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Synthesis of Bridgehead Hydroxy Bicyclo[2.2.2]octane Derivatives[1]

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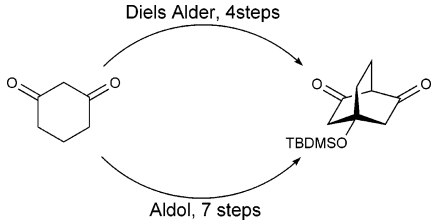
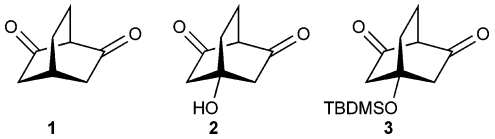


Two independent synthetic routes, starting from 1,3-cyclohexadione, toward the 4-hydroxy bicyclo[2.2.2]octane-2,6-dione derivative **3** are described.

Multifunctionalized bicyclo[2.2.2]octanes are of interest due to their occurrence as subunits in natural products,[2] in natural product synthesis,[3] and as ligands for asymmetric catalysis.[4,5] Four general methods are available in the literature for the synthesis of these systems: double Michael addition,[6] Diels–Alder reaction,[7,8] intramolecular condensation reactions,[9–11] and rearrangement reactions, including the homoallyl–homoallyl radical rearrangement.[12,13]



1 **2** **3**

Our group has been particularly interested in bicyclo[2.2.2]octane-2,6-dione **1**, which we have employed in synthesis[14] and as ligands for asymmetric catalysis.[4,15] For these purposes, we needed easy access to bridgehead hydroxyl derivatives based on **2**. Since **2** was difficult to isolate because of its high water solubility, we chose the protected derivative **3** as more suitable for further manipulations. Two independent methods for the synthesis of **3** are presented in this report.

Our first route based on the aldol addition as a key reaction (**7** → **8**) is shown in Scheme 1 and starts with monoacetal **4**, which was synthesized from commercially available 1,3-cyclohexadione.[16]

Hong and Chin[17] previously reported a synthetic method for the preparation of **7a**, which included allylation of **4**. In our hands, however, allylation of **4** to give **5a** with allyl Grignard reagent in THF led to the formation of a complex product mixture. More successful was the application of the corresponding indium reagent.[18] By reacting **4** with allyl bromide and indium in 3 Å MS-dried methanol at 0 °C, **5a** was obtained in 90% yield.

The initial plan for the continued synthesis was to prepare compound **8a** in a "one-flask operation" (i.e., ozonolysis of **5a**) to give the corresponding aldehyde **9** (Scheme 2), followed by acid-catalyzed deprotection of the ketal and in situ acid-catalyzed intramolecular aldol addition. This methodology has been applied earlier in the synthesis of other bicyclo[2.2.2]octane derivatives.[10,19] However, this operation failed, instead resulting in compound **10**.

It seemed reasonable that the cyclic ketal had to be removed before ozonolysis, but to minimize the risk of water elimination, the tertiary alcohol was protected prior to the ketal cleavage. After several attempts with

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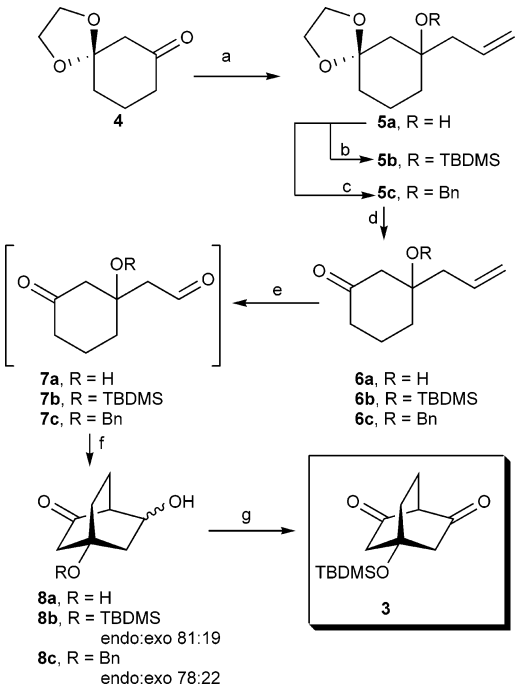
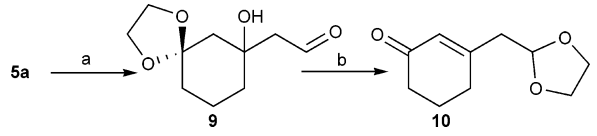
SCHEME 1[a]



[a] Reagents and conditions: (a) In powder (2 equiv), allyl bromide (3 equiv), MeOH (dried), rt, 90%; (b) TBDMSOTf (1.9 equiv), 2,6-lutidine (3.1 equiv), CH_2Cl_2, 0 °C, 95%; (c) BnBr (3 equiv), Ag_2O (3 equiv), EtOAc, rt, 37%; (d) $PdCl_2(CH_3CN)_2$ (5 mol %), acetone: formation of **6a**: −15 °C, 85−90%; formation of **6b**: 0 °C, 90%; formation of **6c**: 0 °C, 86%; (e) O_3, −78 °C, heptane (**7b**) or CH_2Cl_2 (**7c**); (f) SiO_2, TEA, rt, formation of **8b**: heptane, 67% (endo isomer), 16% (exo isomer); formation of **8c**: heptane/toluene 2:1, 50% (endo isomer), 14% (exo isomer); (g) $KMnO_4 \cdot CuSO_4 \cdot 5H_2O$ (2:1 w/w), toluene, 80 °C, 90%.

SCHEME 2[a]



[a] Reagents and conditions: (a) O_3, CH_2Cl_2, −78 °C, Et_3N, 55%; (b) acetone/2 M HCl (100:1 or 200:1), rt then reflux, 35%.

a number of benzyl protection methodologies, **5c** was obtained in 37% yield, at best, using BnBr/Ag_2O in EtOAc.[20] Because of this quite modest result, we decided to test silyl protection. The combination of TBDMSOTf and 2,6-lutidine[21] proved to be very successful, providing **5b** exclusively in 95% yield.

The cleavage of the cyclic ketal by trans-acetalization was examined next. Since we expected that acidic hydrolysis would be difficult considering the problems we had in producing **8a** through acidic deprotection/cyclization, we instead turned our attention to $PdCl_2(CH_3CN)_2$, a soft Lewis acid.[22] Thus, on treating **5b** with a catalytic amount of the palladium catalyst at room temperature, in acetone and darkness, **6b** was obtained in 90% yield. By applying the same conditions to **5c**, **6c** was produced in 86% yield and **5a** gave **6a** in 85% yield, although the temperature had to be lowered to −15 °C in the latter case. Subsequently, oxidative cleavage of the allyl derivatives **6a**−**c** was affected by ozone in CH_2Cl_2 at −78 °C, followed by reductive workup using DMS.

Since the TBDMS-protected derivatives seemed most suitable to work with, we chose to continue the synthesis by using the crude oxidation product **6b**, which, as indicated by ^{1}H NMR, contained the aldehyde **7b**. Thus, the aldol reaction conditions were tested on this crude aldehyde. First, base-catalyzed aldol reactions were examined. However, neither K_2CO_3 nor Cs_2CO_3 in different concentrations in methanol could avoid formation of complex reaction mixtures. This prompted us to look for alternative reagents, and at an early stage our attention was drawn to Al_2O_3, which had been found to efficiently catalyze intramolecular aldolizations of both a keto aldehyde[24] and a diketone.[11] To our satisfaction, when passing crude **7b** through a column containing basic Al_2O_3, the desired bicyclic compound **8b** was collected almost pure as a mixture of *endo*- and *exo*-alcohols in 47% combined yield (starting from **6b**). With the aim to improve the reaction conditions for the cyclization, we examined the influence of different solvents and solid reagents. Three conventional solvents of different polarity (EtOAc, toluene, and heptane) were tested together with Al_2O_3 and high surface SiO_2 (450 m^2/g), respectively. It was found that the highest reaction rates and yields were obtained by using heptane as solvent in combination with Al_2O_3. No product could be isolated in the attempts with SiO_2. However, we found that Kubota et al.[25] had employed mesoporous SiO_2 in combination with amine bases to enhance base-catalyzed aldolizations between different derivatives of benzaldehyde and acetone. This study inspired us to further investigate the potential of high surface SiO_2, this time together with amine bases. Accordingly, a suspension of crude **7b** and high surface SiO_2 in heptane was subjected to primary (pentylamine and propylamine) and secondary (piperidine) amines, but these were unable to promote the reaction. The tertiary amines tributylamine, diisopropylethylamine, and triethylamine, on the other hand, were quite effective, yielding ***endo*-8b** in an isolated yield of 55, 70, and 78%, respectively. Different qualities of Al_2O_3 were also tested but SiO_2 was superior, in contrast to the reactions performed in the absence of base, as mentioned. Since SiO_2 did not promote any reaction in the absence of base, we checked if TEA alone could be responsible for the aldolization, but only traces of **8b** were obtained in this experiment; the unreacted aldehyde was recovered in 56% yield.

Since TEA can be used as a reducing agent in ozonolysis reactions, the possibility to develop a tandem reaction appeared logical. To test this idea, a solution of **6b** in heptane was purged with ozone at −78 °C. After the reaction reached room temperature, TEA and SiO_2 were added. The dual role of TEA was evident since **8b** was obtained as a diastereomeric mixture of *endo*- and *exo*-alcohols, which were separated by column chromatogra-

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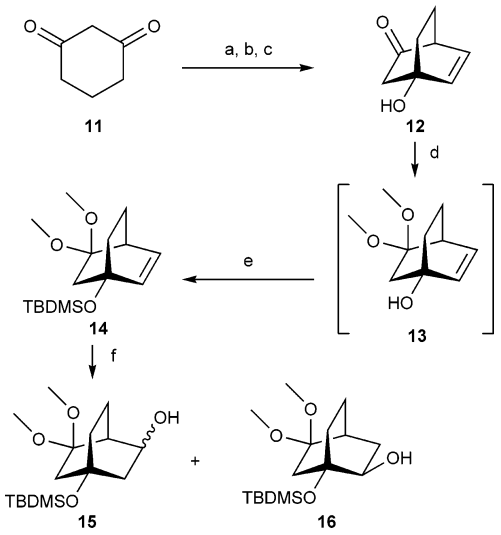
SCHEME 3[a]



[a] Reagents and conditions: (a) isopropenyl acetate (10 equiv), maleic anhydride (1.3 equiv), *p*-TsOH (cat.), reflux, 12 h; (b) H_2O, 80 °C, 12 h; (c) pyridine/H_2O/TEA (10:10:1), electrolysis, 24 h, 55% over three steps; (d) trimethylorthoformate (1.5 equiv), *p*-TsOH (cat.), MeOH, rt, 24 h, quant.; (e) TBDMSCl (5 equiv), 60% NaH (5 equiv), THF, 0 °C → rt, 12 h, 52% over two steps; (f) i. BH_3·THF, THF, 0 °C → rt, ii. 2 M NaOH, 30% H_2O_2, **15**: 0%, **16**: 39%.

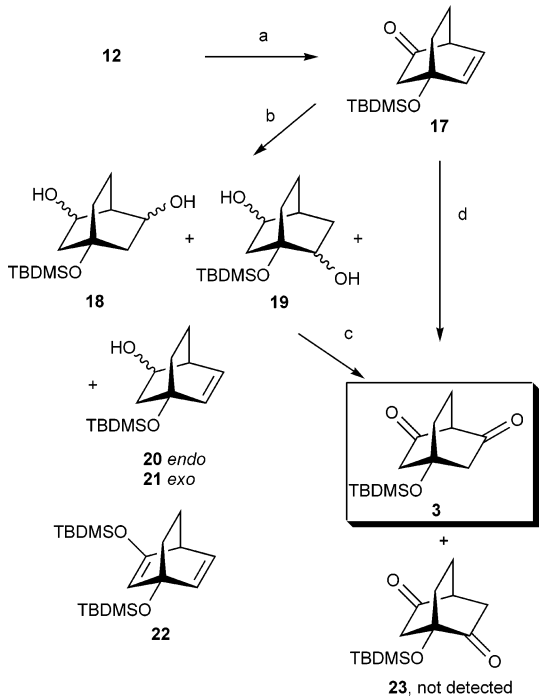
phy to afford ***endo*-8b** and ***exo*-8b** in 67 and 16% yield, respectively (starting from **6b**).

Motivated by the ease of the improved preparation of **8b** from **6b**, the same methodology was planned for **6a** and **6c**, but these compounds were not soluble in heptane and instead the two-step procedure had to be employed, in which CH_2Cl_2 was used as solvent in the ozonolysis reaction. Furthermore, to enhance the solubility of the substrates during the aldolization, toluene was used as cosolvent in combination with heptane. In this way, **8c** was formed as a diastereomeric mixture of *endo*- and *exo*-alcohols, which after separation were obtained in 50 and 14% yield, respectively. In the case of **6a**, the cyclization reaction was very sluggish and irreproducible, and **8a** (45%) was not obtained in a pure state due to the high water solubility and instability of the product. Additionally, the diastereoisomers were difficult to separate by column chromatography. No further efforts were made to optimize the synthesis of **8a**. *meso*-Diketone **3** was then conveniently obtained in 90% yield by oxidation of **8b** by $KMnO_4/CuSO_4 \cdot 5H_2O$.[26]

Our second route toward **3** was based on the Diels–Alder product **12** (from dienol bisacetate of **11** + maleic anhydride) (Scheme 3). Compound **12** was obtained in an overall yield of 55%, starting from **11**, according to a modified literature procedure[8] in which the lead tetraacetate-induced bisdecarboxylation was replaced with a more environmentally friendly Kolbe-like electrolytic bisdecarboxylation.[27]

For the hydration of **12**, hydroboration–oxidation was chosen since varying the size of the borane reagent, in combination with a large protection group at the bridgehead hydroxyl, was thought to increase the probability to obtain the desired regioisomer **15**. In our first attempt,

SCHEME 4[a]



[a] Reagents and conditions: (a) i. TBDMSOTf (1.5 equiv), 2,6-lutidine (2.6 equiv), CH_2Cl_2, 0 °C ii. 1 M HCl, THF, rt, 1 h, 70%; (b) i. hydroboration reagent (see text), THF, 0 °C, 3 h, ii. 2 M NaOH, 30% H_2O_2, rt, 12 h; (c) Jones' oxidation, 64% of **3**; (d) i. BH_3·THF, THF, 0 °C, 3 h, ii. TPAP, NMO, CH_2Cl_2, rt, 4 h, 42%.

the hydroboration was preceded by two protection steps: acetalization of ketone **12** produced **13** quantitatively, which was then TBDMS-protected under the same conditions as for **5a**. Surprisingly, two products were formed. Apart from the expected **14**, deacetalization occurred giving TBDMS-protected **17** (Scheme 4). Due to separation problems of **14** and **17**, TBDMSCl in combination with NaH in THF, which gave **14** as the only product, was used instead, even though full conversion of **13** could not be achieved.

In the first hydroboration–oxidation attempts of **14**, BH_3·THF was chosen. However, several products were formed where only the *exo*-isomer of **16** could be isolated as an impure sample. At first, we anticipated one of the MeO groups of the acetal in **14** to coordinate BH_3, directing it toward C2-attack, which would form the desired regioisomer **15** after oxidation. However, to our surprise, formation of **16** was favored. Apparently, the acetal group was not as small or directing as we anticipated. It is possible that the borane was coordinated by the acetal group in a way remote from the C-2 position, preventing borane addition via a C-2 directive effect. The absence of formation of the *endo*-isomer of **16** might be explained by steric hindrance from the acetal–BH_3 complex, forcing the borane toward exo attack.

Due to the difficulties to synthesize **14** selectively in high yield in combination with several protection and deprotection steps followed by selectivity problems in the hydroboration step, we changed our approach (Scheme 4). Thus, **12** was TBDMS-protected to give **17** and bissilylated enol ether **22**, which was easily cleaved by acidic hydrolysis, resulting in a 70% total yield of **17**.

Starting from **17**, compound **3** could in principle be obtained either via a stepwise hydroboration followed by

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oxidation sequence via **18** or via direct one-pot in situ hydroboration−oxidation.

The stepwise approach was tested first by employing a series of borane reagents (BH_3·THF, disiamyl borane, thexyl borane, catechole borane, 9-BBN, and BBr_2H·SMe_2). A large excess of the borane reagent was used to ensure full conversion of both the carbonyl and the olefin unit. Complex mixtures containing all four alcohols **18/19/20/21** in different ratios were obtained together with several byproducts when more bulky boranes were applied. Complete conversion of **17** into **18** and **19** (49:51) was only observed with BH_3·THF. Next, **18** and **19** were oxidized separately under Jones' conditions where **18** gave **3** (64%). Surprisingly, **23** (the oxidation product of **19**) was not detected. Worth noticing is that the acid-sensitive TBDMS group was resistant toward Jones' conditions.

Attempts were also made to synthesize **3** in a one-step procedure starting from **17**. The most common and frequently used method for this kind of operation was found in the literature to be hydroboration followed by chromic acid oxidation of the organoborane.[28] Since the yields were rather low using this oxidation and seemed to drop on scaling up, hydroboration followed by either PCC oxidation in CH_2Cl_2[29] or TPAP/NMO oxidation were tried.[30] Oxidation with TPAP/NMO was found to be the most promising method for the following reasons: (a) no decrease in yield on scaleup, (b) use of a catalytic amount of TPAP instead of a stoichiometric excess of the chromium reagents, and (c) simple workup by filtration through a pad of SiO_2. This resulted in an overall 42% yield of **3**.

Deprotection of **3** to give **2** was performed in BF_3·Et_2O/CH_3CN at 0 °C,[31] which proceeded nicely, but **2** proved to be very difficult to isolate due to its high water solubility. Thus, the silyl-protecting group positioned at the bridgehead hydroxyl in **3** should preferentially be kept in place prior to further transformations.

In conclusion, two independent synthetic routes toward the bridgehead TBDMS-protected 4-hydroxy bicyclo-[2.2.2]octane-2,6-dione **3** have been developed starting from **11**. Compound **3** and a number of the intermediate compounds presented here may be interesting starting materials for the preparation of more complex organic molecules.

Experimental Section

(±)-*endo*/*exo*-4-(*tert*-Butyldimethylsilanyloxy)-6-hydroxybicyclo[2.2.2]octan-2-one (8b). Ozone was bubbled through a solution of **6b** (1.0 g, 3.73 mmol) in heptane (75 mL) at −78 °C until it turned light blue (ca. 30 min). Excess ozone was then driven off by flushing with argon, and then TEA (14 mL) was added and the reaction mixture was allowed to reach room temperature. Under intense stirring, SiO_2 (450 m^2/g) (17 g) was added, and after a couple of minutes the color had turned deep red. After completion of reaction (TLC), the silica gel was filtered off and washed with EtOAc. The filtrate was collected, the solvent was removed at reduced pressure, and the residue was purified by column chromatography (SiO_2, pentane/ether 1:1) to give ***endo*-8b** (673 mg, 67%) and ***exo*-8b** (166 mg, 16%) as white solids.

***endo*-8b:** R_f 0.14; mp 80.5−81.7 °C; IR (KBr) 3408, 2961, 2856, 1717, 1252, 1132, 835, 773 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 3.50−3.45 (m, 1H), 2.51 (br d_{AB}, J_{AB} = 17.9 Hz, 1H), 2.22 (dd_{AB}, J = 3.3 Hz, J_{AB} = 17.9 Hz, 1H), 2.12−2.11 (m, 1H), 1.85 (ddd_{AB}, J = 3.3, 9.2 Hz, J_{AB} = 13.5 Hz, 1H), 1.57 (d_{AB}, J_{AB} = 13.5 Hz, 1H), 1.28 (d, J = 2.8 Hz, 1H), 1.25−1.19 (m, 3H), 1.06−0.98 (m, 1H), 0.91 (s, 9H), −0.03 (s, 6H); ^{13}C NMR (100 MHz, benzene-d_6) δ 209.5, 72.1, 67.8, 52.4, 50.0, 44.7, 32.5, 25.8, 18.4, 18.0, −2.0; HRMS (FAB+) calcd for $C_{14}H_{27}O_3Si$ (M + H): 271.1729. Found: 271.1736. Anal. Calcd for $C_{14}H_{26}O_3Si$: C, 62.18; H, 9.69. Found: C, 62.23; H, 9.64.

***exo*-8b:** R_f 0.25; mp 45.5−47.6 °C; IR (KBr) 3408, 2949, 2856, 1715, 1252, 1142, 835, 773 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 3.61−3.59 (m, 1H), 2.18−2.02 (m, 4H), 1.79−1.73 (m, 1H), 1.65−1.63 (m, 1H), 1.49 (td_{AB}, J = 3.3 Hz, J_{AB} = 13.5 Hz, 1H), 1.34−1.32 (m, 1H), 1.20−1.19 (m, 1H), 0.91 (br s, 9H), 0.73 (br s, 1H), −0.03 (s, 6H); ^{13}C NMR (100 MHz, benzene-d_6) δ 209.4, 72.6, 64.9, 51.6, 50.8, 45.5, 33.2, 25.8, 18.0, 16.4, −1.99; HRMS (FAB+) calcd for $C_{14}H_{27}O_3Si$ (M + H): 271.1729. Found: 271.1725. Anal. Calcd for $C_{14}H_{26}O_3Si$: C, 62.18; H, 9.69. Found: C, 62.14; H, 9.78.

4-(*tert*-Butyldimethylsilanyloxy)-bicyclo[2.2.2]octan-2,6-dione (3). (a) Oxidation of 8b: A solution of ***endo*/*exo*-8b** (100 mg, 0.37 mmol) in toluene (1.5 mL) was stirred with $KMnO_4$/$CuSO_4$·$5H_2O$ (440 mg, 2:1 w/w) at 80 °C for 12 h. After cooling the mixture, we removed the solid by filtration through a pad of silica gel, which was rinsed thoroughly with ether. The solvent was removed at reduced pressure to leave **3** (90 mg, 90%), which was obtained as white crystals upon recrystallization from pentane. R_f 0.38 (heptane/EtOAc 7:3); mp 88.6−89.2 °C; IR (KBr) 2957, 2351, 1734, 1710 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 3.04 (t, J = 2.8 Hz, 1H), 2.16 (br d_{AB}, J_{AB} = 15.6 Hz, 2H), 2.01 (d_{AB}, J_{AB} = 15.2 Hz, 2H), 1.26−1.15 (m, 4H), 0.85 (s, 9H), −0.16 (s, 6H); ^{13}C NMR (100 MHz, benzene-d_6) δ 202.2, 71.8, 63.1, 52.1, 32.5, 25.7, 20.0, 17.9, −2.3; HRMS (FAB+) calcd for $C_{14}H_{25}O_3Si$ (M + H): 269.1573. Found: 269.1569. Anal. Calcd for $C_{14}H_{24}O_3Si$: C, 62.64; H, 9.01. Found: C, 62.49; H, 9.11.

(b) Hydroboration of 17, Followed by Oxidation. At 0 °C, 2 M BH_3·SMe_2 (4.0 mL, 8.0 mmol) was added to a solution of **17** (518 mg, 2.0 mmol) in ether (6 mL). After 4.5 h at room temperature, H_2O (8 mL) was added, followed by saturation of the aqueous phase with NaCl (s) and extraction with EtOAc (5 × 15 mL). The organic phase was washed with brine (60 mL) and dried (Na_2SO_4) before removal of solvent at reduced pressure. The residue was dissolved in CH_2Cl_2 (7 mL), followed by addition of powdered 4 Å MS, NMO (1.64 g, 14.0 mmol), and TPAP (50 mg, 0.14 mmol). After 12 h at room temperature, the reaction mixture was filtrated through a pad of SiO_2 and eluted with EtOAc. The residue was purified by column chromatography (SiO_2, heptane/EtOAc 9:1) to give **3** (223 mg, 40%) as white crystals. This reaction was repeated several times in different scales (0.5−2 mmol), which gave reproducible yields (40%). See Table 1 in Supporting Information for further details.

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Supporting Information Available: Experimental procedures and other detailed results; ^1H and ^{13}C NMR spectra for compounds **9**, **10**, **14**, **16**, **18**, and **19**; COSY, HMQC, and HMBC spectra for compound **16**; COSY and NOESY spectra for compounds ***endo*-8b** and ***exo*-8b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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