4 positions, since the presence of the ester grouping in **8** might cause serious problems in subsequent steps.

2.2. Functionalization of the allylic position

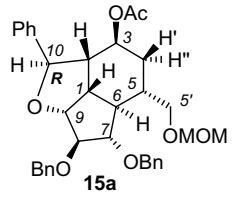
Initially we tried to perform the direct oxidation at the C-4 of olefin **10** (prepared from **9** and MOMCl, Scheme 1). However, although a number of methods are known for the introduction of a heteroatom at the allylic position,[10] none of them were applicable for **10** (either no reaction or decomposition of the starting material was noted). We decided, therefore, to apply the alternative sequence of reactions, that is, oxidation of the double bond, followed by functionalization of the C4 position, based on the well known isomerization of epoxides into allylic alcohols induced with LDA.[11] Epoxidation of **10** should afford 2,3-oxiranes (a mixture of diastereoisomers), which can eventually be converted by action of LDA into the corresponding allylic alcohols. Treatment of **10** with MCPBA indeed afforded a mixture of two stereoisomeric epoxides **12** and **12a** in a ratio of 3:1. The configuration of both isomers was established by the NMR experiments (COSY, HETCOR, NOESY). In the NOESY spectrum of the main derivative **12**, the strong H-3–H-4″ and weak H-1–H-2 correlations were observed. On the other hand, in the spectrum of the minor isomer **12a** the important correlations were detected between H-1–H-2 (strong) and H-3–H-4′ (Scheme 2), thus proving the *trans* geometry for 12 and *cis* for **12a**.[†]



Scheme 2. Reagents and conditions: (i) MCPBA, CH_2Cl_2, rt; (ii) 1. LDA, HMPA, 80 °C, 30 h.

[†] In both compounds **12** and **12a**, NOE's between H-1–H-5, H-1-7, and H-1–H-9 were seen.

The base-induced isomerization of the epoxides, which should have led to allylic alcohols **13** and **14** was found to be troublesome. Under standard conditions (LDA, THF, −78 to 0 °C) and even in refluxing THF, no reaction was observed. The isomerization process was induced in HMPA at elevated temperature. Under these conditions, minor isomer **12a** underwent decomposition, although the main epoxide **12** was converted into a single product, which contained a hydroxyl group. However, the NMR spectra of this product did not support the structure of an allylic alcohol. No double bond was visible in the ^{1}H NMR spectrum; additionally one-proton signal at $\delta = 4.97$ ppm, which correlated (^{1}H–^{13}C g-HSQC) to the carbon resonance at 83.8 ppm was detected. Also one signal of the quaternary (aromatic) carbon atom was shifted strongly toward the lower fields when compared to the starting epoxide. On the basis of these results we propose structure **15**.[‡] This structure was confirmed by NMR experiments performed for the acetyl derivative **15a** including differential NOE and two dimensional correlation experiments such as: COSY, NOESY, as well as gradient selected ^{1}H–^{13}C HSQC and HMBC. Strong NOE effects were noticed for the following pairs of protons: H-10–H-3, H-10–H-6, H-3–H-4″, and H-1–H-2 thus indicating the *cis*-relationship of these protons. As expected, strong NOE's effects were also observed between H-1–H-9, H-1–H-7, H-7–H-5, H-6–H-8 as well as H-7–H-9 indicating the *cis*-relationship between each other (Fig. 2). In this spectrum two sets of protons can be distinguished: (1) H-1, H-2, H-5, H-7, H-9 (with a *cis*-relationship to each other), and (2) H-3, H-4″, H-6, H-8, H-10 (*cis*-relationship). No significant NOE's were observed between any proton from groups (1) and (2).



H6-H10	**9.5%**	**H10-H3**	**5.2%**
H3-H4"	**5.2%**	**H1-H2**	**3.2%**
H7-H9	4.5%	H1-H9	6.2%
H5-H7	4.2%	H6-H8	4.5%

Figure 2. NOE values (C_6D_6 at 303 K) for **15a**.

To explain this unexpected formation of the tricyclic product 13 in a base-catalyzed rearrangement of epoxide **12**, one has to postulate abstraction of a proton from the neighboring benzyloxy group from the C9 position; the thus formed intermediate **16** underwent cyclization via attack of this anion at the C2 position with simultaneous opening of the oxirane ring (Fig. 3).

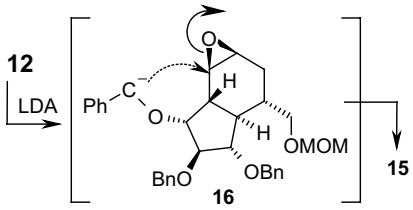
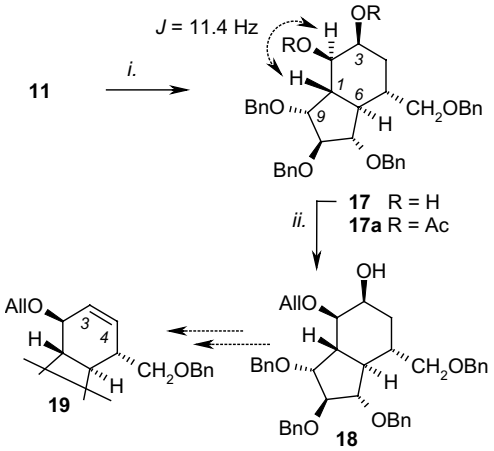


Figure 3. Rearrangement of epoxide **12** with LDA.

Although two stereoisomers are possible (differing at the C10 center) only the one with the *R*-configuration could be formed. The severe interaction between the phenyl ring with the rest of molecule prohibits formation of the alternative (10*S*)-stereoisomer of **15**.

Another approach, based on the *cis*-hydroxylation of the double bond, followed by a selective protection[12] of one of the hydroxyl groups in the resulting diol **17**, and (further) elimination of water molecule, was then applied to functionalize the C-4 position. For this purpose another derivative of alcohol **9**, benzyl ether **11**, was selected (the MOM protected derivative **10**, used in 'epoxidation methodology' might cause problems during elimination of water under acidic conditions). Osmylation of **11** under standard conditions[13] afforded diol **17** as a single product. Its configuration was easily established from the ^{1}H NMR spectrum, in which the large coupling constant between H-1 and H-2 was seen (Scheme 3).

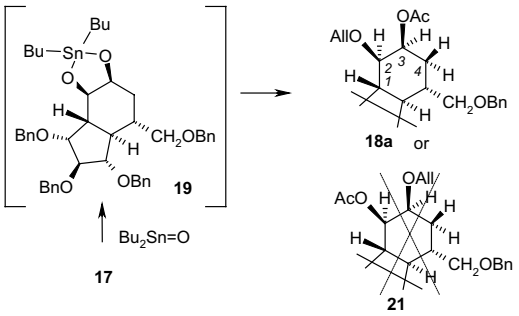


Scheme 3. Reagents and conditions: (i) OsO_4 (cat), NMO, THF/H_2O; (ii) 1. $Bu_2Sn{=}O$, benzene, 80 °C; 2. DMF, 2 h, 100 °C; All-l.

The C-2 hydroxyl group was selectively protected as an allyl ether using the well established tin activation methodology[12] ($Bu_2Sn{=}O$, then allyl iodide[§]). Prove of the structure of **18** (and not the regioisomeric **21**) came from the ^{1}H NMR spectrum of acetate **18a**. The low-field resonance at $\delta = 5.53$ ppm correlated (COSY) to two high and one low field signals (both H-4 and H-2 at $\delta = 1.8$, 2.16, and 3.66 ppm, respectively).

[‡] The alternative structure resulting from the opening of the epoxide ring at the C3 position was excluded on the basis of the NMR correlation experiments.

[§] Reaction with allyl bromide did not afford any product; the starting material remained unchanged.



3. Conclusion

Although the yield of the mono-protected derivative is low, the position of the substitution (protection of the O-2 with the free OH at the C3) is appropriate for further transformations. Thus, after optimization of this last step, the three-step sequence (osmylation, selective protection, and later elimination of water) can be applied for the functionalization of the allylic bridge in the carbobicyclic derivatives.

4. Experimental

4.1. General

NMR spectra were recorded with a Bruker AM 500 spectrometer for solutions in $CDCl_3$ (internal Me_4Si) unless otherwise stated. Most of the resonances were assigned by COSY (^1H–^1H) and/or HETCOR and DEPT correlations. The ^1H- and ^{13}C-aromatic resonances occurring at the typical δ values were omitted for simplicity. The relative configurations of the protons were determined by NOESY and/or NOE experiments. Mass spectra were recorded with an ESI/MS Mariner (PerSeptive Biosystem) mass spectrometer. Column chromatography was performed on silica gel (Merck, 70–230 or 230–400 mesh). Organic solutions were dried over anhydrous magnesium or sodium sulfate. Optical rotations were measured with a Perkin–Elmer 241 apparatus for chloroform solutions (c = 1) at room temperature.

4.2. High pressure Diels–Alder reaction of triene 7

A solution of the triene **7**[8] (1.2 g, 2.4 mmol) in a toluene–benzene mixture (12 mL, 4:1 v/v) was kept in a piston–cylinder type apparatus[14] at room temperature under 10 kbar pressure for 24 h. The product was isolated by column chromatography (hexane–ethyl acetate, 6:1) to afford a mixture of **8** and **8a** (1.0 g, 2.00 mmol, 83%). In the ^1H NMR spectrum of this mixture, signals from (1*R*,5*S*,6*R*,7*S*,8*S*,9*R*)-7,8,9-tri-*O*-benzyl-5-methoxycarbonyl-bicyclo[4.3.0]non-2-ene **8**[8] were detected together with other signals, that can be connected with its (1*S*,5*R*,6*S*)-stereoisomer (isolated and identified in the next step as **9a**).

4.3. Reduction of a mixture of 8 and 8a

To a cooled (to −21 °C) solution of **8** and **8a** (900 mg, 1.81 mmol) in dry CH_2Cl_2 (20 mL), DIBAL (1.2 equiv, 4.2 mL of a 1 M solution in hexane) was added and the mixture stirred for 1 h. Water (5 mL) was carefully added to decompose the excess of the hydride and the mixture partitioned between water (50 mL) and ethyl acetate (50 mL). The organic phase was separated, washed with water (50 mL), dried, concentrated, and the crude products isolated by column chromatography (hexane–ethyl acetate, 5:1) to afford **9** (500 mg, 1.06 mmol, 61%) and **9a** (200 mg, 0.42 mmol, 24%).

4.3.1. (1*R*,5*S*,6*R*,7*S*,8*S*,9*R*)-7,8,9-Tri-*O*-benzyl-5-hydroxymethyl-bicyclo[4.3.0]non-2-ene 9. ^1H NMR δ: 5.82 (m, H-2), 5.73 (m, H-3), 4.75–4.38 (3 × OCH_2Ph), 3.97 (d, J = 3.2 Hz, H-8), 3.86–3.80 (m, J = 10.0, 3.2 Hz, H-7, H-9), 3.63 (dd, J = 11.6, 3.5 Hz, H-5′[¶]), 3.42 (m, second H-5′), 2.35 (m, H-1), 2.15 (m, H-6), 2.07 (m, H-4), 1.96 (m, H-4), 1.81 (m, H-5); ^{13}C NMR δ: 138.4, 137.6, 137.1 ($C_{quat.}$), 128.9 (C-3), 125.5 (C-2), 89.5 (C-8), 88.6 (C-7), 80.9 (C-9), 72.0, 71.7, 71.1 (3 × OCH_2Ph), 65.9 (C-5) 44.6 (C-6), 44.1 (C-1), 41.5 (C-5), 29.1 (C-4); HRMS m/z: 493.2358 [$C_{31}H_{34}O_4Na$ (M+Na^+) requires 493.2349]. $[\alpha]_D$ = +69.7 (c 1, $CHCl_3$).

4.3.2. (1*S*,5*R*,6*S*,7*S*,8*S*,9*R*)-7,8,9-Tri-*O*-benzyl-5-hydroxymethyl-bicyclo[4.3.0]non-2-ene 9a. ^1H NMR δ: 5.98 (m, H-3), 5.67 (m, H-2), 4.70–4.46 (3 × OCH_2Ph), 4.08 (d, J = 3.6 Hz, H-8), 4.05 (d, J = 4.6 Hz, H-7), 3.70 (dd, J = 3.6, 10.3 Hz, H-9), 3.58 (m, H-5′), 2.84 (m, H-1), 2.26 (m, H-4, H-5), 1.84 (m, H-4), 1.66 (m, J = 4.6 Hz, H-6); ^{13}C NMR δ: 127.7 (C-3), 127.3 (C-2), 89.1 (C-9), 88.9 (C-8), 81.7 (C-7), 72.1, 71.6, 70.3 (3 × OCH_2Ph), 66.1 (C-5′), 45.1 (C-6), 44.4 (C-1), 36.2 (C-5), 29.5 (C-4); HRMS m/z: 493.2366 [$C_{31}H_{34}O_4Na$ (M+Na^+) requires 493.2349]. NOESY: H-1–H-4, H-1–H-5, H-1–H-8, H-2–H-3, H-4–H-5′, H-6–H-5′, H-6–H-7, H-6–H-9. $[\alpha]_D$ = −26.0 (c 1, $CHCl_3$).

4.4. Preparation (1*R*,5*S*,6*R*,7*S*,8*S*,9*R*)-7,8,9-tri-*O*-benzyl-5-methoxymethylene-methyl-bicyclo[4.3.0]non-2-ene 10

To a cooled (0 °C) solution of alcohol **9** (500 mg, 1.06 mmol) in DMF (20 mL), sodium hydride (1.2 equiv, 57 mg, 55% suspension in mineral oil) was added and the mixture stirred for 30 min. Methoxymethyl chloride (1.2 equiv, 0.090 mL) was added and the mixture stirred for another 2 h at rt. Water (5 mL) was carefully added to decompose excess of hydride and the mixture partitioned between water (50 mL) and ethyl acetate (50 mL). The organic phase was separated, washed with water (50 mL), dried, concentrated, and the crude product isolated by column chromatography (hexane–ethyl acetate, 5:1). Yield 440 mg (74%); ^1H NMR δ: 5.84–5.72 (m, H-2, H-3), 4.69–4.40 (3 × OCH_2Ph and OCH_2O), 3.90 (d, J = 2.8 Hz, H-8), 3.81 (d, J = 4.4 Hz, H-9), 3.77 (dd, J = 3.9, 10.8 Hz, H-7), 3.72 (dd, J = 2.8, 9.4 Hz, H-5′), 3.43 (m, second H-5′), 3.31 (s, OCH_3), 2.36 (m, H-1, H-4), 2.10 (m, H-6), 1.96 (m, H-4, H-5); ^{13}C NMR δ: 128.8, 119.8 (C-2,

[¶] Numbering 5′ refers to –CH_2OH grouping connected with the C-5 atom.

C-3), 96.7 (OCH_2O), 89.6, 88.9, 86,5 (C-7, C-8, C-9), 71.74, 71.48, 71.22 (3 × OCH_2Ph), 70.9 (C-5′), 55.1 (OCH_3), 44.4, 44.2, 39.9 (C-1, C-5, C-6), 29.7 (C-4); HRMS *m/z*: 537.2606 [$C_{33}H_{38}O_5Na$ (M+Na^+) requires 537.2611]. $[\alpha]_D$ = +15.7 (*c* 1, $CHCl_3$).

4.5. Preparation of (1*R*,5*S*,6*R*,7*S*,8*S*,9*R*)-7,8,9-tri-*O*-benzyl-5-benzyloxy methyl-bicyclo[4.3.0]non-2-ene 11

To a cooled (0 °C) solution of alcohol **9** (500 mg, 1.06 mmol) in DMF (20 mL), sodium hydride (1.2 equiv, 57 mg, 55% suspension in mineral oil) was added and the mixture stirred for 30 min. Benzyl bromide (1.2 equiv, 0.150 mL) was added and the mixture stirred for another 3 h at rt. Water (5 mL) was carefully added to decompose excess of hydride and the mixture partitioned between water (50 mL) and ethyl acetate (50 mL). The organic phase was separated, washed with water (50 mL), dried, concentrated, and the crude product was isolated by column chromatography (hexane–ethyl acetate, 6:1). Yield 460 mg (77%). ^{1}H NMR δ: 5.82 (m, H-2), 5.74 (m, H-3), 4.68–4.38 (4 × OCH_2Ph), 3.88 (d, *J* = 2.8 Hz, H-8), 3.80 (d, *J* = 4.4 Hz, H-9), 3.75 (dd, *J* = 9.3, 4.1 Hz, H-5′), 3.70 (dd, *J* = 9.2, 2.7 Hz, H-7), 3.35 (m, second H-5′), 2.44 (m, H-4), 2.32 (m, H-1), 2.09 (m, H-6), 2.01 (m, H-5), 1.96 (m, H-4); ^{13}C NMR δ: 128.9 (C-3), 125.6 (C-2), 89.6 (C-8), 89.1 (C-7), 80.8 (C-9), 74.1 (C-5′), 72.9, 71.7, 71.6, 70.8 (4 × OCH_2Ph), 44.43 (C-1), 44.39 (C-6), 40.0 (C-5), 31.3 (C-4); HRMS *m/z*: 583.2839 [$C_{38}H_{40}O_4Na$ (M+Na^+) requires 583.2819]. NOESY: H-1–H-2, H-1–H-5, H-1–H-7, H-1–H-9, H-2–H-3, H-3–H-4, H-5–H-7, H-6–H-8. $[\alpha]_D$ = +142.5 (*c* 1, $CHCl_3$).

4.6. Epoxidation of (1*R*,5*S*,6*R*,7*S*,8*S*,9*R*)-7,8,9-tri-*O*-benzyl-5-methoxymethylene-methyl-bicyclo[4.3.0]non-2-ene 10

Compound **10** (500 mg, 0.97 mmol) was dissolved in dry methylene chloride (25 mL) to which *m*-chloroperbenzoic acid (1.5 equiv, 1.5 mmol, 260 mg) was added. The mixture was stirred for 24 h at room temperature and then diluted with ethyl acetate (100 mL). The organic phase was washed with 2% aq NaOH (15 mL), water (100 mL), and brine (100 mL), dried, and concentrated. Column chromatography (hexane–ethyl acetate, 5:1) of the residue afforded **12** (360 mg, 70%) and **12a** (75 mg, 14.5%) as oils.

4.6.1. (1*R*,2*R*,3*S*,5*S*,6*R*,7*S*,8*S*,9*R*)-7,8,9-Tri-*O*-benzyl-2,3-epoxy-5-methoxymethylene-methyl-bicyclo[4.3.0]nonane 12.

^{1}H NMR δ: 3.94 (d, *J* = 4.0 Hz, H-9), 3.89 (d, *J* = 2.8 Hz, H-8), 3.62 (m, H-5′,7), 3.41 (m, H-2,5′), 3.29 (s, OCH_3), 3.23 (m, H-3), 2.38 (dd, *J* = 10.7, 1.0 Hz, H-4), 1.84 (m, H-1,6), 1.60 (m, second H-4 and H-5); ^{13}C NMR δ: 138.1, 138.0, 137.7 ($C_{quat.}$), 96.5 (O–CH_2–O), 88.6 (C-7), 87.8 (C-9), 80,6 (C-8), 71.9, 71.7, 70.7 (3 × OCH_2Ph), 70.5 (C-5′), 55.0 (OCH_3), 53.4 (C-3), 52.8 (C-2), 44,6 (C-1), 43.4 (C-6), 36.7 (C-5), 29.6 (C-4); HRMS *m/z*: 553.2571 [$C_{33}H_{38}O_6Na$ (M+Na^+) requires 553.2561]. NOESY: H-1–H-4, H-1–H-5, H-1–H-7, H-1–H-9, H-2–H-3, H-3–H-4, H-5′–H-6. $[\alpha]_D$ = +21.4 (*c* 1, $CHCl_3$).

4.6.2. (1*R*,2*S*,3*R*,5*S*,6*R*,7*S*,8*S*,9*R*)-7,8,9-Tri-*O*-benzyl-2,3-epoxy-5-methoxymethylene-methyl-bicyclo[4.3.0]nonane 12a.

^{1}H NMR δ: 3.92 (dd, *J* = 4.3 Hz, H-9), 3.88 (m, H-8), 3.68 (dd, *J* = 9.8, 4.2 Hz, H-5′), 3.64 (dd, *J* = 9.3, 3.9 Hz, H-7), 3.35 (m, H-2,5′), 3.30 (s, OCH_3), 3.15 (dd, *J* = 4.5 Hz, H-3), 2.21 (m, H-4,6), 1.99 (dd, *J* = 13.3 Hz, 4.2, H-1), 1.78 (m, H-4), 1.63 (m, H-5); ^{13}C NMR δ: 138.5, 138.3, 137.7 ($C_{quat.}$), 96.6 (O–CH_2–O), 89.1 (C-7), 88.0 (C-8), 80.9 (C-9), 71.8, 71.39, 71.0 (3 × OCH_2Ph), 71.1 (C-5′), 55.1 (OCH_3), 52.7 (C-2), 50.3 (C-3), 45.2 (C-1), 39.4 (C-5), 39.1 (C-6), 28.4 (C-4); HRMS *m/z*: 553.2564 [$C_{33}H_{38}O_6Na$ (M+Na^+) requires 553.2561]. NOESY: H-1–H-2, H-1–H-5, H-1–H-7, H-1–H-9, H-4–H-3, H-4–H-5. $[\alpha]_D$ = +19.9 (*c* 1, $CHCl_3$).

4.7. Isomerization of 12 under strongly basic conditions

To a solution of LDA [freshly prepared from diisopropylamine (0.0924 mL, 0.659 mmol) and BuLi (0.275 mL of a 2.5 M solution in hexane) in 3 mL of dry THF at 0 °C] a solution of **12** (250 mg, 0.47 mmol) in freshly distilled HMPA (5 mL) was added under an argon atmosphere and the solution heated at 80 °C. After 30 h TLC (hexane–ethyl acetate, 4:1) indicated the disappearance of the starting material and the formation of a new more polar product. After cooling to rt, ethyl acetate (10 mL) was added and the organic phase washed with water (2 × 15 mL), brine (15 mL), dried, and concentrated. Purification of the residue by column chromatography (hexane–ethyl acetate, 4:1) afforded **12** (120 mg, 48%).

This product was characterized as (1*S*,2*S*,3*S*,5*R*,6*R*,7*S*,8*S*,9*R*,10*R*)-3-acetoxy-7,8-bis-benzyloxy-10-phenyl-5-methoxy-10-phenyl-5-methoxymethylene-methyl-11-oxa-tricyclo[4.3.0.$2^{2,9}$]undekan **15a**: NMR (benzene-d_6, 303 K; for numbering see Fig. 2): ^{1}H δ: 5.46 (m, H-3), 4.97 (d, *J* = 8.4 Hz, H-10), 4.87 and 4.69 (AB of O^8CH_2Ph, J_{AB} = 11.9 Hz), 4.72 and 4.47 (AB of O^7CH_2Ph, J_{AB} = 11.8 Hz), 4.66 (s, OCH_2O), 4.37 (d, *J* = 5.1 Hz, H-9), 4.16 (d, *J* = 5.6 Hz, H-8), 4.00 (dd, *J* = 3.3, 9.7 Hz, H-5′), 3.83 (dd, *J* = 5.6, 10.7 Hz, H-7), 3.66 (dd, *J* = 7.5, 9.7 Hz, H-5′), 3.33 (s, OCH_3), 2.40 (m, H-2), 2.24 (m, H-1), 2.16 (m, H-4), 2.00 (m, H-5), 1.98 (m, H-6), 1. 75 (m, H-4), 1.63 (s, OCOCH_3); ^{13}C δ: 143.4, 139.3, 138.6 ($C_{quat.}$), 169.0 [CH_3(*C*OO)], 97.0 (OCH_2O), 92.6 (C-8), 88.0 (C-7), 85.3 (C-9), 83.8 (C-10), 72.2 (O^8CH_2Ph), 72.1 (O^7CH_2Ph), 70.5 (C-3), 70.3 (C-5′), 55.0 (OCH_3), 53.5 (C-2), 46.4 (C-1), 41.8 (C-6), 36.6 (C-5), 33.3 (C-4), 20.7 [CH_3(COO)]. HRMS *m/z*: 595.4037 [$C_{35}H_{41}O_7Na$ (M+Na^+) requires 595.4028]. NOESY: H-1–H-2, H-1–H-9, H-1–H-7, H-7–H-5, H-6–H-8, H-3–H-10, H-3–H-4, H-10–H-6, H-7–H-9 (for quantitative NOE values see Fig. 2). $[\alpha]_D$ = +107.7 (*c* 1, $CHCl_3$).

4.8. Osmylation of the olefin 11

To a solution of **11** (150 mg, 0.27 mmol) in THF (5 mL), *t*-butyl alcohol (0.3 mL) and water (0.1 mL), *N*-methylomorpholine *N*-oxide (80 mg, 0.6 mmol) was added followed by a catalytic amount of osmium tetraoxide

(0.5 mL of a 2% solution in toluene). The mixture was stirred at rt until disappearance of the starting material (24 h; TLC control in hexane–ethyl acetate, 4:1). Methanol (15 mL) was added followed by saturated aqueous $NaHSO_3$ solution. After stirring for 30 min, the mixture was partitioned between water (20 mL) and ethyl acetate (50 mL). The organic phase was separated, washed with water (50 mL), brine (20 mL), dried, concentrated, and the crude product purified by column chromatography (hexane–ethyl acetate, 3:1) to afford (1*R*,2*R*,3*R*,5*S*, 6*R*,7*S*,8*S*,9*R*)-7,8,9-tri-*O*-benzyl-2,3-di-hydroxy-5-benzyloxymethyl-bicyclo[4.3.0]nonane **17** (150 mg, 94%). This diol was characterized as diacetate **17a**; ^{1}H NMR δ: 5.51 (m, H-3), 5.11 (dd, J = 2.9 Hz, 11.4, H-2), 3.85 (d, J = 2.45 Hz, H-7), 3.78 (m, H-8), 3.72 (d, J = 3.95 Hz, H-9), 3.70 (m, H-5′), 3.25 (m, H-5′), 2.15 (m, H-1, H-4), 1.96 (m, H-5, H-6), 1.42 (m, H-4); ^{13}C NMR δ: 90.2 (C-7), 87.76 (C-8), 78, 15 (C-9), 72.8 (C-5′), 70.8 (C-2), 73.2, 71.6, 71.7, 70.7 (4 × O*C*H$_2$Ph), 69.11 (C-3), 4.9 (C-6), 42.9 (C-1), 38.6 (C-5), 33.5 (C-4).

4.9. Selective protection of diol 17

To a solution of **17** (200 mg, 0.34 mmol) in benzene (25 mL), dibutyltin oxide (1 equiv, 85 mg) was added and the mixture boiled under reflux for 1 h. The solvent was removed in vacuum and the oily residue dissolved in DMF (10 mL). Allyl iodide (1.5 equiv, 0.050 mL, 0.5 mmol) was added and the mixture heated at 100 °C. Under these conditions TLC (hexane–ethyl acetate, 1:1) showed the formation of a new product; however significant decomposition of the starting material was also observed, so the reaction was stopped after 2 h. After cooling to rt, the mixture was partitioned between diethyl ether (40 mL) and water (40 mL). The organic phase was separated, washed with water (40 mL), brine (20 mL), dried, and concentrated, and product **18** isolated by column chromatography (hexane–ethyl acetate, 4:1 to 2:1) to afford (1*R*,2*R*,3*R*, 5*S*,6*R*,7*S*,8*S*,9*R*)-2-*O*-allyl-7,8,9-tri-*O*-benzyl-3-hydroxy-5-benzyloxymethyl-bicyclo[4.3.0]nonane **18** (40 mg, 19%).

This product was characterized as an acetate; ^{1}H NMR δ: 5.85 (m, OCH$_2$C*H*=CH$_2$), 5.53 (m, H-3), 5.24 and 5.20 (both OCH$_2$CH=C*H*$_2$), 4.13 (m, one of O*C*H$_2$CH=CH$_2$), 3.95 (d, J = 2.1 Hz, H-9), 3.88 (m, second O*C*H$_2$CH=CH$_2$), 3.84 (d, J = 2.6 Hz, H-8), 3.74 (dd, J = 2.6, 8.2 Hz, H-7), 3.66 (m, H-2, H-5′), 3.26 (m, second H-5′), 2.16 (m, H-1, H-4), 1.90 (m, H-5, H-6), 1.8 (m, H-4); ^{13}C NMR δ: 134.9 (C-2′), 117.2 (C-3′), 90.4 (C-7), 88.3 (C-9), 79.5 (C-8), 76.2 (C-2), 73.0, 71.8, 71.7, 71.2 (4 × O*C*H$_2$Ph), 72.6 (C-5′), 70.0 (C-1′), 67.8 (C-3), 45.2 (C-6), 44.6 (C-1), 37.4 (C-5), 33.6 (C-4). HRMS *m*/*z*: 699.3310 [$C_{43}H_{48}O_7Na$ (M+Na$^+$) requires 699.3292]. NOESY: H-1–H-9, H-2–H-3, H-6–H-8, H-5–H-7. $[\alpha]_D$ = +25.4 (*c* 1, $CHCl_3$).

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