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Synthesis of a pericosine analogue with a bicyclo[2.2.2]octene skeleton

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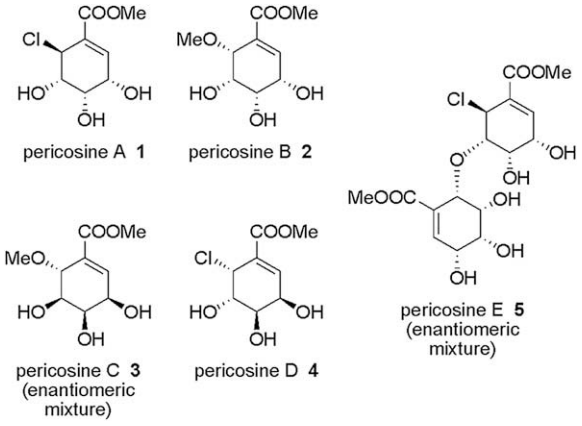
ABSTRACT

A new analogue of the antitumor pericosines possessing a bicyclo[2.2.2]octene skeleton has been synthesized from methyl gallate using oxidative dearomatization and regio- and diastereoselective Diels–Alder reaction as the key steps.

1. Introduction

Pericosines A–E (**1**–**5**, Scheme 1) are natural compounds isolated from the fungus *Periconia byssoides* OUPS-N133 found in the gastrointestinal tract of the sea hare *Aplysia kurodai*.[1,2] Pericosines display in vitro antitumor activity, and **1** was shown to have in vivo antitumor activity.[2]



Scheme 1. Structures of pericosines.

The synthesis of **1**, **2**, **3** and their stereoisomers has already been established and all of these procedures start from (−)-quinic acid, (−)-shikimic acid or other alicyclic compounds.[3,4]

In this study we report on the synthesis of a bridged analogue of pericosines A–D and the evaluation of its biological activity.

2. Results and discussion

Masked *ortho*-benzoquinone (MOB) ketals[5,6] are attractive synthetic intermediates for obtaining complex chemical structures since their Diels–Alder reaction is a versatile tool for the construction of tricyclic compounds. MOBs can be obtained by oxidation of *o*-alkoxyphenols in methanol and one of the most effective reagents is diacetoxyiodobenzene.[6–9] For the synthesis of the target bridged pericosine analogue this dearomatization–Diels–Alder sequence has been chosen.

Methyl gallate (**6**), a cheap, commercially available aromatic compound was selected as starting material. Since our target molecule has five chiral centers an appropriate dearomatization of the gallic ester was necessary as a key step of the synthesis. After protection of two of the phenolic hydroxyl groups in the form of a diphenylmethylene acetal (**7**)[10], oxidative dearomatization with

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diacetoxyiodobenzene in methanol resulted in the dienone double acetal **8**. As this acetal is formed as a racemate, all of the products of the following reactions are racemic, however, for the sake of simplicity only one of the enantiomers is displayed in the schemes. Thermal Diels–Alder reaction of **8** with benzyl vinyl ether[11] gave exclusively **9** with complete regio- and diastereoselectivity. The exact structure of this compound was established by X-ray diffraction (Fig. 1, Scheme 2).

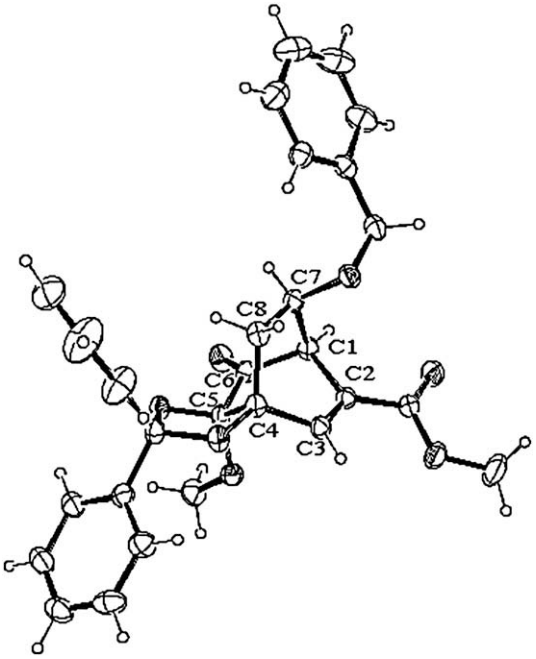
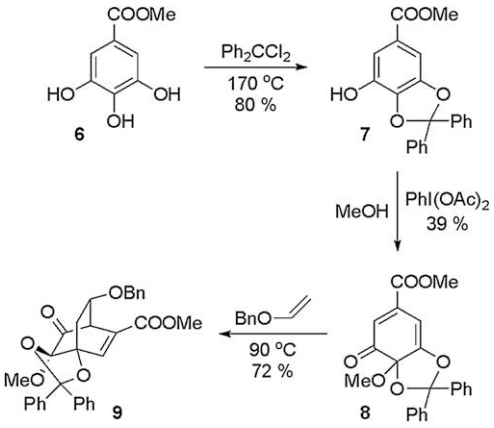


Figure 1. ORTEP view of cycloadduct **9**.



Scheme 2. Route to the Diels–Alder adduct **9**.

The dienophile has an electron releasing substituent, therefore an inverse electron demand Diels–Alder reaction could be suspected, but the presence of both electron releasing and electron withdrawing substituents of the diene prompted us for a theoretical study of this reaction. For this reason we carried out various quantum chemical calculations with the following results.

Upon examination of the possible transition states (TS) we found that the lowest energy belongs to the TS leading to the only product isolated from the Diels–Alder reaction (see Fig. S1 in Supplementary data). Using model reactants (i.e., replacing the phenyl and benzyl groups by hydrogen atoms, this way distinguishing between the steric and electronic effects) gave the same result. It suggests a strong electronic contribution to the observed selectivity. The HOMO and LUMO orbital energies, orbital shapes, and the coefficients of the atomic orbital contributions to the HOMO and LUMO at the diene and dienophile were calculated (see Figs. S2 and S3 in Supplementary data). The cycloaddition turned out to be an inverse electron demand reaction. Regarding the coefficients of the atomic orbitals, the computationally predicted and experimentally observed products do not match, so the reaction violates the Houk rule.[12] Examining the TS geometry, a non-negligible secondary interaction was obtained between the carbonyl oxygen of COOMe and a H atom of the benzyl $-CH_2-$ group (see Fig. S4 in Supplementary data), which stabilizes the TS and it becomes the most favorable one even if it violates the Houk rule. These facts clearly show the qualitative-only features of the HOMO–LUMO interactions and the importance of the secondary interactions.

For the temporary protection of the carbon–carbon double bond, conjugate addition of thiophenol and oxidation of the so-formed sulfide with *m*-chloroperbenzoic acid (*m*-CPBA) to sulfone **10** were performed in the next steps. The addition resulted in a trans product, as shown by the value $J_{2,3}$=4.0 Hz. The long-range coupling between H-3 and H-8b can be explained by a configuration in which the $H_{8b}–C_8–C_4–C_3–H_3$ bonds are in a nearly coplanar W-arrangement. In this case the phenylsulfonyl group points toward the C-8 atom. The configuration of **10** was confirmed by X-ray diffraction (Fig. 2).

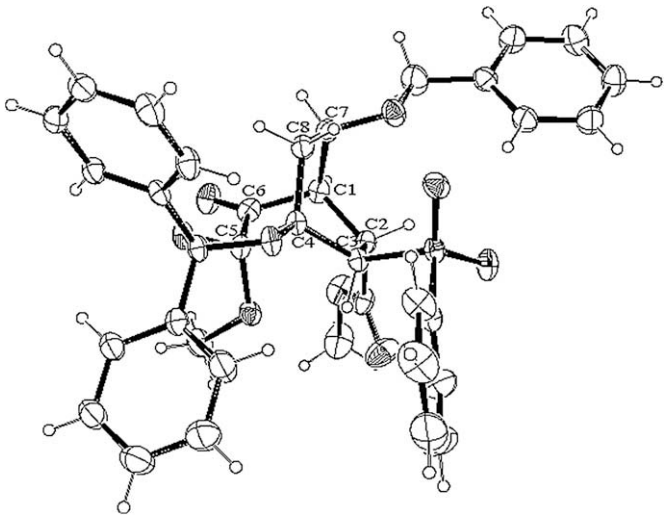


Figure 2. ORTEP view of **10**.

Reduction of the ketone **10** using $NaBH_4$, $LiBH_4$ or $BH_3·DMS$ reagents resulted in **11** and **11′** with low diastereoselectivity (~20% de), while $NaBH_3CN$ and $NaBH(OAc)_3$ did not even reduce the carbonyl group. However, application of the $CeCl_3/NaBH_4$ reagent[13] in methanol preformed prior to the reaction gave rise to a mixture of **11** and **11′** in a 7.2:1 ratio. In this case the reducing agents should be the methoxyborohydrides $NaBH_3OMe$, $NaBH_2(OMe)_2$, and $NaBH(OMe)_3$, the formation of which is facilitated by $CeCl_3$. Steric effect of these hydrides and the bonding of $CeCl_3$ as a Lewis acid to the oxo group of the ketone can contribute to the stereochemical outcome of the reduction alike. However, the ratio of the diastereomers was not adequately reproducible (the formation ratio of methoxyborohydrides and the amount of $NaBH_4$ formed by disproportionation[14] was largely dependent on the reaction time), therefore we chose an alternative reducing agent, sodium tris(trifluoroethoxy)borohydride. This reagent can be prepared from $NaBH_4$ and trifluoroethanol[14], the de achieved by its use was 76%. Separation of **11** and **11′** was performed by column chromatography

and their relative stereochemistry was explored by NMR spectroscopy and X-ray diffraction (Fig. 3).

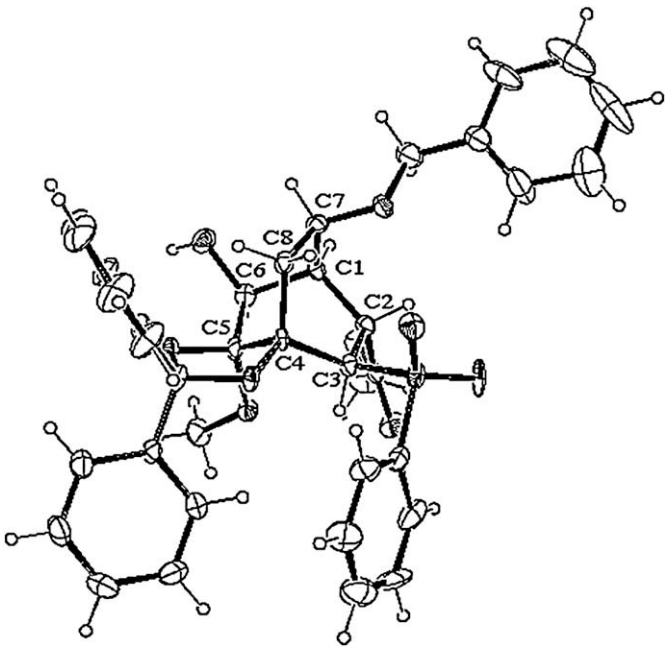


Figure 3. ORTEP view of **11′**.

Acid hydrolysis of the acetal **11** and subsequent stereoselective reduction of the intermediary α-hydroxyketone with $NaBH_4$ in methanol furnished triol **12**. The coupling constant between H-2 and H-3 increased from ~4 Hz (in **10**, **11**, and **11′**) to ~8.5 Hz (in **12** and **13**), which shows a change from the original trans stereochemistry to cis. The epimerization can occur either at H-2 or at H-3 as both have acidic character, however, the change in the coupling constant between H-1 and H-2 from ~4 Hz (in **10**, **11**, and **11′**) to ~2 Hz (in **12** and **13**) showed that it took place at C-2. After removal of the benzyl group by catalytic hydrogenation, the phenylsulfonyl group of **13** had to be eliminated to regenerate the carbon–carbon double bond. Treating **13** with Et_3N or DABCO did not lead to any reaction, the use of DBU triggered lactone formation exclusively. The suitable base was K_2CO_3 in methanol, which led to the formation of the bridged pericosine analogue **14** (Scheme 3).

Unfortunately, **14** was found to have no cytotoxic activity in several cell lines, i.e., Crandell-Rees feline kidney (CRFK), human cervixcarcinoma (HeLa) cells, human embryonic lung (HEL) fibroblasts, Madin-Darby canine kidney (MDCK) cells and African green monkey kidney (Vero) cells (maximum compound concentration tested: 100 μM).

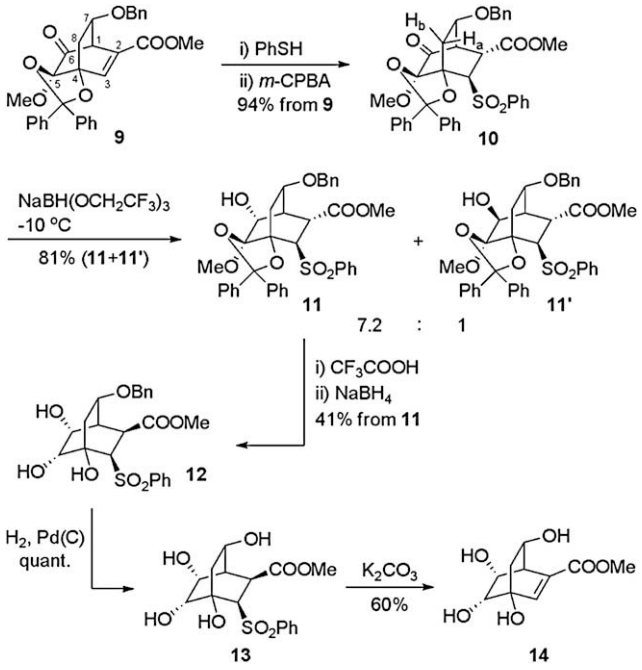
3. Summary

Starting from the achiral aromatic precursor **6** we performed the stereoselective synthesis of **14** with 5 chiral centers in 10 synthetic steps.

4. Experimental

4.1. General methods

Dry dichloromethane, dry methanol, and dry THF were distilled from P_2O_5, Mg, and Na/Ph_2CO (under N_2), respectively. Solutions were concentrated in vacuo at 40 °C. Organic phases were dried over Na_2SO_4. TLC was performed on Merck Kieselgel F_{254} plates, spots



Scheme 3. Transformation of **9** to the perisocine analogue **14**.

were made visible using UV light (254 nm) and/or spraying with acidic (H_2SO_4) ammonium molybdate solution followed by heating. Flash column chromatography was carried out under pressure using Merck Kieselgel 60 silica (0.040–0.063 mm). NMR spectra were recorded on a Bruker Avance DRX 500 or a Bruker Avance 360 spectrometer, at the given frequency and in the given solvent. Chemical shifts are given in parts per million and coupling constants in hertz. NMR assignments were based on 2D COSY and 2D HSQC experiments. High resolution mass spectra were obtained on a Bruker microTOF-Q (ESI-QqTOF) spectrometer. Melting points were measured on a Büchi Melting Point B-540 device and are uncorrected. IR spectra were recorded on a Perkin Elmer 16 PC FT-IR spectrometer. X-ray data were collected on a Bruker-Nonius MACH3 diffractometer at 293 K, Mo Kα radiation λ=0.71073 Å, ω motion. The structure was solved using the SIR-92 software[15] and refined on F^2 using SHELX-97 program,[16] publication material was prepared with the WINGX-97 suite.[17] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were fixed into geometric position except O–H, which could be found at the difference electron density map. Further information on structure determination could be found in Supplementary data (Table S2). Crystallographic data (excluding structure factors) for the structures **9**, **10**, and **11′** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 723534/723535/723536, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk). The quantum chemical calculations were carried out by means of the Gaussian '03 quantum chemical software package.[18] For visualization the Molekel 5.2[19,20] and the Arguslab 4.0.1[21] suites of software were used. The cytotoxicity assays were performed—according to our previous work[22]—in several human and animal cell lines, in which the compound's cytotoxicity was estimated from microscopically visible alterations in cell morphology or from cell viability, determined by the formazan-based MTS assay.

4.2. Sodium tris(trifluoroethoxy)borohydride

Sodium tris(trifluoroethoxy)borohydride was prepared by the method of Golden and co-workers[14] with a few minor changes: the

reaction time was longer (19 h) and after the initial cooling no further cooling was applied. As the reaction mixture yet contained some solid $NaBH_4$, it was filtered off and the filtrate was used.

4.3. Methyl 4,5-dihydroxy-4-methoxy-3-oxo-4,5-*O*-diphenylmethylidenecyclohexa-1,5-dienecarboxylate (8)

To a stirred solution of 4,5-*O*-(diphenylmethylidene)methyl gallate[5] (14.0 g, 40.2 mmol) in dry MeOH (500 mL), PIDA (23.2 g, 72.1 mmol) was added in four portions at 20 °C. The reaction mixture was stirred for 15 min at 20 °C and additional 45 min at room temperature, then $NaHCO_3$ (15 g) was added and the stirring was continued for 15 min. The brown mixture was filtered, washed with CH_2Cl_2, and the filtrate was evaporated in vacuo. The residue was subjected to flash column chromatography (hexane/EtOAc 9:1) to give 5.86 g (39%) **8** as a yellow solid. Mp: 115–118 °C; HRMS *m*/*z* calcd for $C_{22}H_{18}O_6Na$ (M+Na^+) 401.1001, found 401.0994; IR (KBr): 1728, 1706 (C=O), 1555 (C=C) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$): δ 2.99 (s, 3H, 4-OMe), 3.85 (s, 3H, COOMe), 5.87 (d, 1H, ^4J=1.0, H-2/H-6), 6.44 (d, 1H, ^4J=1.0, H-2/H-6), 7.30–7.59 (m, 10H, Ar); ^{13}C NMR (90 MHz, $CDCl_3$): δ 50.4, 52.8 (2C, 4-OMe, COO*Me*), 91.7 (C-6), 99.0 (C-4), 116.9 (*C*Ph_2), 121.5 (C-2), 125.8, 126.0, 128.0, 128.2 (10C, Ar), 128.7, 129.3 (2C, C-2, C-6), 139.6, 140.37, 143.4 (3C, C-5, Ar), 159.4 (C-1), 165.0 (*C*OOMe), 191.2 (C-3).

4.4. Methyl 7-benzyloxy-4,5-dihydroxy-5-methoxy-6-oxo-4,5-*O*-diphenylmethylidenebicyclo[2.2.2]oct-2-ene-2-carboxylate (9)

A solution of **8** (3.01 g, 8.0 mmol) in benzyl vinyl ether[6] (15.0 g, 111.8 mmol) was stirred at 90 °C for 6 h. The reaction mixture was subjected to flash column chromatography (hexane/EtOAc 92:8) to furnish 3.22 g (79%) **9** as a slightly yellowish solid. Removal of the remaining starting material by washing two times with cold ethanol afforded 2.94 g (72%) white solid. Mp: 151–153 °C; HRMS: *m*/*z* calcd for $C_{31}H_{28}O_7Na$ (M+Na^+) 535.1733, found 535.1730; IR (KBr): 1747, 1716 (C=O), 1613 (C=C) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$): δ 7.72 (dd, 1H, $^4J_1$=1.7, $^4J_{8a}\sim{}^4J_{8b}\sim$0.9, H-3), 7.62–7.15 (m, 15H, Ar), 4.56 (d, 1H, J_{gem}=11.3, OCH_2Ph), 4.34 (ddd, J_7=3.5, $^4J_3$=1.7, $^4J_{8b}$=0.9, 1H, H-1), 4.28 (d, 1H, J_{gem}=11.3, OCH_2Ph), 3.90 (ddd, 1H, J_{8a}=8.0, J_1=3.5, J_{8b}=1.6, H-7), 3.79 (s, 3H, COOMe), 2.81 (s, 3H, 5-OMe), 2.10 (ddd, 1H, J_{8a}=14.7, J_7=8.0, $^4J_3$=0.9, H-8b), 1.45 (ddd, 1H, J_{8b}=14.7, $^4J_7$=1.6, $^4J_3$=0.9, H-8a); ^{13}C NMR (90 MHz, $CDCl_3$): δ 194.3 (C-6), 164.3 (*C*OOMe), 143.6, 143.0 (Ar), 140.7 (C-3), 137.0 (C-2), 128.3–124.9 (Ar), 115.1 (*C*Ph_2), 99.7 (C-5), 89.3 (C-4), 73.5 (C-7), 70.5 (OCH_2Ph), 53.0 (C-1), 52.0 (COO*Me*), 51.0 (5-OMe), 36.1 (C-8).

4.5. Methyl 7-benzyloxy-4,5-dihydroxy-5-methoxy-6-oxo-4,5-*O*-diphenylmethylidene-3-phenylsulfonylbicyclo-[2.2.2]octane-2-carboxylate (10)

To a solution of **9** (2.85 g, 5.6 mmol) in CH_3CN (100 mL, flushed thoroughly with argon) thiophenol (0.80 mL, 7.8 mmol) and Et_3N (1.28 mL, 9.2 mmol) were added. The solution was stirred at room temperature under argon for 1 h. Pre-dried (Na_2SO_4) solution of *m*-CPBA (10.60 g in 150 mL CH_2Cl_2; max. 77% *m*-CPBA, ca. 47 mmol) was added dropwise for 45 min at 20 °C and the solution was stirred for further 2 h, then evaporated in vacuo. The residue was dissolved in EtOAc (300 mL) and washed with 10% Na_2SO_3 solution (2×50 mL) and saturated $NaHCO_3$ solution (2×50 mL). The combined aqueous washings were extracted with EtOAc (20 mL). The combined organic extract was dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (hexane/acetone 7:3) to furnish 3.43 g (94%) **10** as a white solid. Mp: 195–198 °C; HRMS: *m*/*z* calcd for $C_{37}H_{34}O_9SNa$ (M+Na^+) 677.1821, found 677.1829; IR (KBr): 1752, 1743 (C=O), 1153 (SO_2) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.27–6.90 (m, 20H, Ar), 4.68 (dd, 1H, J_2=4.0, $^4J_{8b}$=2.0, H-3), 4.68 (d, 1H, J_{gem}=11.9, OCH_2Ph), 4.36 (d, 1H, J_{gem}=11.9, OCH_2Ph), 4.31 (t, 1H, $J_1\sim J_3\sim$4, H-2), 3.76 (dd, 1H, J_{8b}=8.5, J_1=4.6, H-7), 3.67 (s, 3H, COOMe), 3.38 (t, 1H, $J_7\sim J_2\sim$4, H-1), 3.07 (d, 1H, J_{8b}=15.6, H-8a), 2.73 (s, 3H, 5-OMe), 1.56 (ddd, 1H, J_{8a}=15.6, J_7=8.5, $^4J_3$=2.0, H-8b); ^{13}C NMR (125 MHz, $CDCl_3$): δ 196.61 (C-6), 171.7 (*C*OOMe), 143.2–124.6 (Ar), 114.8 (*C*Ph_2), 102.7 (C-5), 86.1 (C-4), 69.9 (C-7), 69.9 (OCH_2Ph), 63.7 (C-3), 52.8 (COO*Me*), 51.2 (C-1), 50.3 (5-OMe), 38.9 (C-2), 29.3 (C-8).

4.6. Methyl 7-benzyloxy-4,5,6-trihydroxy-5-methoxy-4,5-*O*-diphenylmethylidene-3-phenylsulfonylbicyclo[2.2.2]-octane-2-carboxylate (11, 11′)

To a solution of **10** (2.01 g, 3.1 mmol) in dry THF (70 mL) at −10 °C a $NaBH(OCH_2CF_3)_3$ solution (17 mL, ca. 0.9 mM in THF; ca. 15 mmol of hydride) was added in ca. 2 mL portions over 5 min under argon. The solution was stirred for further 45 min at −10 °C then evaporated in vacuo. The residue was dissolved in EtOAc (200 mL) and saturated $NaHCO_3$ solution (30 mL) was added slowly with vigorous stirring (rapid evolution of H_2(g)!) to decompose the excess reagent. Stirring was continued for 10 min and the mixture was transferred to a separating funnel and shaked. The organic phase were extracted with a further 30 mL of saturated $NaHCO_3$ solution, then the combined aqueous phase was washed with EtOAc (20 mL). The combined organic extract was dried (Na_2SO_4), filtered, and evaporated in vacuo. The crude product was purified by flash column chromatography (hexane/CH_2Cl_2/acetone 7:3:1) to furnish **11** (1.43 g, 71%) as a white solid. After the elution of **11**, the eluent was changed to hexane/CH_2Cl_2/acetone 7:4:2 to afford **11′** (0.20 g, 10%). Compound **11**: mp: 194–196 °C; HRMS: *m*/*z* calcd for $C_{37}H_{36}O_9SNa$ (M+Na^+) 679.1978, found 679.1977; IR (KBr): 3479 (OH), 1745 (C=O), 1151 (SO_2) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.23–6.89 (m, 20H, Ar), 4.71 (d, 1H, J_{gem}=11.9, OCH_2Ph), 4.50 (dd, 1H, J_2=4.0, $^4J_{8b}$=2.1, H-3), 4.30 (d, 1H, J_{gem}=11.9, OCH_2Ph), 4.28 (dd, 1H, J_3=4.0, J_1=3.8, H-2), 4.17 (d, 1H, J_6=10.3, OH), 3.89 (d, 1H, J_{OH}=10.3, H-6), 3.78 (dd, 1H, J_{8b}=8.4, J_1=4.6, H-7), 3.76 (s, 3H, COOMe), 2.81 (d, 1H, J_{8b}=15.2, H-8a), 2.76 (t, 1H, $J_7\sim J_2\sim$4, H-1), 2.71 (s, 3H, 5-OMe), 1.44 (ddd, 1H, J_{8a}=15.2, J_7=8.4, $^4J_3$=2.1, H-8b); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.1 (*C*OOMe), 144.3–124.8 (Ar), 113.4 (*C*Ph_2), 107.0 (C-5), 85.0 (C-4), 73.7 (C-6), 71.0 (C-7), 69.3 (OCH_2Ph), 64.6 (C-3), 53.2 (COO*Me*), 52.8 (5-OMe), 42.4 (C-1), 38.6 (C-2), 27.5 (C-8). Compound **11′**: mp: 178–181 °C; HRMS: *m*/*z* calcd for $C_{37}H_{36}O_9SNa$ (M+Na^+) 679.1978, found 679.1975; IR (KBr): 3491 (OH), 1736 (C=O), 1151 (SO_2) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.23–6.89 (m, 20H, Ar), 4.75 (d, 1H, J_{gem}=11.9, OCH_2Ph), 4.62 (dd, 1H, J_2=4.2, $^4J_{8b}$=2.1, H-3), 4.27 (d, 1H, J_{gem}=11.9, OCH_2Ph), 4.25 (t, 1H, $J_1\sim J_3\sim$4.5, H-2), 4.19 (dd, 1H, J_1=5.0, J_{OH}=2.4, H-6), 4.09 (dd, 1H, J_{8b}=8.2, J_1=4.6, H-7), 3.67 (s, 3H, COOMe), 3.10 (q, 1H, $J_2\sim J_6\sim J_7\sim$4.5, H-1), 2.88 (d, 1H, J_{8b}=14.8, H-8a), 2.53 (s, 3H, 5-OMe), 2.13 (d, 1H, J_6=2.4, OH), 1.62 (ddd, 1H, J_{8a}=14.8, J_7=8.2, $^4J_3$=2.1, H-8b); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.3 (*C*OOMe), 143.8–124.7 (Ar), 114.2 (*C*Ph_2), 105.0 (C-5), 85.6 (C-4), 69.7 (OCH_2Ph), 69.3 (C-7), 66.5 (C-6), 63.3 (C-3), 52.4 (COO*Me*), 47.9 (5-OMe), 39.9 (C-1), 38.4 (C-2), 27.1 (C-8).

4.7. Methyl 7-benzyloxy-4,5,6-trihydroxy-3-phenyl-sulfonylbicyclo[2.2.2]octane-2-carboxylate (12)

The solution of **11** (518 mg, 0.8 mmol) in trifluoroacetic acid (25 mL) was stirred for 2 h at room temperature, diluted with dry toluene (15 mL), and evaporated in vacuo at 35 °C. The remaining acid was removed by distilling a further 15 mL toluene from the residue. The crude product was dissolved in methanol (20 mL) and $NaBH_4$ (120 mg, 3.2 mmol) was added in portions with stirring. After 20 min the reaction mixture was neutralized with Serdolit-

Red cation-exchanger, the resin was filtered off, washed with methanol, and the filtrate was concentrated in vacuo. From the residue methanol was evaporated four times. The crude triol was subjected to flash column chromatography (CH_2Cl_2/MeOH 96:4) to furnish **12** (150 mg, 41%) as an off-white solid. Mp: 164–167 °C; HRMS: *m/z* calcd for $C_{23}H_{26}O_8SNa$ ($M+Na^+$) 485.1246, found 485.1233; IR (KBr): 3445 (OH), 1738 (C=O), 1145 (SO_2) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.97–7.29 (m, 10H, Ar), 4.59 (d, 1H, J_{gem}=11.9, OC*H*$_2$Ph), 4.55 (d, 1H, J_{gem}=11.9, OC*H*$_2$Ph), 4.45 (s, 1H, 4-OH), 4.37 (dd, 1H, J_2=8.6, $^4J_{8b}$=2.1, H-3), 3.93 (ddd, 1H, J_1=4.0, J_5=8.8, $J_{6\text{-OH}}$=3.0, H-6), 3.80 (dd, 1H, J_1=2.0, J_3=8.6, H-2), 3.68 (ddd, 1H, J_{8b}=9.8, J_{8a}=4.4, J_1=2.6, H-7), 3.55 (d, 1H, J_6=8.8, $J_{5\text{-OH}}\sim$1.0, H-5), 3.53 (s, 3H, COOMe), 3.31 (d, 1H, $J_5\sim$1.0, 5-OH), 3.14 (d, 1H, J_6=3.0, 6-OH), 2.86 (ddd, 1H, J_6=4.0, J_7=2.6, J_2=2.0, H-1), 2.65 (dd, 1H, J_{8b}=14.1, J_7=4.4, H-8a), 1.82 (ddd, 1H, J_{8a}=14.1, J_7=9.8, $^4J_3$=2.1, H-8b); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.5 (*C*OOMe), 140.4–127.7 (Ar), 72.3 (C-4), 71.1 (C-5), 70.1 (O*C*H$_2$Ph), 69.7 (C-7), 65.5 (C-6), 60.5 (C-3), 52.3 (COO*Me*), 40.8 (C-1), 37.2 (C-2), 35.2 (C-8).

4.8. Methyl 4,5,6,7-tetrahydroxy-3-phenylsulfonyl-bicyclo[2.2.2]octane-2-carboxylate (13)

To a solution of **12** (223 mg, 0.5 mmol) in the mixture of methanol (5 mL) and ethyl acetate (5 mL) Pd(C) (99 mg, 10% Pd) was added. After flushing with argon, the mixture was hydrogenated for 5 h. The reaction mixture was filtered through a pad of Celite, then the Celite was washed with methanol and ethyl acetate. Evaporation of the filtrate gave rise to 185 mg (quant.) white powder, which was pure enough for the next reaction. Analytically pure **13** was obtained by recrystallization from MeOH/CH_2Cl_2/hexane. Mp: 181–185 °C. HRMS: *m/z* calcd for $C_{16}H_{20}O_8SNa$ ($M+Na^+$) 395.0777, found: 395.0764; IR (KBr): 3418 (OH), 1732 (C=O), 1141 (SO_2) cm^{-1}; ^1H NMR (500 MHz, CD_3OD): δ 7.99–7.55 (m, 5H, Ar), 4.51 (dd, 1H, J_2=8.7, $^4J_{8b}$=2.1, H-3), 4.00 (ddd, 1H, J_{8b}=10.1, J_{8a}=4.1, J_1=3.1, H-7), 3.90 (dd, 1H, J_1=3.5, J_5=8.7, H-6), 3.69 (dd, 1H, J_1=2.1, J_3=8.7, H-2), 3.61 (s, 3H, COOMe), 3.44 (d, 1H, J_6=8.7, H-5), 2.58 (dd, 1H, J_{8b}=14.1, J_7=4.1, H-8a), 2.53 (dd, 1H, $J_6\sim J_7\sim$3.5, J_2=2.1, H-1), 1.75 (ddd, 1H, J_{8a}=14.1, J_7=10.1, $^4J_3$=2.1, H-8b); ^{13}C NMR (125 MHz, CD_3OD): δ 175.6 (*C*OOMe), 143.2, 134.6, 130.1, 130.0 (Ar), 73.6 (C-4), 73.0 (C-5), 66.7 (C-6), 64.6 (C-7), 61.5 (C-3), 52.8 (COO*Me*), 46.4 (C-1), 37.3 (C-2), 37.1 (C-8).

4.9. Methyl 4,5,6,7-tetrahydroxybicyclo[2.2.2]oct-2-ene-2-carboxylate (14)

To a solution of **13** (160 mg, 0.4 mmol) in dry methanol (20 mL) K_2CO_3 (172 mg, 1.0 mmol) was added and the reaction mixture was stirred at room temperature for 24 h. After neutralizing the solution with Serdolit-Red, the resin was filtered off and washed with methanol. The filtrate was evaporated and the crude product was purified by flash column chromatography (CH_2Cl_2/MeOH 85:15) to obtain 59 mg (60%) **14** as a slightly yellowish hygroscopic substance. HRMS: *m/z* calcd for $C_{10}H_{14}O_6Na$ ($M+Na^+$) 253.0688, found: 253.0698; IR (KBr): 3338 (OH), 1703 (C=O), 1629 (C=C) cm^{-1}; ^1H NMR (500 MHz, CD_3OD): δ 7.12 (dd, 1H, $^4J_1$=2.5, $^4J_5\sim{}^4J_{8a}\sim{}^4J_{8b}\sim$1, H-3), 4.02 (dt, 1H, J_{8b}=8.4, $J_1\sim J_{8a}\sim$2.9, H-7), 3.93 (dd, 1H, J_1=2.7, J_5=7.8, H-6), 3.75 (s, 3H, COOMe), 3.57 (dd, 1H, J_6=7.8, $^4J_3$=1.4, H-5), 3.42 (m, 1H, H-1), 1.96 (ddd, 1H, J_{8a}=13.5, J_7=8.4, $^4J_3$=1.0, H-8b), 1.23 (ddd, 1H, J_{8b}=13.5, J_7=2.9, $^4J_3$=1.0, H-8a); ^{13}C NMR (125 MHz, CD_3OD): δ 167.4 (*C*OOMe), 147.1 (C-3), 132.1 (C-2), 76.6 (C-4), 74.5 (C-5), 67.9 (C-6), 66.2 (C-7), 52.3 (COO*Me*), 47.2 (C-1), 41.7 (C-8).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.07.084.

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