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TETRAHEDRON: *ASYMMETRY*

Synthesis of highly oxygenated enantiomerically pure *cis*-bicyclo[4.3.0]nonanes from secondary sugar allyltin derivatives☆

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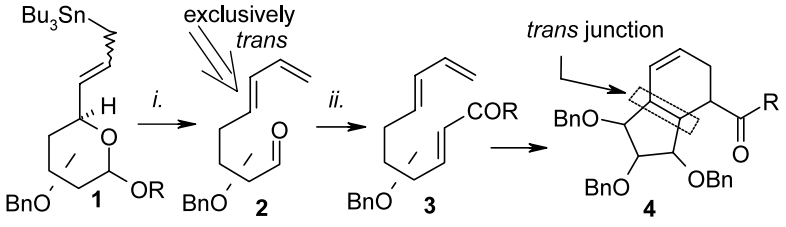
Abstract—Secondary sugar allyltin derivatives of the D-series: Sug-CH($SnBu_3$)-CH=CH_2 (obtained in an S_N2' reaction of the corresponding primary allylic mesylates with 'Bu_3SnCu') with the *S*-configuration at the stereogenic center bearing the -$SnBu_3$ group decompose at 140°C to dienoaldehydes: CH_2=CH-CH=CH-[$(CHOR)_3$]-CHO with the *cis* geometry across the internal double bond. Such aldehydes react with the stabilized Wittig reagents to afford trienes, cyclization of which provides highly oxygenated enantiomerically pure *cis*-bicyclo[4.3.0]nonenes. This methodology is complementary to that recently proposed by us leading to such bicyclic systems, but with the *trans* junction between the five- and six-membered rings.

1. Introduction

Carbobicyclic compounds (bicyclo[4.3.0]nonanes and bicyclo[4.4.0]decanes) are interesting synthetic targets. One of the most useful routes leading to such derivatives consists of an intramolecular Diels–Alder reaction of the corresponding trienes, e.g. **3** (Scheme 1).[2] They may be prepared from appropriate dienoaldehydes, e.g. **2**, by reaction with ylides. We have previously reported, that dienes **2** with the *trans* configuration across the internal double bond are conveniently prepared by controlled decomposition of the primary sugar allyltins **1** with a Lewis acid (Scheme 1).[3]

Stereoselective [4+2] cyclization of trienes **3** provides highly oxygenated bicyclo[4.3.0]nonanes **4** with a *trans* ring-junction; the geometry of the bicyclic product **4** arises from the *endo* transition state of this IMDA process (Scheme 1).[4]

The alternative perhydroindane with the *cis* ring-junction should be prepared from the dienoaldehyde with the opposite *cis*-configuration across the internal double bond if the *endo* transition state is assumed. Recently we have found, that such *cis*-dienes are formed during thermal decomposition of secondary sugar allyltins[1] obtained by reaction of sugar allylic



Scheme 1. *Reagents and conditions*: *i.* Ref. 3; $ZnCl_2$, methylene chloride, rt, 2 h; *ii.* Ref. 4; Ph_3P=CHCOR; then cyclization.

☆ See Ref. 1.

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mesylates (or bromides) with tri-*n*-butyltin cuprate.[3,5] Herein, application of secondary sugar allyltins in stereocontrolled synthesis of highly oxygenated bicyclo[4.3.0]nonanes with the *cis* junction between the carbocyclic rings is reported.

2. Thermal reaction of secondary sugar allyltin derivatives with ylides: synthesis of highly oxygenated *cis*-bicyclo[4.3.0]perhydroindanes

Secondary D-*gluco*-configurated sugar allylltin derivative **6a** was obtained by the S_N2' reaction of the corresponding allylic mesylate **5a** with the soft nucleophile tri-*n*-butyltin cuprate ('Bu_3SnCu').[6] This process was highly stereoselective; only one isomer of **6** was produced[3] with the *S*-configuration at the newly created stereogenic center.[5]

Compound **6** decomposed at high temperature (140°C) to dienoaldehyde **7a** with the *cis*-geometry across the internal double bond as determined from the ^1H NMR spectrum of its derivative **8a** (Scheme 2).

The aldehyde formed by thermal decomposition of the appropriate allyltin could be either isolated pure or react in situ with ylides, thus forming trienes, e.g. **9a** (Scheme 2), which may further undergo cyclization. Indeed, thermal decomposition of **6a** performed in the presence of methoxycarbonylmethylene triphenylphosphorane provided the *cis*-perhydroindene **10a** as the only isomer in good yield.[1] Configuration of this derivative was assigned from the ^1H NMR (NOESY) experiments. The strong NOE correlation between H-1 and H-6 indicated the *cis* ring-junction, while correlations H6–H8, H5–H7, and H5–H9 indicated the 5*S*,6*S* and consequently 1*S* configurations in **10a** (see Scheme 2 and Section 4).

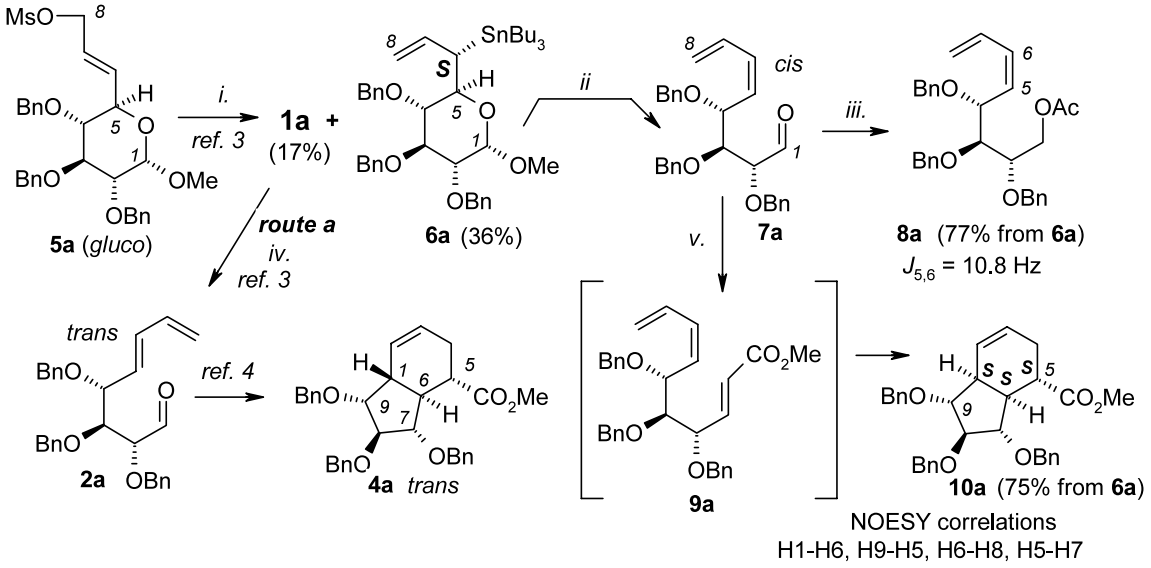
As shown in Scheme 2, the synthesis of bicyclo[4.3.0]nonene system from the *cis*-dienoaldehyde **7a** is complementary to that demonstrated previously by us (route a in Scheme 2) leading to the bicyclic derivative **2a** with the *trans* ring-junction.[4]

The D-*manno*-configurated derivative **6b**[5] behaved similarly. Its thermal decomposition at 140°C provided the *cis*-dienoaldehyde **7b**; the coupling constant $J_{5,6}=10.1$ Hz observed in the spectrum of acetate **8b** confirmed the geometry of the internal double bond. When the decomposition experiment was conducted in the presence of $Ph_3P{=}CHCO_2Me$ the tandem Wittig/Diels–Alder reaction occurred affording the *cis*-bicyclo [4.3.0]nonene derivative **10b** as a mixture of two stereoisomers in the ratio 6:1 (Scheme 3).

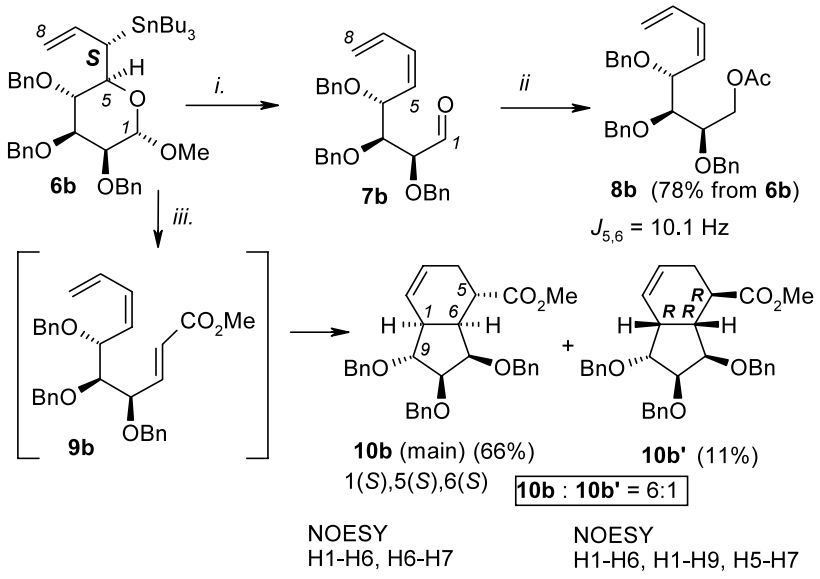
The configurations of both stereoisomers were established on the basis of the NOESY correlation spectra. In both compounds the strong H1–H6 correlations indicated the *cis*-junction between the five- and six-membered rings. In the spectrum of **10b** the correlation between H-6 and H-7 was observed, thus establishing the 6*S* configuration. In the spectrum of the minor isomer **10b**′ the NOE effect between H-1 and H-9 indicated the 1*R* configuration.

The high *cis* selectivity of the cyclization might be explained assuming an *endo* transition state. The preferred transition state (**A** in Fig. 1) in the cyclization of the triene **9a** should lead to the bicyclic isomer **10a** with the *cis* ring-junction. The other possible transition state (**B** in Fig. 1) is disfavored, because of two severe steric interactions and, therefore, the alternative *cis*-perhydroindene (**10a**′) is not formed.

The situation is similar with **9b**. Again the transition state **C** (Fig. 2) is preferred providing the perhydroindene derivative **10b** with the same (as in **10a**) configura-



Scheme 2. *Reagents and conditions*: *i.* 'Bu_3SnCu'; *ii.* xylene (140°C), 3 h; *iii.* $NaBH_4$, then Ac_2O; *iv.* $ZnCl_2$; *v.* 140°C, $Ph_3P{=}CHCO_2Me$.



Scheme 3. *Reagents and conditions*: *i.* Boiling xylene (140°C), 4 h; *ii.* $NaBH_4$, then Ac_2O; *iii.* boiling xylene, $Ph_3P{=}CHCO_2Me$, 3–4 h.

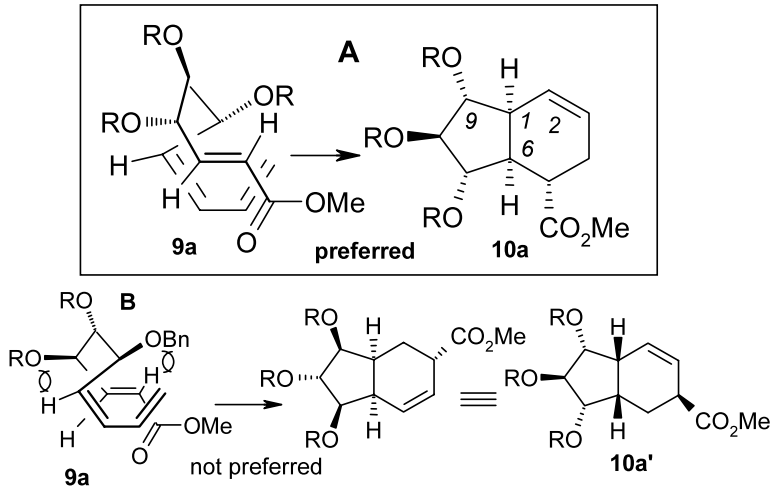


Figure 1. The transition states in the intramolecular cyclization of the triene **9a**.

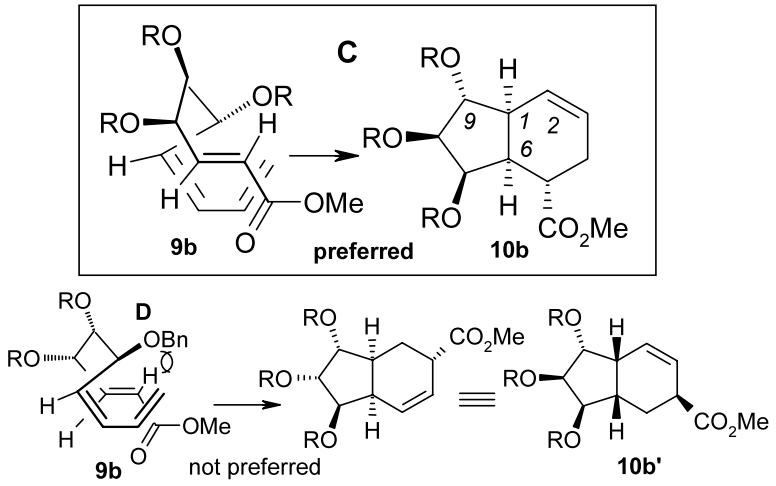


Figure 2. The transition states in the intramolecular cyclization of the triene **9b**.

tion at the ring junction. However, the alternative *endo*-transition state (**D** in Fig. 2) is less disfavored (than **B** in Fig. 1) and the alternative 1*R*,6*R* isomer is formed in significant amounts.

3. Summary

The secondary sugar allyltin derivatives of the D-series, with the *S*-configuration at the stereogenic center bearing the -$SnBu_3$ group decompose at 140°C affording the dienoaldehydes with the *cis*-configuration across the internal double bond. If the thermal decomposition is conducted in the presence of $Ph_3P{=}CHCO_2Me$, the dienaldehydes react with the ylide providing the corresponding trienes, which in situ undergo cyclization to *cis*-perhydroindenes in good yields. The method presented in this paper is complementary to that reported previously by us, which allows preparation of the bicyclo[4.3.0]nonenes with the *trans* ring-junction between both rings.

4. Experimental

4.1. General

Optical rotations were measured with a JASCO DIP 360 automatic polarimeter at 20±2°C. NMR spectra were recorded with Bruker AM-500 (500 MHz) specrometer in $CDCl_3$ solutions with Me_4Si as an internal standard. ^1H and ^{13}C signal of aromatic groups occurred at the expected chemical shifts were omitted in the description of spectra. ^{13}C NMR spectra were recorded in the DEPT 135 mode. The proton and carbon resonances in **8a**,**b** and **10a**,**b**,**b′** were assigned by the COSY and HETCOR correlations. Mass spectra (LSIMS, positive mode) were recorded on an AMD-604 mass spectrometer. HPLC was carried out on a Shimadzu instrument: central unit C-R4A, pump unit LC-8A, UV detector SPD-6A on a column Machery Nagel Nucleosil 100-7. TLC was performed on silica gel HF-254 ready plates and column chromatography on silica gel 230–400 or 70–230 mesh (E. Merck). Organic solutions were dried over anhydrous magnesium or sodium sulfate.

4.2. Thermal decomposition of secondary sugar allyltin derivatives

A solution of the corresponding allyltin derivative **6a** or **6b** (763 mg, 1 mmol) was dissolved in dry xylene (5 mL) and boiled under reflux until TLC (hexane–ethyl acetate, 5:1) indicated disappearance of the starting material and formation of a new more polar product (2–3 h). The mixture was cooled to room temperature, concentrated and the residue was dissolved in methanol/water (5:1 v/v, 6 mL). Sodium borohydride (50 mg) was added and the mixture was stirred for 30 min at room temperature. Water (10 mL) was added, the organic phase was separated, dried, and concentrated to ca half of the volume. To a residue (co-evaporated twice with toluene) pyridine (4 mL) and acetic anhydride (2 mL) were added followed by a catalytic amount of DMAP (20 mg) and the mixture was kept at rt for 30 min. It was then concentrated in vacuum and the product was isolated by column chromatography (hexane–ethyl acetate, 10:1). From **6a** acetate **8a** was obtained in 77% yield (374 mg) and from **6b** compound **8b** in 78% yield (379 mg).

4.2.1. (2*S*,3*S*,4*R*,*Z*)-1-Acetoxytribenzyloxyocta-5,7-diene 8a. $[\alpha]_D^{20}=-9.4$ (*c* 1.3, $CHCl_3$). ^1H NMR δ: 6.66 (ddd, H-7), 6.27 (dd, $J_{6,7}$ 11.5 Hz, H-6), 5.49 (dd, $J_{5,6}$ 10.8 Hz, H-5), 5.28 (dd, $J_{6,8b}$ 0.9, $J_{7,8b}$ 16.7 Hz, H-8b) 5.14 (d, $J_{7,8a}$ 10.0 Hz, H-8a), 4.82 and 4.70 (AB, *J* 11.4 Hz, CH_2Ph), 4.64 (dd, $J_{4,5}$ 9.5 Hz, H-4), 4.59 and 4.36 (AB, *J* 11.7 Hz, CH_2Ph), 4.57 and 4.51 (AB, *J* 11.6 Hz, CH_2Ph), 4.22 (dd, $J_{1a,2}$ 4.9 Hz, H-1a), 4.13 (dd, $J_{1a,1b}$ 11.6, $J_{1b,2}$ 5.9 Hz, H-1b), 3.79 (ddd, H-2), 3.61 (dd, $J_{2,3}$ 4.6, $J_{3,4}$ 5.7 Hz, H-3), 1.95 [s, OC(O)CH_3]. ^{13}C NMR δ: 170.5 [O*C*(O)CH_3], 138.4, 138.3, 138.2 (3×C_{quat} benzyl), 133.7 (C-6), 131.8 (C-7), 128.6 (C-5), 120.0 (C-8), 81.0 (C-3), 77.5 (C-2), 75.0 (C-4), 75.0, 73.0 and 70.5 (3×*C*H_2Ph), 63.7 (C-1), 20.8 [OC(O)*C*H_3]. Anal. calcd for $C_{31}H_{34}O_5$: C, 76.51; H, 7.04. Found: C, 76.26; H, 7.18.

4.2.2. (2*R*,3*S*,4*R*,*Z*)-1-Acetoxytribenzyloxyocta-5,7-diene 8b. $[\alpha]_D^{20}=-2.4$ (*c* 0.85, $CHCl_3$). ^1H NMR δ: 6.58 (ddd, H-7), 6.25 (dd, $J_{6,7}$ 11.2 Hz, H-6), 5.55 (dd, $J_{5,6}$ 10.1 Hz, H-5), 5.29 (d, $J_{7,8b}$ 16.7 Hz, H-8b), 5.19 (d, $J_{7,8a}$ 10.3 Hz, H-8a), 4.73 and 4.65 (AB, *J* 11.3 Hz, CH_2Ph), 4.62 and 4.31 (AB, *J* 11.9 Hz, CH_2Ph), 4.57 (dd, $J_{4,5}$ 8.8 Hz, H-4), 4.54 and 3.35 (AB, *J* 11.4 Hz, CH_2Ph), 4.52 (dd, $J_{1a,1b}$ 12.1, $J_{1b,2}$ 2.8 Hz, H-1b), 4.17 (dd, $J_{1a,2}$ 5.3 Hz, H-1a), 3.86 (ddd, $J_{2,3}$ 6.2 Hz, H-2), 3.67 (dd, $J_{3,4}$ 4.3 Hz, H-3), 1.99 [s, OC(O)CH_3]. ^{13}C NMR δ: 170.8 [O*C*(O)CH_3], 138.3, 138.2, 138.1 (3×C_{quat} benzyl), 133.3 (C-6), 131.8 (C-7), 129.2 (C-5), 119.9 (C-8), 81.5 (C-3), 77.0 (C-2), 74.2 (C-4), 75.0, 72.1 and 70.3 (3×*C*H_2Ph), 63.2 (C-1), 20.9 [OC(O)*C*H_3]. Anal. calcd for $C_{31}H_{34}O_5$: C, 76.51; H, 7.04. Found: C, 76.57; H, 6.82.

4.3. Decomposition of secondary sugar allyltins in the presence of $Ph_3P{=}CHCO_2Me$

To a solution of allyltin **6a** or **6b** (763 mg, 1 mmol) in dry xylene (10 mL) $Ph_3P{=}CHCO_2Me$ (500 mg, 1.5 mmol) was added and the mixture was boiled under reflux for 3–4 h. It was then cooled to room temperature, concentrated and the product was isolated by column chromatography (hexane–ethyl acetate, 10:1) and further purified by HPLC (hexane–ethyl acetate, 20:1). From **6a** compound **10a** was obtained in 75% yield (373 mg). Reaction of **6b** afforded two stereoisomers: **10b** (66%, 328 mg) and **10b′** (11%, 54 mg).

4.3.1. (1*S*,5*S*,6*S*,7*S*,8*S*,9*R*)-Tribenzyloxy-5-methoxycarbonylbicyclo[4.3.0]non-2-ene 10a. $[\alpha]_D^{20}=+63.1$ (*c* 0.6, $CHCl_3$). ^1H NMR δ: 5.72 (m, $J_{2,3}$ 10.1 Hz, H-2), 5.65 (m, H-3), 4.59 (m, 3×CH_2Ph), 4.04 (dd, $J_{8,9}$ 5.0 Hz, H-8), 3.69 (dd, $J_{6,7}$ 11.5, $J_{7,8}$ 5.5 Hz, H-7), 3.66 (m, H-9), 3.62 [s, C(O)OCH_3], 2.79 (m, H-1) 2.68 (ddd, $J_{4b,5}$ 6.0, $J_{5,6}$ 7.5 Hz, H-5), 2.64 (ddd, $J_{1,6}$ 5.4 Hz, H-6), 2.29 (m, $J_{4a,4b}$ 17.7 Hz, H-4b), 1.99 (m, H-4a). ^{13}C NMR δ: 175.4 [*C*(O)OCH_3], 138.5, 138.3, 138.2 (3×C_{quat} benzyl), 127.8 (C-2), 124.8 (C-3), 90.3 (C-8), 88.4 (C-7), 83.0 (C-9), 72.1, 71.8, 71.5 (3×*C*H_2Ph), 51.7 [C(O)O*C*H_3],

40.6 (C-6), 39.9 (C-1), 38.5 (C-5), 25.1 (C-4). NOESY: H1–H6, H9–H5, H6–H8, H5–H7. HRMS m/z: 521.23039 [$C_{32}H_{34}O_5Na$ (M+Na$^+$) requires 521.23364]. Anal. calcd for $C_{32}H_{34}O_5$: C, 77.08; H, 6.87. Found: C, 77.04; H, 6.80.

4.3.2. (1*S*,5*S*,6*S*,7*R*,8*S*,9*R*)-7,8,9-Tribenzyloxy-5-methoxycarbonylbicyclo[4.3.0]non-2-ene 10b. $[\alpha]_D^{20} = +106.4$ (c 1.1, $CHCl_3$). ^{1}H NMR δ: 5.83 (m, $J_{2,3}$ 9.8, $J_{1,2} \sim J_{2,4a}$ 3.0 Hz, H-2), 5.75 (m, H-3), 4.76 and 4.64 (AB, J 12.0 Hz, CH_2Ph), 4.62 and 4.49 (AB, J 11.6 Hz, CH_2Ph), 4.59 and 4.54 (AB, J 11.7 Hz, CH_2Ph), 4.08 (dd, $J_{7,8}$ 5.2, $J_{6,7}$ 6.2 Hz, H-7), 3.90 (dd, H-8), 3.77 (dd, $J_{1,9}$ 6.8, $J_{8,9}$ 3.6 Hz, H-9), 3.44 [s, C(O)OCH_3], 2.95 (ddd, $J_{4a,5}$ 11.0, $J_{4b,5}$ 4.7 Hz, H-5), 2.88 (ddd, $J_{1,6}$ 8.5, $J_{5,6}$ 11.6 Hz, H-6), 2.45 (m, H-1), 2.27 (ddd, $J_{4a,4b}$ 16.6, $J_{3,4b}$ 5.3 Hz, H-4b), 1.99 (m, H-4a). ^{13}C NMR δ: 177.0 [C(O)OCH$_3$], 2×138.7, 138.3 (3×C$_{quat}$ benzyl), 127.8 (C-3), 125.5 (C-2), 87.8 (C-9), 83.7 (C-8), 80.1 (C-7), 73.0, 72.5, 72.3 (3×CH$_2$Ph), 51.2 [C(O)OCH$_3$], 41.0 (C-1), 39.7 (C-6), 38.5 (C-5), 28.0 (C-4). NOESY: H1–H6, H6–H7. Anal. calcd for $C_{32}H_{34}O_5$: C, 77.08; H, 6.87. Found: C, 77.01; H, 6.83.

4.3.3. (1*R*,5*R*,6*R*,7*R*,8*S*,9*R*)-7,8,9-Tribenzyloxy-5-methoxycarbonylbicyclo[4.3.0]non-2-ene 10b′. $[\alpha]_D^{20} = -48.4$ (c 0.7, $CHCl_3$). ^{1}H NMR δ: 5.80 (m, $J_{2,3}$ 10.1 Hz, H-3), 5.74 (m, H-2), 4.25 (m, 3×CH_2Ph), 4.08 (dd, $J_{1,9}$ 6.9, $J_{8,9}$ 4.2 Hz, H-9), 3.87 (dd, $J_{8,7}$ 5.0 Hz, H-8), 3.81 (dd, $J_{6,7}$ 5.2 Hz, H-7), 3.64 [s, C(O)OCH_3], 3.06 (m, H-1), 2.63 (m, $J_{1,6} \sim J_{5,6}$ 8.8 Hz, H-6), 2.52 (m, $J_{5,4a}$ 8.2, $J_{5,4b}$ 5.4 Hz, H-5), 2.27 (m, $J_{4a,4b}$ 17.2, $J_{2,4b}$ 2.9 Hz, H-4b), 2.13 (m, $J_{2,4a}$ 1.8 Hz, H-4a). ^{13}C NMR δ: 175.7 [C(O)OCH$_3$], 138.5, 138.4, 138.3 (3×C$_{quat}$ benzyl), 126.0 (C-3), 125.7 (C-2), 83.5 (C-9), 81.4 (C-8), 80.7 (C-7), 72.1, 72.0, 71.7 (3×CH$_2$Ph), 51.7 [C(O)OCH$_3$], 42.1 (C-6), 41.4 (C-5), 37.2 (C-1), 26.0 (C-4). NOESY: H1–H6, H1–H9, H5–H7. HRMS m/z: 521.23313 [$C_{32}H_{34}O_5Na$ (M+Na$^+$) requires 521.23364].

Acknowledgements

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