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Stereoselective synthesis of highly substituted 8-oxabicyclo[3.2.1]octanes and 2,7-dioxatricyclo[4.2.1.0^{3,8}]nonanes

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ABSTRACT

The synthesis of new polyhydroxylated 8-oxabicyclo[3.2.1]octanes and 2,7-dioxatricyclo[4.2.1.0^{3,8}]nonanes is described. These structures is an interesting synthetic blocks for potential bioactive molecules. The precursor, 3-chloro-8-oxabicyclo[3.2.1]oct-6-ene-2,4-dione was obtained from reaction of tetrachlorocyclopropene with furan, then it was involved in carbonyl groups reduction and double bond oxidation, resulted in the formation of a polyhydroxylated derivatives, differently substituted at C-3 position, with five new stereocenters.

Using intramolecular transannular hydroxycyclization, bicyclic epoxy diacetate was transformed into 2,7-dioxatricyclo[4.2.1.0^{3,8}]nonane in high yield through an alkoxide intermediate. Compounds thus obtained have a structure close to certain molecules with antitumor and glycosidase inhibitors activity.

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1. Introduction

Our research interests lie in the synthesis of new polyhydroxylated cycloheptane scaffolds, which could possess various biological activities, and act as linkers for the building of complex hybrid structures through hydroxyl group functionalization. Here, we describe the application of some simple chemical transformation (carbonyl group reduction, double bond oxidation, intramolecular hydroxycyclization) in high diastereoselectivity, to create five new stereocenters in oxabicyclooctane structures.

8-Oxabicyclo[3.2.1]octane derivatives can be considered as structural analogs and synthetic precursors of tropane alkaloids (e.g., calystegines[1] and scopoline,[2] see Fig. 1), and other bioactive compounds (e.g., polyketides[3] and tetrahydropyrans[4]). Calystegines and other tropane alkaloids show remarkable inhibitory activities against several glycosidase enzymes, so the same activity is expected from their analogs. Glycosidase inhibitors were a subject of a number of works in the past decade, most of which has been reviewed.[5] These compounds have already been used or tested in the treatment of diabetes and HIV infection, as antifungal agents and are expected to arouse increasing interest as therapeutic agents as our understanding of the role of glycosidases in recognition processes improves. It is also worth mentioning that carba-analogs of oligosaccharides (carbasugars) generated by replacing the endocyclic oxygen atom in monosaccharides are thought to be more promising drug candidates than natural sugars, since they are hydrolytically stable.[6]

Hoffmann et al. used 8-oxabicyclo[3.2.1]octanes to generate the 2,7-dioxatricyclo[4.2.1.0^{3,8}]nonane core of the antitumor terpenic natural product dictyoxetane.[7] The elaboration of the oxetane and oxolane rings of ingenol and thromboxane A_2 analogs has been elegantly carried out.[8] Recently several 8-oxabicyclo[3.2.1]octanes have been found to possess moderate anti-HIV activity.[9] Moreover, 8-oxabicyclo[3.2.1]octane derivatives have shown broad utility as chiral building blocks for construction of *C*-linked nucleosides[10] and disaccharides.[11] De novo synthesis of a full set of hybrid *C*-glycosides and thymine polyoxin C starting with the unsaturated 8-oxabicyclo[3.2.1]octane framework was reported.[12]

Lautens et al. showed that 8-oxabicyclo[3.2.1]octane derivatives can be readily transformed to non-bridged cycloheptane derivatives.[13] Thus, our methodology could be an efficient way to wide range of non-natural carbasugar molecules.

Here, we report on concise stereoselective way to polyhydroxylated bridged cycloheptane derivatives as potential glycosidase inhibitors, antitumor agents and building blocks for complex nature-type carbasugars.

2. Results and discussion

There are several synthetic ways to 8-oxabicyclo[3.2.1]octane core. The [4+3]-cycloaddition reaction is the most common.[14] An

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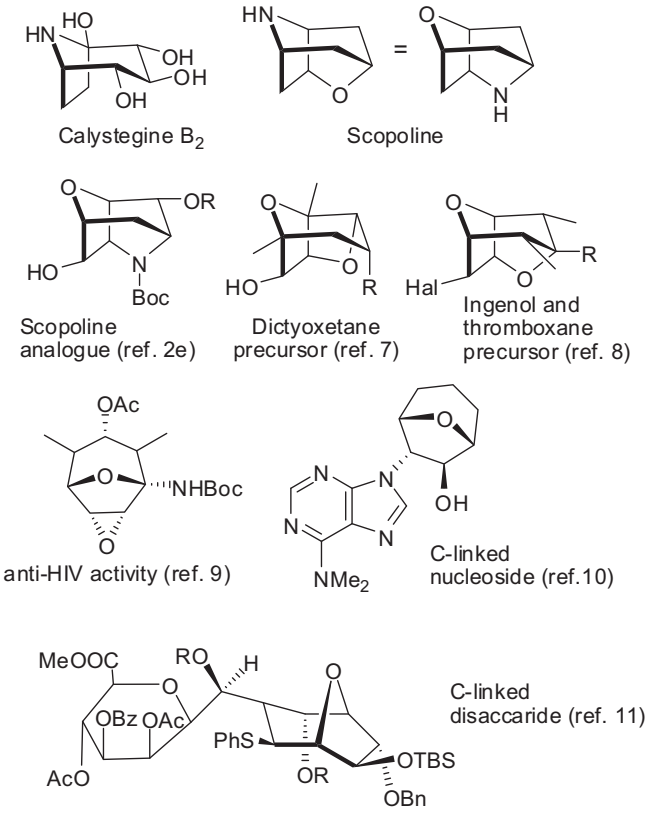
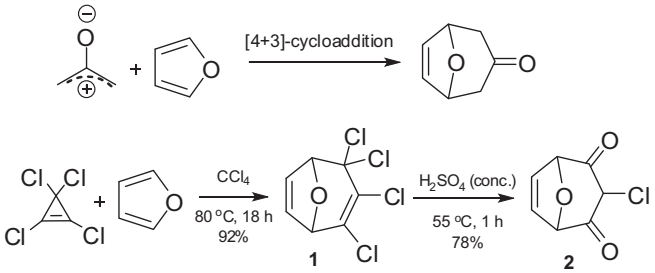


Fig. 1. Examples of some bioactive bridged cycloheptane derivatives.

alternative approach is the Tobey and Law synthesis of the 1,3-diketone **2** (Scheme 1) in just two steps from commercially available tetrachlorocyclopropene.[15]

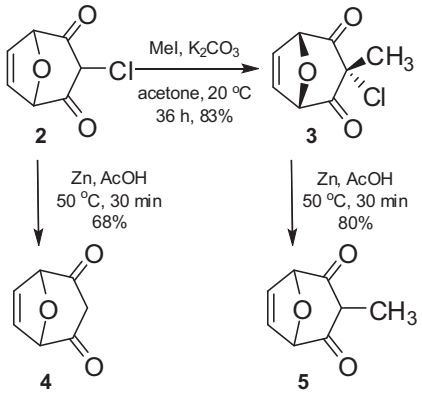


Scheme 1. Synthesis of 8-oxabicyclo[3.2.1]octanes core.

Cyclocondensation of tetrachlorocyclopropene and furan proceeds through an initial Diels–Alder reaction to produce **1** in high yield. Direct hydrolysis of **1** under strongly acidic conditions and elevated temperatures delivers the 1,3-dione **2**. Reported yield for this step was moderate (42%) but we optimized the conditions to get 78% of yield so **2** could be easily produced in multigram quantities. As mentioned above, the main objective of our work is the synthesis of polyhydroxylated cycloheptane core, with the selective creating of new stereocenters. Therefore, following transformations of diketone **2** should involve reduction of the carbonyl groups and oxidation of the double bond. As far as we know, diketone **2** never been used for constructing of polyhydroxylated cycloheptane derivatives, probably because of difficulties with carbonyl group reduction.

Actually, the reduction of diketone **2** by complex hydride reagents ($NaBH_4$, $LiAlH_4$) was challenging due to its high C–H acidity (pK ~ 5). It caused the vigorous decomposition of hydrides and low conversion of starting materials (5–15%), but fortunately, we have found that the use of diisobutylaluminum hydride (DIBAL-H) allows to overcome those problem.[16]

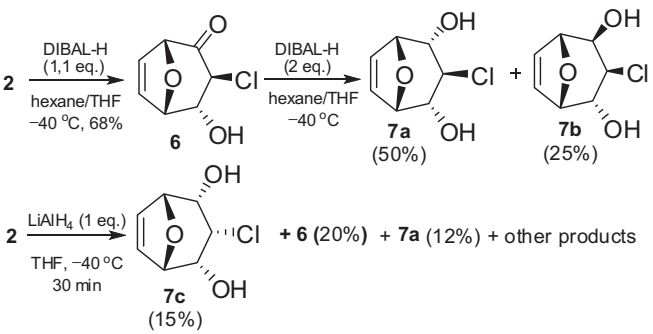
Here we describe two other ways to avoid the difficulties by modification of the C-3 position in diketone **2**, namely, alkylation and chlorine reduction. Early, methylation of **2** was investigated by Wright et al.[17] It has been shown that the activated proton in **2** is acidic enough to use Et_3N as a base for alkylation, and compound **3** was readily obtained. Its configuration was proved by X-ray diffraction analysis with methyl group in *exo*-position. We increased the yield of methylation using methyl iodide in acetone with K_2CO_3 as a base (Scheme 2).



Scheme 2. Synthesis of diketones **3**–**5**.

The same authors described the dechlorination protocol using zinc in acidic media, however, the isolation of diketone **4** was mentioned to be difficult owing to high water solubility and ready deprotonation. We applied flash chromatography for purification, and compound **4** was isolated in good yield (Scheme 2). Using the same conditions for dechlorination of diketone **3**, compound **5** was obtained in high yield. Compared with the diketone **4**, it was much more stable and easy to isolate.

As already mentioned above, the reduction of diketone **2** by complex hydrides was complicated. Many reducers were tested, among them $NaBH_4$, $LiAlH_4$, $LiAl(OR)_3H$, LiR_3BH and others, but the best conditions tested so far was treatment with DIBAL-H. Straight reduction was unsuccessful, in all cases complex mixture were afforded, so two-steps methodology was proposed (Scheme 3). Thus, reduction of **2** was performed with 1 equiv of DIBAL-H in anhydrous THF at −40 °C, obtaining the ketoalcohol **6** in 68% yield. Then, a further reduction of **6** with the 2 equiv of DIBAL-H afforded the mixture of diastereomeric diols **7a** and **7b** in 2:1 ratio, which were separated.



Scheme 3. Reduction of diketone **2**.

The stereochemistry of both compounds has been established by careful ^{1}H and ^{13}C NMR correlation studies. However, NMR spectroscopic studies did not allow to assign exact configuration of all stereocenters in the six-membered ring so isomer **7a** was subjected to X-ray analysis,[16] resulted in the proposed structure with Cl and OH-groups in equatorial positions (Fig. 2).

The corresponding coupling constants are $^{1,2}J$=4.3 and $^{2,3}J$=8.1 Hz for *e*–*a* and *a*–*a* pairs, respectively. Small coupling constant $^{4,5}J$=1.0 Hz in the *trans*-isomer **7b** associated with *e*–*e* configuration. These configurational assignments were confirmed with NOE experiments: positive effect (1.5–3%) in case of *e*–*a* and *e*–*e* proton pairs corroborate it once again (Fig. 3).

Configuration of ketoalcohol **6** could be established easily by similar NMR data with the diol **7a**. One more Cl-containing isomer **7c** was isolated from the reaction mixture of diketone **2** with $LiAlH_4$ in anhydrous THF (Scheme 3).

Subsequently the reduction of diketones **3**–**5** was investigated. As expected, methylated diketone **3** was smoothly reduced with $NaBH_4$ in methanol at room temperature obtaining the only di-*endo* diol isomer **7d** in 75% yield (Scheme 4). Attempting the $LiAlH_4$ reduction led to a complex mixture even at −60 °C, from which the diols **7d** and **7e** were isolated in poor yields.

Diol **7e** was the major product of diketone **5** reduction with $NaBH_4$ (Scheme 4). Several other isomers were detected in NMR spectra of reaction mixture, but they were not isolated. Coupling constant $^{1,2}J$=4.3 Hz was in good agreement with proposed configuration of OH-groups, but stereochemistry of methyl group was ambiguous and recourse was made to X-ray crystallography. Since diol **7e** was isolated as an oil we synthesized crystalline diacetate **8e**.

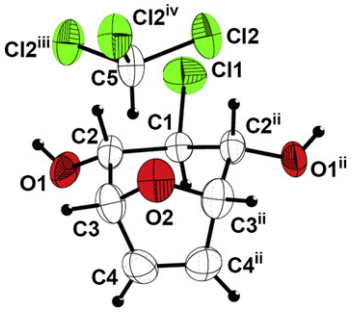


Fig. 2. X-ray structure of diol **7a**.

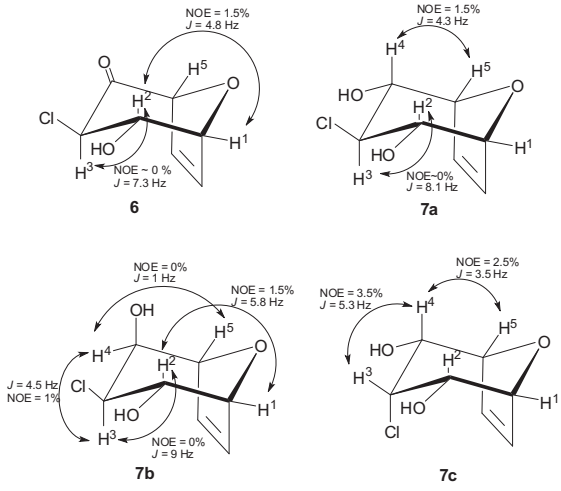
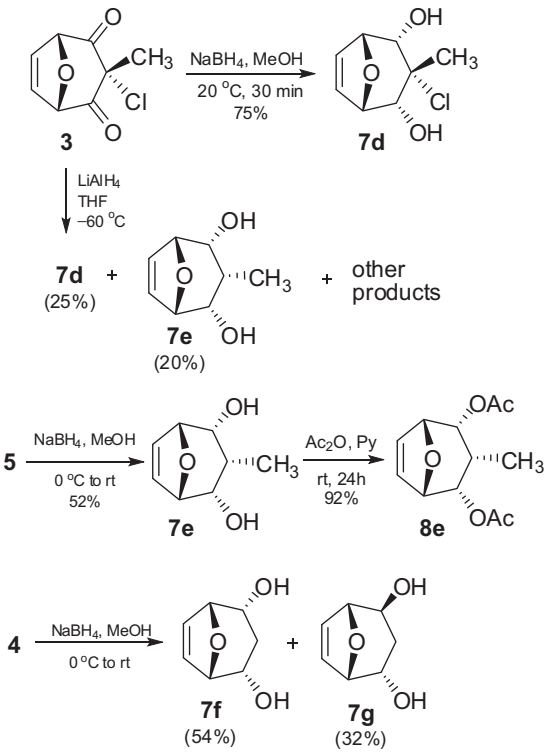


Fig. 3. NOE dif. couplings of some Cl-containing alcohols.



Scheme 4. Reduction of diketones **3**–**5** with $NaBH_4$.

X-ray diffraction analysis showed the axial position of methyl group (Fig. 4), thus the configuration of diol **7e** was completely defined.[18]

Finally, diketone **4** was reduced with $NaBH_4$ in methanol at room temperature to produce mixture of two isomeric diols **7f** and **7g** in 3:2 ratio (Scheme 4). They were separated and purified by column chromatography and spectroscopically characterized.

For further transformations we carried out protection of the OH-groups. A benzyl ether was the protecting group of choice here because of its stability and the simplicity of its removal. Alcohols were thus treated with NaH and BnBr in anhydrous THF under the classical Williamson reaction conditions (Scheme 5). In most cases, corresponding benzyl derivatives **9** was synthesized in high yields. As an exception, diols **7c** and **7d** containing axial Cl atom failed in the Williamson reaction. Complex mixtures were obtained with only traces of benzyl ethers. Most probably, the intramolecular nucleophilic attack was preferable in these cases though corresponding epoxides were not isolated. At the same time acylation of diols **7c** and **7d** proceed smoothly under the same conditions as those applied for **7e** to afford acetates **8c** and **8d** in high yield.

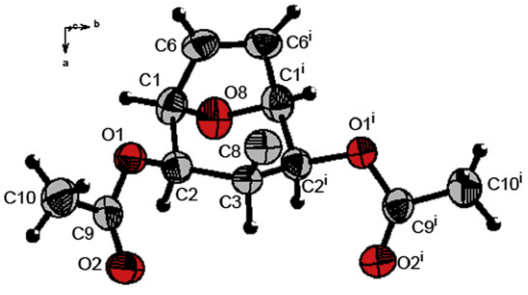
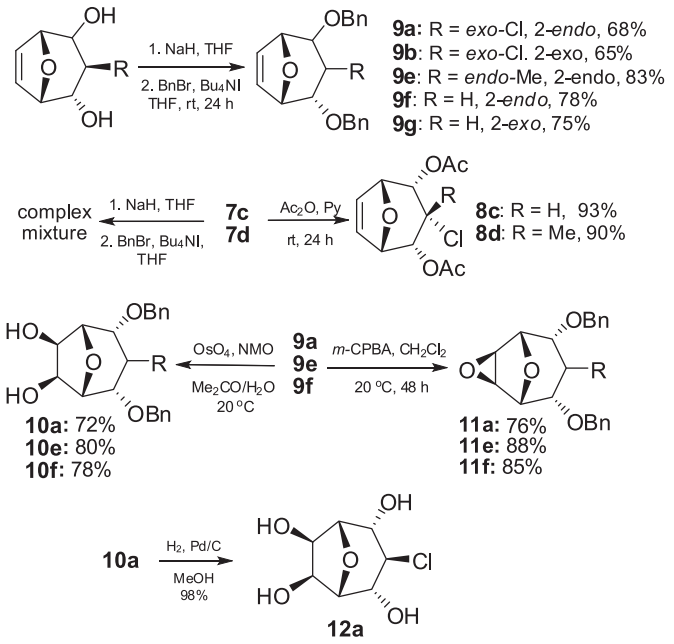


Fig. 4. X-ray structure of diacetate **8e**.



Scheme 5. Protection of OH-groups and oxidation of double bond.

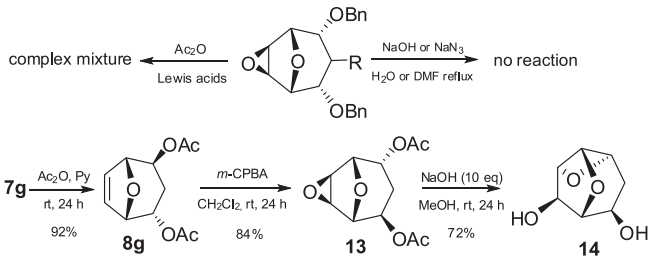
Further functionalization of 8-oxabicyclo[3.2.1]octane skeleton was achieved by the double bond oxidation. According to the symmetry in the molecule, the hydroxylation reagent can approach with the *endo*- as well as from the *exo*-face. Previous research consider this reaction proceed with high *exo*-stereoselectivity.[19] Actually, treatment of symmetrical ethers **9a**, **9e** and **9f** with OsO_4/NMO gave only a single *exo*-isomers **10** (Scheme 5) without considerable $^{1,7}J$ or $^{2,6}J$ coupling constants. Epoxidation of ethers **9a**, **9e** and **9f** was performed by *m*-CPBA in anhydrous CH_2Cl_2 at room temperature. The reaction was completed after 48 h, affording single stereoisomers of epoxides **11** in 76–85% yield.

Removal of the benzyl protecting groups with H_2 and Pd/C in methanol gave the tetraol **12a** in almost quantitative yield. Notably, Cl atom was retained after hydrogenation. Thereby we suggest versatile way to create five new stereocenters in the 8-oxabicyclo [3.2.1]octane core. Our approach is flexible providing different polyhydroxylated compounds in stereocontrolled fashion, that could act as glycosidase inhibitors. Frameworks thus obtained could be convenient linkers for construction of complex molecules as well. Hydroxyl groups introduced step by step might be functionalized in different manner.

In order to use synthetic potential of the epoxide ring moiety compounds **11a**, **11e**, **11f** were treated with some basic and acidic reagents. All attempts of nucleophilic ring opening with NaOH or NaN_3 were unsuccessful: even after refluxing in DMF or aqueous media only starting materials were recovered. Reactions with Ac_2O in the presence of Lewis acids (BF_3–Et_2O or $ZnCl_2$) afforded the complex mixture of rearrangement products. Thus we decided to explore the intramolecular nucleophilic reaction.

As already mentioned above, Hoffmann et al. reported the synthesis of the 2,7-dioxatricyclo[4.2.1.0^{3,8}]nonane core from some 8-oxabicyclo[3.2.1]octanes. These oxetanes can be considered as structural analogs of antitumor terpenic natural product dictyoxetane.[7] We decided to apply this methodology to our substrates.

We synthesized the diacetate **13** using the same procedures as described above to indirectly generate the alkoxide from hydroxyl group by using NaOH. Treating with 10 equiv NaOH in MeOH at room temperature after 24 h gave the dioxatricycle **14** in 72% yield (Scheme 6) with the structure close to dictyoxetane analogs investigated by Hoffmann.



Scheme 6. Synthesis of oxetane diol **14**.

Thus we demonstrated the concise and practical route to different polyhydroxylated polycyclic scaffolds, based on cheap and easy available substrates and reagents. High stereoselectivity was observed.

3. Conclusions

In summary, we have established a methodology to obtain 3-functionalized polyhydroxylated 8-oxabicyclo[3.2.1]octanes with good yield and a high stereoselectivity. By this method it is possible to prepare a wide variety of derivatives (alkyl, chloro) under mild conditions. Acetyl protected epoxy alcohol was successfully converted to tricyclic oxetane diol. Substances thus obtained could possess different biological activity and be precursors of other carbasugars and complex structures.

All compounds synthesized have been isolated, purified and physically and spectroscopically characterized. The stereochemistry has been unequivocally assigned by a careful correlation of ^{1}H, ^{13}C and NOE NMR data and confirmed by X-ray diffraction analysis.

4. Experimental section

4.1. General methods

All the solvents were distilled prior to use. Dry solvents were prepared according to the standard procedures. Reactions requiring an inert atmosphere were carried out under argon. All reactions were monitored by TLC using Merck 60 F254 precoated silica gel plates (0.25 mm thickness). Flash and column chromatography was performed by using silica gel 60 from Macherey–Nagel. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 with a Bruker Avance 400 (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR) instrument. Data for ^{1}H NMR spectra are reported as chemical shift (δ [ppm]), number of protons, multiplicity (s=singlet, d=doublet, t=triplet, m=multiplet) and coupling constant (J [Hz]). Data for ^{13}C NMR spectra are reported as chemical shift (δ [ppm]). Chemical shifts were reported in parts per million from the residual solvent as an internal standard. Infrared (IR) spectra were recorded in KBr pellets on a Thermo Nicolet IR-200 spectrometer. Elemental analyses were carried on Vario MICRO cube analyzer.

Crystallographic data for the structures in this paper have been deposited at the Cambridge Crystallographic Data Center and allocated the deposit numbers CCDC 741610 for **7a** and 841294 for **8e**.

4.2. 3-Chloro-8-oxabicyclo[3.2.1]oct-6-ene-2,4-dione (2)

It was prepared by the modified procedure of Tobey and Law.[15] Compound **1** (9.00 g, 37.0 mmol) was mixed with 130 mL of conc. H_2SO_4 (d=1.84 g/mL) and heated at 50–55 °C with good stirring during 1 h (until the intensive gas evolving stopped). The resulting mixture was cooled to room temperature and poured into the ice-cold water (500 mL) followed by extraction with methylene chloride (5×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to yield

crude product, which after recrystallization from chloroform gave diketone **2** (5.04 g, 78%) as a white crystalline solid, mp 137–138 °C ($CHCl_3$). (lit. 139–140 °C[15]); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.40 (2H, s), 5.91 (1H, s), 5.49 (2H, s); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.88 (2H, s), 5.20 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.0, 132.3, 86.6, 72.6; IR (cm^{-1}): $\tilde{\nu}$ 3100, 2920, 1770, 1740, 1675, 1145, 1068, 941.

4.3. 3-*endo*-Chloro-3-*exo*-methyl-8-oxabicyclo[3.2.1]oct-6-ene-2,4-dione (3)

To a solution of diketone **2** (0.50 g, 2.90 mmol) in acetone (10 mL) K_2CO_3 (0.83 g, 6.01 mmol) and MeI (1.38 g, 9.72 mmol) were added. The mixture was stirred at room temperature for 36 h, then concentrated under reduced pressure. The residue was purified via silica gel flash chromatography (EtOAc/CH_2Cl_2=1:9), to give a pale yellow crystalline solid of diketone **3** (0.45 g, 83%); mp 97–98 °C (diethyl ether); R_f 0.5 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.47 (2H, s), 5.35 (2H, s), 1.98 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.0, 132.5, 86.3, 75.8, 27.6; IR (cm^{-1}): $\tilde{\nu}$ 3100, 2920–2960, 1745, 1650, 1470, 1380, 1210, 1090, 935; Anal. Calcd for $C_8H_7ClO_3$: C, 51.50; H, 3.78. Found: C, 51.48; H, 3.76.

4.4. 8-Oxabicyclo[3.2.1]oct-6-ene-2,4-dione (4)

To a solution of diketone **2** (0.50 g, 2.90 mmol) in 5 mL of glacial acetic acid Zn powder (0.28 g, 4.28 mmol) was added with stirring. After the beginning of heating-up the mixture was stirred at 50 °C for 30 min and then concentrated under reduced pressure. The residue was filtered through a plug of silica gel with CH_2Cl_2/EtOAc (5:1) mixture as eluent to give after removal of the solvent compound **4** as a yellow oil (0.27 g, 68%); R_f 0.6 (CH_2Cl_2/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.38 (2H, s), 5.15 (2H, s), 3.80 (1H, d, *J* 19.7 Hz), 3.45 (1H, d, *J* 19.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 132.0, 86.8, 52.8; IR (cm^{-1}): $\tilde{\nu}$ 3090, 2980, 1720, 1680, 1220, 1085, 950; Anal. Calcd for $C_7H_6O_3$: C, 60.87; H, 4.48. Found: C, 60.62; H, 4.63.

4.5. 3-Methyl-8-oxabicyclo[3.2.1]oct-6-ene-2,4-dione (5)

To a solution of diketone **3** (0.40 g, 2.14 mmol) in 4 mL of glacial acetic acid Zn powder (0.23 g, 3.52 mmol) was added. The mixture was then heated to 50 °C and stirred for 30 min. Then 20% aqueous NaOH was added dropwise till producing of the solid. The solid was dissolved by addition of 1 mL 0.1 N HCl, the mixture was extracted with CH_2Cl_2 (5×20 mL), the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to yield compound **5** (0.26 g, 80%) as a pale yellow crystalline solid, mp 87–88 °C; R_f 0.55 (CH_2Cl_2/EtOAc=4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.33 (2H, s), 5.24 (2H, s), 4.05 (1H, q, *J* 6.8 Hz), 1.26 (3H, d, *J* 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.5, 132.1, 77.9, 58.9, 7.4; IR (cm^{-1}): $\tilde{\nu}$ 3100, 3010, 2880, 1730, 1670, 1315, 1190, 1095, 950; Anal. Calcd for $C_8H_8O_3$: C, 63.15; H, 5.30. Found: C, 63.21; H, 5.42.

4.6. 1*S*(*R*),3*R*(*S*),4*S*(*R*),5*R*(*S*)-3-Chloro-4-hydroxy-8-oxabicyclo[3.2.1]oct-6-en-2-one (6)

1 M hexane solution of DIBAL-H (6.00 mL, 6.00 mmol) was added dropwise during 10 min at −30 °C to a solution of diketone **2** (1.00 g, 5.75 mmol) in 30 mL of dry THF under argon atmosphere, followed by stirring for 30 min. After that the methanol (10 mL) was added, resulting mixture was stirred at room temperature for 6 h and concentrated in vacuum, then filtered through a plug of silica gel with CH_2Cl_2/EtOAc mixture (1:1). Removal of the solvents under reduced pressure yielded crude ketoalcohol **6**, which was purified by flash chromatography (CH_2Cl_2/Et_2O=2:3) to give a pale yellow oil (682 mg, 68%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.56 (1H, d, *J* 6.1 Hz), 6.44 (1H, d, *J* 6.1 Hz), 5.06 (1H, d, *J* 4.8 Hz), 4.78 (1H, s), 4.68 (1H, d, *J* 7.3 Hz), 4.23 (1H, dd, *J* 4.8, 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.7, 134.2, 131.4, 85.0, 82.2, 75.9, 65.1; IR (cm^{-1}): $\tilde{\nu}$ 3380–3460, 3090, 2960, 1747, 1733, 1660, 1322, 1050, 935; Anal. Calcd for $C_7H_7O_3Cl$: C, 48.14; H, 4.01. Found: C, 47.97; H, 4.22.

4.7. Reduction of ketoalcohol (6) with DIBAL-H

1 M hexane solution of DIBAL-H (8.00 mL, 8.00 mmol) was added dropwise during 10 min at −60 °C to a solution of ketoalcohol **6** (700 mg, 4.01 mmol) in 30 mL of dry THF under argon atmosphere followed by stirring for 30 min. After that MeOH (10 mL) was added, resulting mixture was stirred at room temperature for 6 h, concentrated in vacuum, and filtered through a plug of silica gel with EtOAc as an eluent. Solvent was removed under reduced pressure. The residue consisting of a mixture of diols **7a** and **7b** was separated by column chromatography on silica gel with CH_2Cl_2/Et_2O/EtOAc (1:4:1) as an eluent to give diol **7a** as the first fraction (R_f 0.55) and diol **7b** as the second fraction (R_f 0.32).

*4.7.1. 1R(S),2S(R),3R,4R(S),5S(R)-3-Chloro-8-oxabicyclo[3.2.1]oct-6-ene-2,4-diol (**7a**).* Yield 352 mg (50%), colorless crystals from CH_2Cl_2/Et_2O/EtOAc (1:4:1), mp 115–117 °C. Crystals suitable for diffraction analysis were obtained by slow evaporation of chloroform solution. For crystallographic data see ref. 16; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.29 (2H, s), 4.53 (2H, d, *J* 4.3 Hz), 3.50 (2H, dd, *J* 4.3, 8.1 Hz), 3.44 (1H, t, *J* 8.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 130.5, 81.0, 70.6, 68.0; IR (cm^{-1}): $\tilde{\nu}$ 3300–3450, 2965, 2940, 1655, 1285, 1050, 940; Anal. Calcd for $C_7H_9O_3Cl$: C, 47.61; H, 5.14. Found: C, 47.64; H, 5.26.

*4.7.2. 1R(S),2S(R),3R(S),4S(R),5S(R)-3-Chloro-8-oxabicyclo[3.2.1]oct-6-ene-2,4-diol (**7b**).* Yield 175 mg (25%), colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.32 (1H, d, *J* 6.3 Hz), 6.22 (1H, d, *J* 6.3 Hz), 4.56 (1H, d, *J* 1.0 Hz), 4.54 (1H, d, *J* 5.8 Hz), 3.92 (1H, dd, *J* 4.5, 9.0 Hz), 3.63 (1H, dd, *J* 5.8, 9.0 Hz), 3.59 (1H, dd, *J* 1.0, 4.5 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 132.7, 131.8, 83.7, 81.7, 68.9, 66.6, 65.9; IR (cm^{-1}): $\tilde{\nu}$ 3250–3450, 2970, 2940, 1660, 1290, 1055, 940; Anal. Calcd for $C_7H_9O_3Cl$: C, 47.61; H, 5.14. Found: C, 47.64; H, 5.26.

4.8. Reduction of diketone (2) with $LiAlH_4$

To a solution of diketone **2** (0.50 g, 2.90 mmol) in anhydrous THF (20 mL) a suspension of $LiAlH_4$ (75.0 mg, 1.97 mmol) in THF was added dropwise at −40 °C under the argon atmosphere followed by stirring for 30 min. To the resulting mixture methanol (5 mL) and 1 M aqueous solution of AcOH (20 mL) were added and it was allowed to reach the room temperature. The mixture was extracted with EtOAc (5×20 mL), the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to yield a mixture of ketoalcohol **6** and diols **7a** and **7c**. Pure compounds were obtained by column chromatography on silica gel with CH_2Cl_2/Et_2O/EtOAc (1:4:1) as an eluent to give ketoalcohol **6** (100 mg, 20%) as the first fraction (R_f 0.72), diol **7a** (60.0 mg, 12%) as the second fraction (R_f 0.55) and diol **7c** as the third fraction (R_f 0.45).

*4.8.1. 1R(S),2S(R),3S,4R(S),5S(R)-3-Chloro-8-oxabicyclo[3.2.1]oct-6-ene-2,4-diol (**7c**).* Yield 75.0 mg (15%), colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.22 (2H, s), 4.55 (1H, t, *J* 5.3 Hz), 4.40 (2H, d, *J* 3.6 Hz), 3.92 (2H, dd, *J* 3.6, 5.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 133.1, 80.3, 65.5, 65.3; IR (cm^{-1}): $\tilde{\nu}$ 3300–3500, 2975, 2950,

1655, 1290, 1050, 940; Anal. Calcd for $C_7H_9O_3Cl$: C, 47.61; H, 5.14. Found: C, 47.75; H, 5.31.

4.9. 1*R*(*S*),2*S*(*R*),4*R*(*S*),5*S*(*R*)-3-*endo*-Chloro-3-*exo*-methyl-8-oxabicyclo[3.2.1]oct-6-ene-2,4-diol (7d)

To a solution of diketone **3** (0.37 g, 1.98 mmol) in anhydrous MeOH (10 mL) the $NaBH_4$ powder (0.50 g, 13.2 mmol) was added portionwise at room temperature followed by stirring for 30 min. Then, a saturated aqueous solution of NH_4Cl (10 mL) was added at 0 °C and the reaction mixture was extracted with EtOAc (5×20 mL), combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to yield a 0.33 g (75%) of diol **7d** as pale yellow crystals: mp 106–108 °C; R_f 0.45 (CH_2Cl_2/Et_2O=1:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.33 (2H, s), 4.63 (2H, d, *J* 4.3 Hz), 3.79 (2H, dd, *J* 4.3, 7.0 Hz), 2.21 (2H, d, *J* 11.4 Hz), 1.76 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.8, 81.0, 80.8, 71.8, 30.4; IR (cm^{-1}): $\tilde{\nu}$ 3250–3500, 2960, 2915, 1680, 1400, 1260, 1050, 930; Anal. Calcd for $C_8H_{11}O_3Cl$: C, 50.41; H, 5.82. Found: C, 50.29; H, 5.95.

4.10. Reduction of diketones (4) and (5) with $NaBH_4$

To a stirred solution of diketone (1.30 mmol) in MeOH (15 mL) $NaBH_4$ powder (0.50 g, 13.2 mmol) was added portionwise during 3 h, reaction temperature was kept between 0 and 5 °C (avoiding vigorous gas evolution). Afterward, the reaction was stirred at room temperature for 12 h, then solid NH_4Cl (0.50 g, 9.35 mmol) was added followed by 1 N HCl (0.5 mL). The solvents were evaporated under reduced pressure, the residue was eluted by EtOAc/Me_2CO (1:1) through a silica gel plug to give a yellow oil after evaporation. Mixture of isomers thus obtained was separated by column chromatography on silica gel eluting with EtOAc/Me_2CO mixture of increased polarity. In the case of diketone **4** diols **7f** and **7g** were afforded. For diketone **5** only one isomer was isolated, diol **7e**.

*4.10.1. 1R(S),2R(S),4S(R),5S(R)-8-Oxabicyclo[3.2.1]oct-6-ene-2,4-diol (**7f**).* Yield 100 mg (54%), colorless oil; R_f 0.6 (EtOAc/Me_2CO=5:1); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.21 (2H, s), 4.37 (2H, d, *J* 4.0 Hz), 3.49 (2H, ddd, *J* 4.0, 5.7, 9.9 Hz), 1.93 (1H, dd, *J* 9.9, 10.1 Hz), 1.25 (1H, d, *J* 5.7, 10.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 135.1, 82.7, 63.2, 35.9; IR (cm^{-1}): $\tilde{\nu}$ 3200–3550, 2970, 2945, 1650, 1290, 1060, 935; Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 58.85; H, 7.24.

*4.10.2. 1R(S),2R(S),4R(S),5S(R)-8-Oxabicyclo[3.2.1]oct-6-ene-2,4-diol (**7g**).* Yield 58 mg (32%), colorless oil; R_f 0.4 (EtOAc/Me_2CO=5:1); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.32 (1H, d, *J* 6.1 Hz), 6.17 (1H, d, *J* 6.1 Hz), 4.73 (1H, d, *J* 4.3 Hz), 4.63 (1H, d, *J* 3.8 Hz), 4.45 (1H, d, *J* 3.8 Hz), 4.33 (1H, s), 3.79–3.84 (1H, m), 3.38–3.42 (1H, m), 1.55–1.70 (2H, m); ^{13}C NMR (100 MHz, DMSO-d_6): δ 133.23, 131.4, 83.3, 81.9, 63.9, 62.1, 35.4; IR (cm^{-1}): $\tilde{\nu}$ 3250–3550, 2980, 2945, 1660, 1290, 1075, 940; Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 58.85; H, 7.24.

*4.10.3. 1R(S),2R(S),3R,4S(R),5S(R)-3-Methyl-8-oxabicyclo[3.2.1]oct-6-ene-2,4-diol (**7e**).* Yield 105 mg (52%), colorless oil; R_f 0.7 (EtOAc/Me_2CO=5:1); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.25 (2H, s), 4.31 (2H, d, *J* 4.1 Hz), 3.80 (2H, dd, *J* 4.1, 7.6 Hz), 2.33–2.43 (1H, m), 0.91 (3H, d, *J* 7.8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 134.2, 81.6, 66.2, 38.3, 11.1; IR (cm^{-1}): $\tilde{\nu}$ 3200–3500, 2965, 2945, 1665, 1285, 1060, 935; Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.40; H, 7.82.

4.11. General procedure for acetylation of diols

Diol (0.60 mmol) was dissolved in dry pyridine (5 mL) and acetic anhydride (3.00 mL, 30.0 mmol) was added. The mixture was stirred for 24 h at room temperature, then concentrated under reduced pressure (1 mmHg) to give thick brown oil. Chromatographic purification of the crude compound using silica gel (gradient elution with 10–50% EtOAc in CH_2Cl_2) yielded pure diacetates as colorless crystals.

*4.11.1. 1R(S),2S(R),3S,4R(S),5S(R)-3-Chloro-8-oxabicyclo[3.2.1]oct-6-ene-2,4-diyl diacetate (**8c**).* It was prepared from **7c**. Yield 145 mg (93%), colorless crystals: mp 162–163 °C; R_f 0.6 (CH_2Cl_2/Et_2O=6:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.29 (2H, s), 5.15 (2H, dd, *J* 4.1, 5.9 Hz), 4.52 (2H, d, *J* 4.1 Hz), 4.41 (1H, t, *J* 5.9 Hz), 2.09 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 134.4, 81.1, 72.2, 59.2, 21.1; IR (cm^{-1}): $\tilde{\nu}$ 2920–2980, 2880, 1745, 1735, 1650, 1460, 1380, 1230, 1080; Anal. Calcd for $C_{11}H_{13}O_5Cl$: C, 50.68; H, 5.03. Found: C, 51.06; H, 5.13.

*4.11.2. 1R(S),2S(R),4R(S),5S(R)-3-endo-Chloro-3-exo-methyl-8-oxabicyclo[3.2.1]oct-6-ene-2,4-diyl diacetate (**8d**).* It was prepared from **7d**. Yield 148 mg (0.54 mmol, 90%), colorless crystals: mp 142–144 °C; R_f 0.5 (CH_2Cl_2/Et_2O=8:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.33 (2H, s), 5.11 (2H, d, *J* 4.0 Hz), 4.69 (2H, d, *J* 4.0 Hz), 2.18 (6H, s), 1.54 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 132.5, 78.6, 71.3, 69.4, 31.4, 20.8; IR (cm^{-1}): $\tilde{\nu}$ 3010, 2956, 2945, 1740, 1730, 1650, 1250, 1035; Anal. Calcd for $C_{12}H_{15}O_5Cl$: C, 52.47; H, 5.50. Found: C, 52.66; H, 5.38.

*4.11.3. 1R(S),2R(S),3r,4S(R),5S(R)-3-Methyl-8-oxabicyclo[3.2.1]oct-6-ene-2,4-diyl diacetate (**8e**).* It was prepared from **7e**. Yield 132 mg (0.55 mmol, 92%), colorless crystals: mp 157–159 °C; R_f 0.55 (CH_2Cl_2/Et_2O=6:1). Crystals suitable for diffraction analysis were obtained by slow evaporation of dichloromethane–hexane solution. For crystallographic data see ref. 18; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.30 (2H, s), 5.03 (2H, dd, *J* 4.5, 7.3 Hz), 4.69 (2H, d, *J* 4.5 Hz), 2.92–3.02 (1H, m), 2.06 (6H, s) 0.90 (3H, d, *J* 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 133.3, 79.1, 67.9, 32.3, 20.8, 11.4; IR (cm^{-1}): $\tilde{\nu}$ 3023, 2942, 2940, 1740, 1660, 1230, 1048; Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 60.23; H, 6.71.

*4.11.4. 1R(S),2R(S),4R(S),5S(R)-8-Oxabicyclo[3.2.1]oct-6-ene-2,4-diyl diacetate (**8g**).* It was prepared from **7g**. Yield 125 mg (92%), colorless oil; R_f 0.4 (CH_2Cl_2/Et_2O=6:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.37 (1H, dd, *J* 1.8, 6.1 Hz), 6.29 (1H, dd, *J* 1.8, 6.3 Hz), 5.11–5.16 (1H, m), 4.82 (1H, d, *J* 4.3 Hz), 4.72–4.75 (1H, m), 4.73 (1H, d, *J* 1.3 Hz), 2.13 (3H, s), 2.03 (3H, s), 1.96–2.11 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 170.0, 132.4, 131.8, 80.8, 78.9, 66.9, 64.6, 28.6, 21.3, 21.0; IR (cm^{-1}): $\tilde{\nu}$ 3080, 2985, 2960, 1735, 1650, 1255, 1234, 1050, 1030; Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.55; H, 6.15.

4.12. General procedure for benzylation of diols

The diol (1.50 mmol) was dissolved in anhydrous THF (15 mL) and treated with NaH (96.0 mg, 4.00 mmol) and BnBr (600 mg, 3.51 mmol) at 0 °C. Then reaction mixture was stirred for 24 h at rt and quenched with MeOH (2 mL) and H_2O (15 mL). Organic solvents were evaporated at reduced pressure. The residue was extracted with MTBE (4×10 mL), and the combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The benzyl ethers were purified by flash chromatography on silica gel (gradient elution with 5–20% EtOAc in CH_2Cl_2).

*4.12.1. 1R(S),2S(R),3r,4R(S),5S(R)-2,4-Bis(benzyloxy)-3-chloro-8-oxabicyclo[3.2.1]oct-6-ene (**9a**).* It was prepared from **7a**. Yield 364 mg (68%), pale yellow oil; R_f 0.65 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.45 (10H, m), 6.26 (2H, s), 4.81 (2H, d, *J* 11.6 Hz) 4.69 (2H, d, *J* 11.6 Hz), 4.65 (2H, d, *J* 4.3 Hz), 3.90 (1H, t, *J* 8.6 Hz), 3.64 (2H, dd, *J* 4.3, 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 130.9, 128.4,

127.9, 127.9, 78.8, 78.4, 73.7, 64.4; Anal. Calcd for $C_{21}H_{21}O_3Cl$: C, 70.68; H, 5.93. Found: C, 70.74; H, 5.80.

*4.12.2. 1R(S),2S(R),3R(S),4S(R),5S(R)-2,4-Bis(benzyloxy)-3-chloro-8-oxabicyclo[3.2.1]oct-6-ene (**9b**).* It was prepared from **7b**. Yield 347 mg (65%), pale yellow oil; R_f 0.55 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.42 (10H, m), 6.29 (1H, d, J=6.1 Hz), 6.21 (1H, d, J 6.1 Hz), 4.69–4.88 (4H, m), 4.77 (1H, d, J 4.3 Hz), 4.74 (1H, d, J 1.7 Hz), 4.26 (1H, dd, J 4.8, 8.8 Hz), 3.86 (1H, dd, J 4.3, 8.8 Hz), 3.58 (1H, dd, J 1.7, 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.1, 137.9, 132.6, 131.4, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 81.1, 79.6, 77.1, 74.4, 73.9, 73.4, 61.6; Anal. Calcd for $C_{21}H_{21}O_3Cl$: C, 70.68; H, 5.93. Found: C, 70.74; H, 5.80.

*4.12.3. 1R(S),2R(S),3r,4S(R),5S(R)-2,4-Bis(benzyloxy)-3-methyl-8-oxabicyclo[3.2.1]oct-6-ene (**9e**).* It was prepared from **7e**. Yield 418 mg (83%), pale yellow oil; R_f 0.6 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.38 (10H, m), 6.33 (2H, s), 4.63 (2H, d, J 4.1 Hz), 4.60 (2H, d, J 11.9 Hz) 4.49 (2H, d, J 11.9 Hz), 3.80 (2H, dd, J 4.1, 7.1 Hz), 2.82–2.91 (1H, m), 1.17 (3H, d, J 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4, 133.7, 128.4, 127.7, 127.5, 80.0, 73.8, 71.1, 33.5, 10.6; Anal. Calcd for $C_{22}H_{24}O_3$: C, 78.54; H, 7.19. Found: C, 78.66; H, 7.05.

*4.12.4. 1R(S),2R(S),4S(R),5S(R)-2,4-Bis(benzyloxy)-8-oxabicyclo[3.2.1]oct-6-ene (**9f**).* It was prepared from **7f**. Yield 377 mg (78%), pale yellow oil; R_f 0.5 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.43 (10H, m), 6.29 (2H, s), 4.73 (2H, d, J 4.0 Hz), 4.60 (2H, d, J 11.9 Hz), 4.52 (2H, d, J 11.9 Hz), 3.57 (2H, ddd, J 4.0, 5.8, 9.9 Hz), 2.35 (1H, dd, J 5.8, 12.4 Hz), 1.64 (1H, dd, J 9.9, 12.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.0, 130.7, 129.3, 127.1, 126.3, 78.0, 69.7, 69.3, 29.3; Anal. Calcd for $C_{21}H_{22}O_3$: C, 78.23; H, 6.88. Found: C, 78.29; H, 6.78.

*4.12.5. 1R(S),2R(S),4R(S),5S(R)-2,4-Bis(benzyloxy)-8-oxabicyclo[3.2.1]oct-6-ene (**9g**).* It was prepared from **7g**. Yield 362 mg (75%), pale yellow oil; R_f 0.4 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.30–7.45 (10H, m), 6.31 (1H, d, J 6.1 Hz), 6.28 (1H, d, J 6.1 Hz), 4.90 (1H, d, J 3.6 Hz), 4.79 (1H, d, J 1.4 Hz), 4.60–4.65 (4H, m), 3.98–4.03 (1H, m), 3.43 (1H, d, J 5.1 Hz), 2.20–2.25 (1H, m), 1.86–1.93 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 138.4, 132.1, 128.5, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 80.8, 79.7, 71.5, 71.2, 70.6, 70.2, 29.7; Anal. Calcd for $C_{21}H_{22}O_3$: C, 78.23; H, 6.88. Found: C, 78.29; H, 6.78.

4.13. General procedure for *syn*-hydroxylation

O-Benzyl protected diol (0.30 mmol) was dissolved in acetone (5 mL). Water (2 mL), OsO_4 (0.01 mmol, 0.25 mL of 2.5 wt % solution in *t*BuOH) and NMO (200 mg, 1.50 mmol) were added. The mixture was stirred at room temperature for 72 h, and an aqueous solution of Na_2SO_3 (10 wt %, 10 mL) was added. From the resulted mixture acetone was removed by evaporation under reduced pressure. The residue was extracted with EtOAc (4×10 mL), organic phase was washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The *syn*-diols were purified by flash chromatography on silica gel (gradient elution with 10–50% EtOAc in CH_2Cl_2).

*4.13.1. 1R(S),2S(R),3r,4R(S),5S(R),6S(R),7R(S)-2,4-Bis(benzyloxy)-3-chloro-8-oxabicyclo[3.2.1]octane-6,7-diol (**10a**).* It was prepared from **9a**. Yield 84.0 mg (72%), colorless oil; R_f 0.55 (CH_2Cl_2/EtOAc=3:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.43 (10H, m), 4.78 (2H, d, J 11.6 Hz, OCH_2Ph) 4.71 (2H, d, J 11.6 Hz, OCH_2Ph), 4.32 (2H, s, C*H*OH), 4.16 (2H, d, J 4.8 Hz), 3.56 (2H, dd, J 4.8, 9.4 Hz), 3.45 (1H, t, J 9.4 Hz, CHCl); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.5, 128.5, 128.2, 128.0, 83.6, 79.0, 73.7, 70.6, 62.8; IR (cm^{-1}): $\tilde{\nu}$ 3400, 3300, 3090, 3030, 2960, 2900, 1360, 1210, 1100, 1090, 950; Anal. Calcd for $C_{21}H_{23}O_5Cl$: C, 64.53; H, 5.93. Found: C, 64.62; H, 5.80.

*4.13.2. 1R(S),2R(S),3r,4S(R),5S(R),6S(R),7R(S)-2,4-Bis(benzyloxy)-3-methyl-8-oxabicyclo[3.2.1]octane-6,7-diol (**10e**).* It was prepared from **9e**. Yield 89.2 mg (80%), colorless oil; R_f 0.50 (CH_2Cl_2/EtOAc=3:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.42 (10H, m), 4.61 (2H, s, C*H*OH), 4.59 (2H, d, J 11.9 Hz, OCH_2Ph) 4.56 (2H, d, J 11.9 Hz, OCH_2Ph); 4.16 (2H, d, J 4.6 Hz), 3.68 (2H, dd, J 4.6, 7.3 Hz), 2.71–2.81 (1H, m), 1.03 (3H, d, J 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.1, 128.5, 127.8, 127.5, 84.2, 73.9, 71.1, 71.0, 33.6, 8.3; IR (cm^{-1}): $\tilde{\nu}$ 3350–3450, 3300, 3090, 3050, 2900, 1340, 1230, 1210, 1120, 1085, 950; Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.07. Found: C, 71.52; H, 6.90.

*4.13.3. 1R(S),2R(S),4S(R),5S(R),6S(R),7R(S)-2,4-Bis(benzyloxy)-8-oxabicyclo[3.2.1]octane-6,7-diol (**10f**).* It was prepared from **9f**. Yield 83.3 mg (78%), colorless oil; R_f 0.45 (CH_2Cl_2/EtOAc=3:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.43 (10H, m), 4.58 (2H, d, J 11.9 Hz, OCH_2Ph) 4.57 (2H, d, J 11.9 Hz, OCH_2Ph), 4.40 (2H, s, C*H*OH), 4.24 (2H, d, J 4.3 Hz), 3.50–3.55 (2H, m), 2.35–2.41 (1H, m), 1.01–1.10 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.0, 128.5, 127.9, 127.7, 83.4, 71.8, 71.2, 71.0, 32.2. IR (cm^{-1}): $\tilde{\nu}$ 3250–3400, 3070, 3040, 2850–2900, 1320, 1200, 1100, 960; Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.62; H, 6.90.

4.14. General procedure for epoxidation

Alkene (0.30 mmol) was dissolved in methylene chloride (10 mL) and *m*-CPBA (86.0 mg, 0.50 mmol) was added, then the reaction was stirred at room temperature for 2–3 days (every day a small portion (10.0 mg) of *m*-CPBA was added). The progress of the reaction was monitored by thin layer chromatography. After completion of the reaction, 10 mL of methylene chloride was added, and reaction mixture was washed with saturated aqueous solution of Na_2SO_3 and then aqueous $NaHCO_3$. The aqueous solution was extracted with methylene chloride, combined organic phases were washed with brine and dried (Na_2SO_4). Evaporation of solvent under reduced pressure and purification of product by flash chromatography on silica gel (gradient elution with 10–20% EtOAc in CH_2Cl_2) gave epoxides as colorless oils.

*4.14.1. 1R(S),2S(R),4R(S),5S(R),6R(S),7s,8S(R)-6,8-Bis(benzyloxy)-7-chloro-3,9-dioxatricyclo[3.3.1.0^{2,4}]nonane (**11a**).* It was prepared from **9a**. Yield 85.4 mg (76%), colorless oil; R_f 0.6 (CH_2Cl_2/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24–7.45 (10H, m, Ph), 4.84 (2H, d, J 11.6 Hz, OCH_2Ph), 4.72 (2H, d, J 11.6 Hz, OCH_2Ph), 4.14 (2H, d, J 4.6 Hz, bridgehead), 4.06 (1H, t, J 8.6 Hz, CHCl), 3.77 (2H, dd, J 4.6, 8.6 Hz, CHOBn), 3.75 (2H, s, oxiran ring); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.5, 128.6, 128.3, 128.0, 80.9, 74.2, 72.8, 63.8, 51.0; IR (cm^{-1}): $\tilde{\nu}$=3070, 2950–3000, 2920, 1470, 1250, 1210, 1060; Anal. Calcd for $C_{21}H_{21}O_4Cl$: C, 67.65; H, 5.68. Found: C, 67.74; H, 5.80.

*4.14.2. 1R(S),2R(S),4S(R),5S(R),6R(S),7s,8S(R)-6,8-Bis(benzyloxy)-7-methyl-3,9-dioxatricyclo[3.3.1.0^{2,4}]nonane (**11e**).* It was prepared from **9e**. Yield 93.0 mg (88%), colorless oil; R_f 0.55 (CH_2Cl_2/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26–7.45 (10H, m, Ph), 4.64 (2H, d, J 11.9 Hz, OCH_2Ph) 4.54 (2H, d, J 11.9 Hz, OCH_2Ph), 4.25 (2H, d, J 4.3 Hz, bridgehead), 3.86 (2H, dd, J 4.3, 6.8 Hz, CHOBn), 3.77 (2H, s, oxiran ring), 2.79–2.86 (1H, m), 1.23 (3H, d, J 7.6 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 129.8, 128.6, 127.9, 127.5, 75.4, 73.7, 71.3, 52.6, 33.4, 9.9; IR (cm^{-1}): $\tilde{\nu}$ 3070, 3040,

2930–2960, 2880, 1480, 1280, 1100, 1080; Anal. Calcd for $C_{22}H_{24}O_4$: C, 74.98; H, 6.86. Found: C, 75.14; H, 6.80.

*4.14.3. 1R(S),2R(S),4S(R),5S(R),6R(S),8S(R)-6,8-Bis(benzyloxy)-3,9-dioxatricyclo[3.3.1.0^{2,4}]nonane (**11f**).* It was prepared from **9f**. Yield 86.5 mg (85%), colorless oil; R_f 0.45 (CH_2Cl_2/EtOAc=5:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.42 (10H, m), 4.62 (2H, d, J 11.9 Hz, OCH_2Ph) 4.59 (2H, d, J 11.9 Hz, OCH_2Ph), 4.22 (2H, d, J 4.1 Hz, bridgehead), 3.82 (2H, s), 3.73–3.78 (2H, m, CHOBn), 2.39–2.46 (1H, m), 1.61–1.69 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 128.6, 128.0, 127.7, 73.5, 72.1, 71.3, 51.5, 32.1; IR (cm^{-1}) 3050–3100, 2950, 2920, 1460, 1300, 1245, 1150; Anal. Calcd for $C_{21}H_{22}O_4$: C, 74.54; H, 6.55. Found: C, 75.44; H, 6.50.

*4.14.4. 1R(S),2R(S),4S(R),5S(R),6S(R),8R(S)-3,9-Dioxatricyclo[3.3.1.0^{2,4}]non-6,8-diyl diacetate (**13**).* It was prepared from **8g**. Yield 61.2 mg (84%), colorless crystals: mp 143–144 °C; R_f 0.55 (CH_2Cl_2/EtOAc=3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.16 (1H, m), 4.98 (1H, d, J 5.2 Hz), 4.26 (1H, d, J 4.5 Hz), 4.24 (1H, s), 3.72 (1H, d, J 2.9 Hz), 3.62 (1H, d, J 2.9 Hz), 2.12–2.18 (1H, m), 2.11 (3H, s), 2.08 (3H, s) 1.77–1.84 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 169.8, 73.8, 71.6, 68.1, 65.5, 51.3, 50.2, 29.6, 21.1, 21.0; IR (cm^{-1}): $\tilde{\nu}$ 3000, 2970, 1730, 1430, 1255, 1240; 1045, 970; Anal. Calcd for $C_{11}H_{14}O_6$: C, 54.54; H, 5.83. Found: C, 54.48; H, 5.64.

4.15. 1*R*(*S*),2*S*(*R*),3r,4*R*(*S*),5*S*(*R*),6*S*(*R*),7*R*(*S*)-3-Chloro-8-oxabicyclo[3.2.1]octane-2,4,6,7-tetraol (12a)

To a solution of compound **10a** (100 mg, 0.26 mmol) in MeOH (10 mL) Pd–C (10%, 3.0 mg, 0.026 mmol) was added under H_2 atmosphere then the mixture was stirred for 24 h at rt. The mixture was filtered through a short pad of Celite and washed with MeOH (30 mL). The filtrate was evaporated under reduced pressure to afford the unprotected tetraol **12a** (53.0 mg) in 98% yield as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.94 (2H, s, C*H*OH), 3.83 (2H, d, J 5.1 Hz, bridgehead), 3.44 (2H, dd, J 5.1, 9.6 Hz), 3.26 (1H, t, J 9.6 Hz, CHCl); ^{13}C NMR (100 MHz, DMSO-d_6): δ 86.2, 72.1, 69.5, 67.2; IR (cm^{-1}): $\tilde{\nu}$ 3250–3400, 2950, 1400, 1230, 1055; Anal. Calcd for $C_7H_{11}O_5Cl$: C, 39.92; H, 5.26. Found: C, 40.14; H, 5.36.

4.16. 1*S*(*R*),3*R*(*S*),5*R*(*S*),6*R*(*S*),8*S*(*R*),9*R*(*S*)-2,7-Dioxatricyclo[4.2.1.0^{3,8}]nonane-5,9-diol (14)

Compound **13** (125 mg, 0.516 mmol) was dissolved in MeOH (5 mL) and NaOH (206 mg, 5.16 mmol) was added. The reaction mixture was stirred at rt for 48 h and afterward conc. HCl (0.5 mL) was added. Evaporation of solvent under reduced pressure and purification of product by flash chromatography on silica gel (EtOAc/acetone=1:2) gave diol **15**. Yield 58.0 mg (72%), colorless crystals: mp 67–69 °C; R_f 0.35 (EtOAc/acetone=1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.98 (1H, d, J 4.3 Hz, OH), 4.79 (1H, d, J 5.7 Hz, OH), 3.82–3.90 (2H, m), 3.86 (1H, d, J 12.0 Hz), 3.72 (1H, t, J 5.1 Hz), 3.61 (2H, dd, J 2.8, 4.8 Hz), 1.69–1.74 (1H, m), 1.46–1.53 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 76.3, 74.4, 65.7, 62.9, 51.9, 50.4, 36.1; IR (cm^{-1}): $\tilde{\nu}$ 3200–3550, 2955, 2940, 2890, 1335, 1275, 1075, 1020, 970, 910; Anal. Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 53.02; H, 6.29.

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Supplementary data

These data include MOL files of the most important compounds described in the article and copies of ^{1}H and ^{13}C NMR spectra of all new compounds. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2012.05.029. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. (a) Derwick, P. M. *Medicinal Natural Products*; Wiley: Chichester, UK, 1998; (b) *Iminosugars: From Synthesis to Therapeutic Applications*; Compain, P., Martin, O. R., Eds.; John Wiley: Chichester, UK, 2007; (c) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680; (d) Re, D. L.; Franco, F.; Sánchez-Cantalejo, F.; Tamayo, J. A. *Eur. J. Org. Chem.* **2009**, *74*, 1984–1993; (e) Dräger, B. *Nat. Prod. Rep.* **2004**, *21*, 211–223; (f) Biastoff, S.; Dräger, B. *Alkaloids* **2007**, *64*, 49–102.
2. (a) Heusner, A. *Chem. Ber.* **1954**, *87*, 1063–1067; (b) Fodor, G.; Kovacs, O. *J. Chem. Soc.* **1953**, 2341–2344; (c) Fodor, G. *Tetrahedron* **1957**, *1*, 86–102; (d) Waters, J. A.; Creveling, C. R.; Witkop, B. *J. Med. Chem.* **1974**, *17*, 488–491; (e) Pascual, M. V.; Proemmel, S.; Beil, W.; Wartchow, R.; Hoffmann, H. M. R. *Org. Lett.* **2004**, *6*, 4155–4158.
3. (a) Schwenter, M. E.; Vogel, P. *Chem.—Eur. J.* **2000**, *6*, 4091–4103; (b) Csaky, A. G.; Vogel, P. *Tetrahedron: Asymmetry* **2000**, *11*, 4935–4944; (c) Schwenter, M. E.; Vogel, P. *J. Org. Chem.* **2001**, *66*, 7869–7872; (d) Gerber-Lemaire, S.; Vogel, P. *Eur. J. Org. Chem.* **2003**, 2959–2963; (e) Meilert, K. M.; Schwenter, M. E.; Shatz, Y.; Dubbaka, S. R.; Vogel, P. *J. Org. Chem.* **2003**, *68*, 2964–2967; (f) Coste, G.; Gerber-Lemaire, S. *Tetrahedron: Asymmetry* **2005**, *16*, 2277–2283.
4. (a) Misske, A. M.; Hoffmann, H. M. R. *Chem.—Eur. J.* **2000**, *6*, 3313–3320; (b) Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 1096–1109; (c) Candy, M.; Audran, G.; Bienayme, H.; Bressy, C.; Pons, J.-M. *Org. Lett.* **2009**, *11*, 4950–4953.
5. (a) Asano, N. *Glycobiology* **2003**, *13*, 93–104; (b) Heightman, T. D.; Vasella, A. T. *Angew. Chem., Int. Ed.* **1999**, *38*, 750–770; (c) Ogawa, S. In *Carbohydrate Mimics: Concept and Methods*; Chapleur, Y., Ed.; Wiley-VCH: Weinheim, Germany, 1998; (d) Dwek, A. *Chem. Rev.* **1996**, *96*, 683–720; (e) Varki, A. *Glycobiology* **1993**, *3*, 97–130.
6. (a) Ogawa, S.; Hirai, K.; Odagiri, T.; Matsunaga, N.; Yamajaki, T.; Nakajima, A. *Eur. J. Org. Chem.* **1988**, 1099–1109; (b) Ogawa, S.; Ohmura, M.; Hisamatsu, S. *Synthesis* **2000**, 312–316; (c) Saumi, T. *Top. Curr. Chem.* **1990**, *154*, 257–283; (d) Saumi, T.; Ogawa, S. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 21–90.
7. (a) Reinecke, J.; Hofmann, H. M. R. *Chem.—Eur. J.* **1995**, *1*, 368–373; (b) Wittenberg, J.; Beil, W.; Hofmann, H. M. R. *Tetrahedron Lett.* **1998**, *39*, 8259–8262; (c) Stark, C. B. W.; Eggert, U.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1266–1268; (d) Stark, C. B. W.; Pierau, S.; Warthhow, R.; Hoffmann, H. M. R. *Chem.—Eur. J.* **2000**, *6*, 684–691; (e) Beck, H.; Stark, C. B. W.; Hoffmann, H. M. R. *Org. Lett.* **2000**, *2*, 883–886; (f) Proemmel, S.; Warthhow, R.; Hoffmann, H. M. R. *Tetrahedron* **2002**, *58*, 6199–6206.
8. (a) Bowers, K. G.; Mann, J. *Tetrahedron Lett.* **1985**, *26*, 4411–4412; (b) Bowers, K. G.; Mann, J.; Walsh, E. B.; Howarth, O. W. *J. Chem. Soc. Perkin Trans. 1* **1987**, 1657–1666; (c) Corey, E. J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 455–465; (d) Grainger, R. S.; Owoare, R. B. *Org. Lett.* **2004**, *6*, 2961–2964.
9. Montana, A. M.; Barcia, J. A.; Kociok-Kohn, G.; Font-Bardia, M. *Tetrahedron* **2009**, *65*, 5308–5321.
10. (a) Gender, W. J.; Chan, S.; Ball, D. B. *J. Org. Chem.* **1981**, *46*, 3407–3415; (b) Knapp, S. *Chem. Rev.* **1995**, *95*, 1859–1876; (c) Gethin, D. M.; Simpkins, N. S. *Tetrahedron* **1997**, *53*, 14417–14436; (d) Roy, B. G.; Maiti, J. K.; Drew, M. G. B.; Achari, B.; Mandal, S. B. *Tetrahedron Lett.* **2006**, *47*, 8821–8825; (e) Tripathi, S.; Roy, B. G.; Drew, M. G. B.; Achari, B.; Mandal, S. B. *J. Org. Chem.* **2007**, *72*, 7427–7430; (f) Ghosh, R.; Maiti, J. K.; Achari, B.; Mandal, S. B. *J. Org. Chem.* **2010**, *75*, 2419–2422.
11. (a) Gerber, P.; Vogel, P. *Tetrahedron Lett.* **1999**, *40*, 3165–3168; (b) Gerber, P.; Vogel, P. *Helv. Chim. Acta* **2001**, *84*, 1363–1395.
12. (a) Doucey, M.-A.; Hess, D.; Blommers, M. J. J.; Hofsteenge, J. *Glycobiology* **1999**, *9*, 435–441; (b) Anzeveno, P. B.; Creemer, L. J.; Danile, J. K.; King, C.-H. R.; Liu, P. S. *J. Org. Chem.* **1989**, *54*, 2539–2542; (c) Hoffmann, H. M. R.; Dunkel, R.; Mentzel, M.; Reuter, H.; Stark, C. B. W. *Chem.—Eur. J.* **2001**, *7*, 4771–4789.
13. (a) Lautens, M.; Rovis, T. *J. Am. Chem. Soc.* **1997**, *119*, 6478–6487.
14. (a) Chiu, P.; Lautens, M. *Top. Curr. Chem.* **1997**, *190*, 1–85; (b) Harmata, M. *Tetrahedron* **1997**, *53*, 6235–6280; (c) Rigby, J. H.; Pigge, F. C. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, NY, 1997; 51, pp 351–478; (d) Hosomi, A.; Tominaga, Y. In; Trost, B. M., Fleming, I., Eds. *Comprehensive Organic Synthesis*; Pergamon: Oxford, 1991; vol. 5; (e) Mann, J. *Tetrahedron* **1986**, *42*, 4611–4659; (f) Noyori, R.; Hayakawa, Y. *Org. React.* **1983**, *29*, 163–344.
15. (a) Law, D. C. F.; Tobey, S. W. *J. Am. Chem. Soc.* **1968**, *90*, 2376–2386; (b) Tobey, S. W.; Law, D. C. F. U.S. Patent 3,538,117, Nov. 3, **1970**.
16. Tafeenko, V. A.; Aslanov, L. A.; Proskurnina, M. V.; Sosonyuk, S. E.; Khlevin, D. A. *Acta Crystallogr.* **2009**, *E65*, 1580.
17. Batson, W. A.; Abboud, K. A.; Battiste, M. A.; Wright, D. L. *Tetrahedron Lett.* **2004**, *45*, 2093–2096.
18. Tafeenko, V. A.; Aslanov, L. A.; Proskurnina, M. V.; Sosonyuk, S. E.; Khlevin, D. A. *Acta Crystallogr.* **2011**, *E67*, 2127.
19. (a) Yang, W.; Koreeda, M. *J. Org. Chem.* **1992**, *57*, 3836–3839; (b) Daniels, R.; Fischer, J. L. *J. Org. Chem.* **1963**, *28*, 320–322.