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Efficient synthesis of 8-oxa-bicyclo[3.2.1]octane derivatives from D-arabinose

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Abstract—Our studies of the TIBAL-promoted Claisen rearrangement reaction and ring-closing metathesis (RCM) resulted in the development of an efficient synthetic route to polyfunctional seven-membered carbasugar synthons from D-arabinose. Moreover, the construction of 8-oxa-bicyclo[3.2.1]octane derivatives **10** and **13** was achieved by BCl_3 or iodide-promoted intramolecular electrophilic addition reactions, which were regio- and stereoselective.

1. Introduction

Seven-membered carbocyclic compounds are widely present as a structural motif in many biologically important molecules and natural products.[1] Similarly, 8-oxa-bicyclo[3.2.1]octane derivatives have been widely used as key precursors for the synthesis of natural and unnatural products, such as sesquiterpenes (1,5-epoxysalvia-4(14)-ene),[2] diterpenes (Cladiellin),[3] alkaloids (Aspergillin PZ,[2] pyrrolizidine alkaloids[4]), tropane analogues,[5] and Phamoidride B,[6] which show interesting biological activities. Recently, more attention has been paid to the synthesis of conformationally restricted sugar analogues, because they are likely to be resistant to the action of glycosidases and glycosyl transferases.[7]

Two strategies are available for the construction of 8-oxa-bicyclo[3.2.1]octane derivatives. One is to create the cyclic systems in one step employing reactions such as [4+3] cycloaddition,[3,8] oxidopyrylium [5+2] cycloaddition,[4,6] and Prins-Pinacol reaction.[2] Another is to create the cyclic systems by stepwise processes, including SmI_2-mediated nucleophilic acyl addition[9] and intramolecular oxymercuration.[5] At present, various methods have been used for the conversion of sugars to seven-membered carbocyclic compounds,[10] but the enantioselective synthesis and specific spatial distribution of the hydroxyl groups on the ring are often problematic. In this report, the TIBAL-promoted Claisen rearrangement of allyl vinyl ethers and ring-closing metathesis (RCM) were used to construct the polyhydroxycyclic heptenes. The hydroxycyclic heptene precursor prepared could be converted to 8-oxa-bicyclo[3.2.1]octane compounds in the presence of BCl_3 or iodine (Fig. 1). These reactions showed good regioselectivity and stereoselectivity. This methodology will provide a practical method to prepare 8-oxa-bicyclo[3.2.1]octane compounds as a new type of chiral building blocks.

2. Results and discussion

Compound **1**, as the starting material, was easily obtained from D-arabinose.[11] After Wittig olefination, the unsaturated alcohol **2** was obtained in good yield.[12] Alcohol **2** was oxidized with PCC to afford the known ketone **3**.[13] Ketone **3** was then reacted with an excess of vinylmagnesium bromide in THF at −78 °C to give the enol **4** exclusively.[14] In the presence of iodine and a base, compound **5** was obtained in 94% yield from compound **4**, and the configuration of C-5 in the formed sugar ring was retained.[15] Following the elimination of HI by DBU, the key intermediate **6** was obtained in 67% overall yield from pentose **1**. The polyhydroxyl seven-membered carbasugars **7a** and **7b** were then prepared by the TIBAL-promoted Claisen rearrangement from intermediate **6** (Scheme 1).

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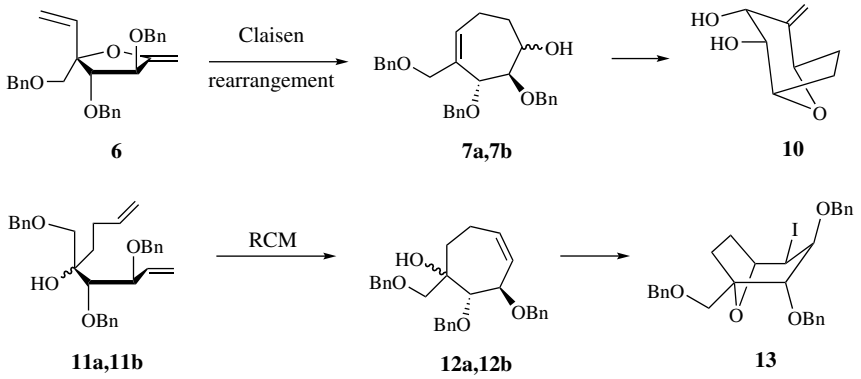
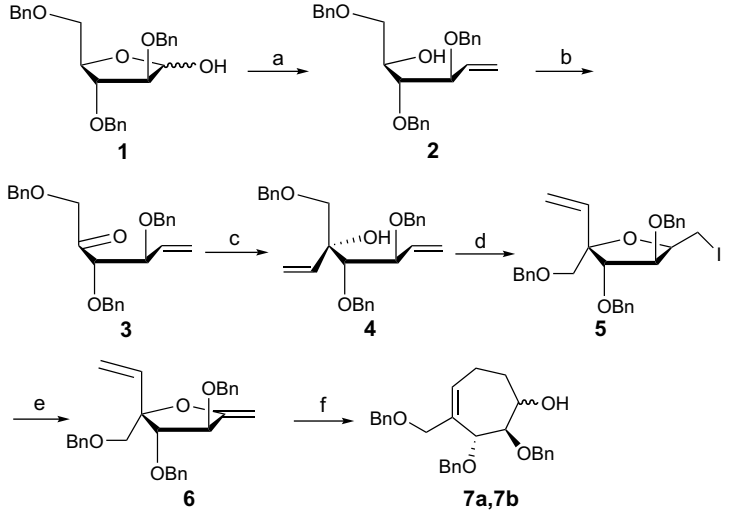


Figure 1. Synthesis of 8-oxa-bicyclo[3.2.1]octane derivatives.



Scheme 1. Reagents and conditions: (a) Ph_3PCH_3Br, *n*-BuLi, THF, reflux, 3 h, 87.6%; (b) PCC, 4 Å MS, DCM, 87.2%; (c) $CH_2CHMgBr$, THF, −78 °C, 3 h, 96.2%; (d) 5% I_2 in ether, satd aq $NaHCO_3$, THF, 5 h, 94.2%; (e) DBU, THF, 80 °C, overnight, 97.0%; (f) 1 M TIBAL, toluene, 60 °C, 3 h, 91%.

The structure of product **5** was determined by ^1H and ^{13}C NMR spectra. The coupling constant between H-2 and H-3 ($J_{2,3} = 5.0$ Hz) agreed with the dihedral angle for a *cis* relationship. Additional support for the 'β' configurational assignment of **5** came from the ^{13}C NMR chemical shift of C-1. The ^{13}C NMR of compound **5** showed that C-1 was at 3.02 ppm. This was consistent with the reports from Ohrui et al. that the ^{13}C-chemical shifts of anomeric centers in the 2,3-*cis* isomers of furanoses were 3–4 ppm upfield of those of the corresponding 2,3-*trans* isomers,[16] and the chemical shift for C-1 of α isomer appeared at 7.14 ppm.[17]

The likely mechanism for the formation of compound **5** was shown in Figure 2, in which an iodonium ion formed at C-1 and C-2 was involved. Subsequent attack by the 5-hydroxyl group from the least-hindered side led to the formation of **5** with a favored conformation.[18]

The Claisen rearrangement was under thermodynamical control, and the ratio of **7a** and **7b** was related to the reaction temperature (from 60 to 110 °C). The results indicated that the overall yields of **7a** and **7b** were decreased with an increase of the temperature. The highest yield of **7b** was

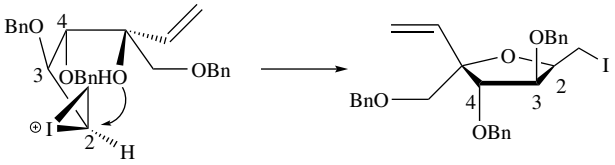


Figure 2. Mechanism of the formation of compound **5**.

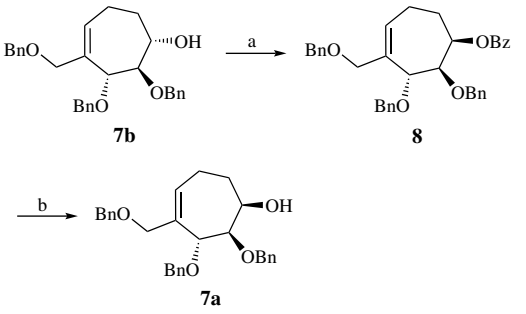
generated at 60 °C (Table 1). NMR spectra showed that **7a** and **7b** were a pair of C-1 epimers. Moreover,

Table 1. Optimization of reaction conditions for Claisen rearrangement

Temperature (°C)	Yield (%)	
	7a	**7b**
60	27	64
80	40	52
90	25	44
100	19	31
Reflux	36	ND[a]

[a] ND: not detected.

cycloheptene **7b** can easily be converted to **7a** by a Mitsunobu reaction to form the *O*-Bz derivative **8**, in which the configuration was inverted at C1. After hydrolysis, **7a** was furnished (Scheme 2). According to the mechanism of Claisen rearrangement reaction, the formation of a seven-membered ring should be completed via an *endo* or *exo* transition state (Fig. 3). Obviously, an attack from the *endo*-side is favored due to less steric hindrance and thus compound **7b** is produced preferentially. The configurations of C-2 and C-3 hydroxyls of cycloheptene **7a**/**7b** were the same as that of precursor **6**. However, the orientation of the C-1 hydroxyl group of **7a** and **7b** had been identified by ^{1}H NMR. The coupling constant of H-1 and H-2 ($J_{1,2}$ value) of cycloheptene **7a** was 3.0 Hz, similar to the value of the reported analogue,[19] indicating a *cis* relationship between H-1 and H-2. Therefore, the hydroxyl group was oriented in a β configuration. The configuration of C-1 hydroxyl group of compound **7b** was also confirmed by the formation of compound **10**.



Scheme 2. Reagents and conditions: (a) BzOH, Ph_3P, DEAD, THF, rt, 3 h, 96.4%; (b) K_2CO_3, CH_3OH, rt, 22 h, 84.5%.

The debenzylation of cycloheptene **7b** was performed with 1 M BCl_3 in CH_2Cl_2. However, the expected carbasugar **9** was not obtained in this reaction, and 8-oxa-bicyclo[3.2.1]octane **10** was formed instead.[20] The 2D NOESY NMR spectra of **10** showed strong NOE interactions between H-3 and β-oriented H-6 and between H-3 and β-oriented H-7, clearly indicating that H-3 and β-oriented H-6 and H-7 were located at the same orientation and the oxygen bridge was located on the opposite side. The formation of 8-oxa-bicyclo[3.2.1]octane **10** was likely achieved by the attack of 1-hydroxyl group of **7b** at the C4, C5 double bond to form the oxygen bridge and the terminal olefin, and after hydrolysis **10** was afforded (Scheme 3). According to the structure of compound **10** and the stereochemistry during the reaction, the C1 hydroxyl of compound **7b** was α-oriented.

To synthesize more 8-oxa-bicyclo[3.2.1]octane derivatives, polyfunctional cycloheptene **12a**/**12b** were obtained from intermediate **3**.[21] Compound **3** was reacted with

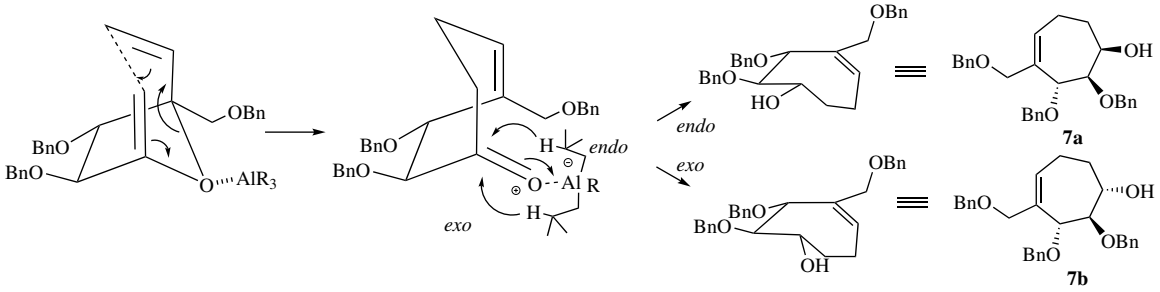
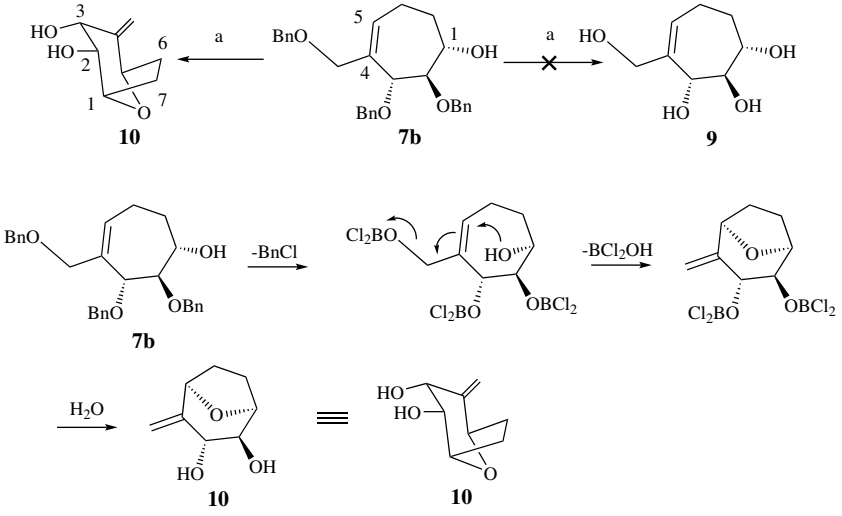
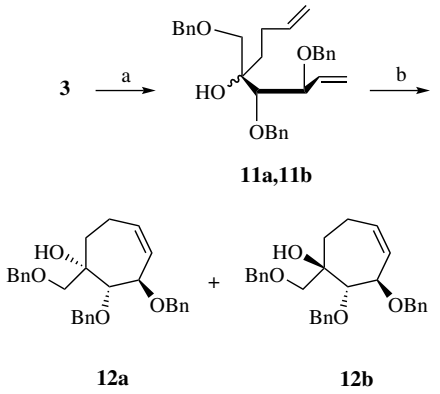


Figure 3. The formation of compound **7a** and **7b**.



Scheme 3. Reagents and conditions: (a) BCl_3, DCM, −78 °C, −rt, 2 h, 71.2%.



Scheme 4. Reagents and conditions: (a) Butenylmagnesium bromide, THF, −10 °C→rt, overnight, 75.6%; (b) Grubb's catalyst, CH_2Cl_2, rt, 48 h, 86.3%.

butenylmagnesium bromide in THF at −10 °C to yield compounds **11a** and **11b** (5:1) in 75.6%, and the cyclization of **11a** and **11b** was completed by the Grubb's catalyst to afford cycloheptene **12a/12b** (5:1) in quantitative yield (Scheme 4). Compound **12a** was isolated easily by column chromatography and treated with NIS in CH_2Cl_2 to give 8-oxa-bicyclo[3.2.1]octane **13** as a single regioisomer in good yield (Scheme 5).

^{1}H NMR and HMQC confirmed that the oxygen bridge of compound **13** was formed between C-1 and C-5 and the iodine was bonded to C-2. Due to the effect of the iodine heavy atom, the ^{13}C-chemical shift of C-2 was shifted upfield. 2D NOESY NMR spectra showed a strong NOE interaction between H-4 and β-oriented H-6, demonstrating that H-4 and β-oriented H-6 were located on the same face and the oxygen bridge was located on the opposite side. Moreover, ^{1}H NMR showed that there was a signal peak for H-2 and H-3, revealing a *cis* relationship between H-2 and H-3. The formation of an oxygen bridge was via a manner of *trans*-attack of the 5-hydroxyl to an iodonium ion. The reaction was stereoselective and no β-oxygen bridge isomer was found (Scheme 5).

3. Conclusion

In summary, we have developed an efficient and highly regioselective and stereoselective method for the synthesis of polyfunctional cyclic heptene synthons and 8-oxa-bicyclo[3.2.1]octane derivatives from D-arabinose. This synthetic method could be applied for the synthesis of a growing number of biologically active substances containing seven-membered rings and an 8-oxa-bicyclo[3.2.1]-octane skeleton.

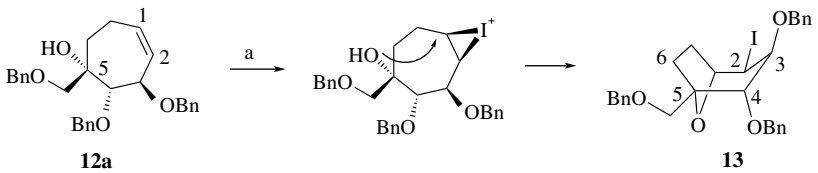
4. Experimental

4.1. General experimental detail

All chemicals were purchased as reagent grade and used without further purification, unless otherwise noted. Solvents were dried by refluxing for at least 24 h. Dichloromethane (CH_2Cl_2) was distilled over calcium hydride (CaH_2). Tetrahydrofuran (THF) and toluene was distilled from sodium, indicated by diphenylketone. All reactions were carried out under anhydrous conditions with freshly distilled solvents, unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC), and were detected by an ethanol solution of phosphomolybdic acid. Column chromatography was performed on silica gel (200–300 mesh). NMR spectra were recorded with Varian INOVA-500 and Varian VXR-300. Chemical shifts were relative to TMS (δ 0.0) as an internal standard. Mass spectra were obtained on PE SCLEX QSTAR mass spectrometer. Elemental analyses were performed on Varian ELIII analyzer. Optical rotations were measured at 20 ± 2 °C at the sodium D line (589 nm) and were in units of deg mL $(\mathrm{dm\ g})^{-1}$.

4.2. 2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-iodo-5-vinyl-L-mannohexitol 5

To alkene **4**[14] (2.63 g, 5.92 mmol) dissolved in THF (42 mL) was added saturated aqueous $NaHCO_3$ (50 mL, 60.0 mmol) under argon, followed by dropwise addition of 5% solution of iodine in ether (152 mL, 29.9 mmol). The reaction mixture was stirred for 6 h at rt, quenched by the addition of NaS_2O_3 at 0 °C, and extracted with EtOAc for three times. Organic extracts were combined, dried by $NaSO_4$, filtered, and the solvent was evaporated. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 50:1) to give **5** as a primrose yellow oil (3.17 g, 94%). $[\alpha]_D^{20} = +18.1$ (c 0.09, CH_2Cl_2), ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34–7.24 (m, 15H, H-arom.), 5.98 (dd, $J_{6,7b} = 11.0$ Hz, $J_{6,7a} = 17.5$ Hz, 1H, H-6), 5.40 (dd, $J_{7a,7b} = 1.5$ Hz, $J_{6,7a} = 17.5$ Hz, 1H, H-7a), 5.13 (dd, $J_{7a,7b} = 1.5$ Hz, $J_{6,7b} = 11.0$ Hz, 1H, H-7b), 4.56, 4.53 (dd, $J = 12.0$ Hz, 2H, CH_2Ph), 4.56, 4.52 (dd, $J = 12.0$ Hz, 2H, CH_2Ph), 4.51, 4.44 (dd, $J = 12.0$ Hz, 2H, CH_2Ph), 4.50 (m, $J_{1a,2} = 7.5$ Hz, $J_{1b,2} = 8.5$ Hz, $J_{2,3} = 5.0$ Hz, 1H, H-2), 4.18 (dd, $J_{2,3} = 5.0$ Hz, $J_{3,4} = 3.0$ Hz, 1H, H-3), 4.00 (d, $J_{3,4} = 3.0$ Hz, 1H, H-4), 3.61 (dd, $J = 9.5$ Hz, 1H, H-8), 3.39 (dd, $J_{1a,2} = 7.5$ Hz, $J_{1a,1b} = 9.5$ Hz, 1H, H-1a), 3.25 (dd, $J_{1b,2} = 8.5$ Hz, $J_{1a,1b} = 9.5$ Hz, 2H, H-1b). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.2 (C-6), 138.4, 137.8, 137.7 ($3 \times C_{ipso}$), 128.4–127.4 (aromatic C), 114.4 (C-7), 86.5 (C-5), 86.2 (C-2), 83.2 (C-4), 80.4 (C-3), 73.5 (C-8), 72.9, 72.4, 72.2 ($3 \times CH_2Ph$),



Scheme 5. Reagents and conditions: (a) NIS, CH_2Cl_2, 0 °C→rt, overnight, 87%.

3.0 (C-1). MS (ESI-TOF, positive, *m/z*): 571 $[M+H]^+$, 588 $[M+NH_4]^+$, 593 $[M+Na]^+$. Anal. Calcd for $C_{29}H_{31}IO_4$: C, 61.06; H, 5.48. Found: C, 61.09; H, 5.59.

4.3. (2*S*,3*S*,4*S*)-3,4-Dibenzyloxy-2-benzyloxymethyl-5-methylene-2-vinyl-tetrahydro furan 6

To iodide **5** (2.00 g, 3.51 mmol) dissolved in THF (51 mL) was dropwise added DBU (4.2 mL, 28.08 mmol) under argon, and the mixture was then stirred for 20 h at 80 °C, cooled to room temperature, and concentrated. The residue was purified on a silica gel column (0.1% Et_3N in cyclohexane/EtOAc, 120:1) to afford **6** as a colorless oil (1.50 g, 97%). ^{1}H NMR (500 MHz, C_6D_6): δ 7.26–7.05 (m, 15H, H-arom.), 5.93 (dd, $J_{7,8b} = 11.0$ Hz, $J_{7,8a} = 17.5$ Hz, 1H, H-7), 5.51 (dd, $J_{8a,8b} = 1.5$ Hz, $J_{7,8a} = 17.5$ Hz, 1H, H-8a), 5.03 (dd, $J_{8a,8b} = 1.0$ Hz, $J_{7,8b} = 11.0$ Hz, 1H, H-8b), 4.92 (dt, $J_{6a,6b} = 1.5$ Hz, $J_{4,6a} = 5.5$ Hz, 1H, H-6a), 4.74 (t, $J_{6a,6b} = 1.5$ Hz, 1H, H-6b), 4.56, 4.47 (dd, $J = 11.5$ Hz, 2H, CH_2Ph), 4.44, 4.39 (dd, $J = 12.0$ Hz, 2H, CH_2Ph), 4.39, 4.32 (dd, $J = 12.0$ Hz, 2H, CH_2Ph), 4.32 (t, $J = 1.5$ Hz, 1H, H-3), 4.11 (d, $J_{4,6a} = 5.5$ Hz, 1H, H-4), 3.69 (dd, $J = 10.0$ Hz, 2H, H-9). ^{13}C NMR (125 MHz, C_6D_6): δ 160.8 (C-5), 138.9, 138.8, 138.5 ($3\times C_{ipso}$), 138.2 (C-7), 128.5–127.6 (aromatic C), 114.9 (C-8), 87.3 (C-6), 86.5 (C-2), 83.7 (C-3), 82.8 (C-4), 73.8 (C-9), 73.0, 72.3, 71.6 ($3\times CH_2Ph$). MS (ESI-TOF, positive, *m/z*): 443 $[M+H]^+$, 460 $[M+NH_4]^+$, 465 $[M+Na]^+$, 481 $[M+K]^+$. Anal. Calcd for $C_{29}H_{30}O_4$: C, 78.71; H, 6.83. Found: C, 78.47; H, 6.64.

4.4. (1*R* and 1*S*,2*R*,3*R*)-4-Benzyloxymethyl-2,3-dibenzyloxycyclohepta-4-ene-1-ol 7a and 7b

To a solution of compound **6** (850 mg, 1.92 mmol) in toluene (65 mL) was added dropwise 1 M TIBAL (19 mL, 19.0 mmol) in toluene at rt under argon. The mixture was stirred at 60 °C for 3 h, cooled down to 0 °C, and quenched with 20% aqueous NaOH solution. The mixture was extracted with toluene. The organic layers were combined, dried, and concentrated. The residue was purified on a silica gel column (petroleum ether/acetone, 20:1). Two products **7a** as a colorless oil (230 mg, 27%) and **7b** as a colorless oil (546 mg, 64%) were obtained. Compound **7a**: $[\alpha]_D^{20} = -63.1$ (*c* 0.08, MeOH), ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35–7.21 (m, 15H, H-arom.), 6.12 (dd, $J = 5.0$ Hz, $J = 9.0$ Hz, 1H, H-5), 4.63, 4.46 (dd, $J = 11.5$ Hz, 2H, CH_2Ph), 4.59, 4.44 (dd, $J = 12.0$ Hz, 2H, CH_2Ph), 4.51, 4.43 (dd, $J = 12.0$ Hz, 2H, CH_2Ph), 4.32 (d, $J_{2,3} = 6.5$ Hz, 1H, H-3), 4.14 (dd, $J_{1,2} = 3.0$ Hz, $J_{1,7} = 7.0$ Hz, 1H, H-1), 3.93 (dd, $J_{1,2} = 3.0$ Hz, $J_{2,3} = 6.5$ Hz 1H, H-2), 3.89 (dd, $J = 12.0$ Hz, 2H, H-8), 2.32–2.26 (m, 1H, H-6a), 2.19 (br, 1H, OH), 2.14–2.07 (m, 1H, H-6b), 1.78–1.65 (m, 2H, H-7). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.7, 138.3 ($3\times C_{ipso}$), 136.4 (C-4), 133.5 (C-5), 128.4–127.4 (aromatic C), 79.4 (C-2), 75.2 (C-8), 74.3 (C-3), 73.2 (CH_2Ph), 72.0 (C-1), 71.8, 71.1 ($2\times CH_2Ph$), 30.8 (C-7), 22.2 (C-6). MS (ESI-TOF, positive, *m/z*): 445 $[M+H]^+$, 462 $[M+NH_4]^+$, 467 $[M+Na]^+$, 483 $[M+K]^+$. Anal. Calcd for $C_{29}H_{32}O_4$: C, 78.35; H, 7.26. Found: C, 78.11; H, 6.92.

Compound **7b**: $[\alpha]_D^{20} = -28.4$ (*c* 0.12, MeOH), ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.23 (m, 15H, H-arom.), 6.34 (t, $J = 7.0$ Hz, 1H, H-5), 4.66, 4.53 (dd, $J = 12.0$ Hz, 2H, CH_2Ph), 4.63, 4.51 (dd, $J = 12.0$ Hz, 2H, CH_2Ph), 4.52, 4.47 (dd, $J = 12.0$ Hz, 2H, CH_2Ph), 4.27 (d, $J_{2,3} = 6.0$ Hz, 1H, H-3), 3.96 (s, 3H, H-1 and H-8), 3.71 (t, $J_{2,3} = 6.0$ Hz, 1H, H-2), 3.67 (d, $J = 6.5$ Hz, 1H, OH), 2.59–2.53 (m, 1H, H-6a), 2.03–1.94 (m, 2H, H-6b and H-7a), 1.78–1.71 (m, 1H, H-7b). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.3, 138.3, 138.0 ($3\times C_{ipso}$), 136.8 (C-4), 133.2 (C-5), 128.4–127.5 (aromatic C), 79.3 (C-2), 79.0 (C-3), 74.2 (C-1), 73.6 (C-8), 73.1, 72.2, 72.0 ($3\times CH_2Ph$), 29.9 (C-7), 20.9 (C-6). MS (ESI-TOF, positive, *m/z*): 445 $[M+H]^+$, 462 $[M+NH_4]^+$, 467 $[M+Na]^+$, 483 $[M+K]^+$. Anal. Calcd for $C_{29}H_{32}O_4$: C, 78.35; H, 7.26. Found: C, 78.15; H, 6.99.

4.5. (1*R*,2*R*,3*R*)-4-Benzyloxymethyl-2,3-dibenzyloxycyclohept-4-enyl benzoate 8

To a solution of Ph_3P (240 mg, 0.92 mmol) in dry THF (3 mL) previously cooled in ice bath was added dropwise 2.2 M DEAD in toluene (0.42 mL, 0.92 mmol) under argon. After 30 min, this solution was added dropwise to a solution of alcohol **7b** (203 mg, 0.45 mmol) and benzoic acid (84 mg, 0.68 mmol) in dry THF (10 mL), which was also cooled in an ice bath under argon. The mixture was stirred for 30 min at 0 °C, then stirred at rt for 3 h. The volatiles were removed and the residue was purified on a silica gel column (petroleum ether/acetone, 55:1) to yield **8** as a colorless oil (225 mg, 96.4%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (m, 2H, H-arom.), 7.58–7.18 (m, 18H, H-arom.), 6.13 (dd, $J_{5,6a} = 9.0$ Hz, $J_{5,6b} = 4.5$ Hz, 1H, H-5), 5.72 (dt, $J_{1,7a} = 1.8$ Hz, $J_{1,7b} = 2.1$ Hz, $J_{1,2} = 11.7$ Hz, 1H, H-1), 4.70, 4.59 (dd, $J = 12.3$ Hz, 2H, CH_2Ph), 4.57, 4.53 (dd, $J = 12.9$ Hz, 2H, CH_2Ph), 4.51, 4.44 (dd, $J = 12.0$ Hz, 2H, CH_2Ph), 4.21 (d, $J_{2,3} = 15.0$ Hz, 1H, H-3), 4.19 (s, 1H, H-1, H-8a), 3.92 (dd, $J_{1,2} = 12.0$ Hz, $J_{2,3} = 15.0$ Hz, 1H, H-2), 3.91 (s, 1H, H-8b), 2.52–2.43 (m, 1H, H-6a), 2.23–2.08 (m, 2H, H-6b and H-7a), 1.89 (m, 1H, H-7b). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6 (PhCO), 138.5, 138.4, 138.4 ($3\times C_{ipso}$), 136.8 (BzC_{ipso}), 132.8 (C-5), 130.6 (C-4), 129.7–127.5 (aromatic C), 76.7 (C-1), 76.2 (C-2), 75.7 (C-8), 74.5 (C-3), 73.4, 71.8, 70.9 ($3\times CH_2Ph$), 27.0 (C-7), 22.6 (C-6). MS (ESI-TOF, positive, *m/z*): 566 $[M+NH_4]^+$, 571 $[M+Na]^+$, 587 $[M+K]^+$. Anal. Calcd for $C_{36}H_{36}O_5$: C, 78.81; H, 6.61. Found: C, 78.52; H, 6.35.

4.6. Hydrolysis of compound 8

Compound **8** (271 mg, 0.49 mmol) was dissolved in MeOH (7 mL) and treated with K_2CO_3 (340 mg, 2.46 mmol). The solution was stirred at rt for 22 h. The reaction solution was subsequently filtered and concentrated. The residue was purified on a silica gel column (petroleum ether/acetone, 20:1) to give **7a** as a colorless oil (185 mg, 84.5%).

4.7. (1*S*,2*S*,3*R*,5*R*)-4-Methylene-8-oxa-bicyclo[3.2.1]-octane-2,3-diol 10

To compound **7b** (28 mg, 0.063 mmol) dissolved in CH_2Cl_2 (3 mL) was dropwise added 1 M BCl_3 (0.5 mL, 0.50 mmol) in CH_2Cl_2 at −78 °C under argon. The mixture was then

stirred and warmed to 0 °C over 2 h, quenched with MeOH, and concentrated. The residue was purified on a silica gel column (CH_2Cl_2/MeOH, 30:1) to afford **10** as a white solid (7 mg, 71%). $[\alpha]_D^{20} = -16.7$ (*c* 0.10, MeOH), ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.14 (d, $J = 4.5$ Hz, 1H, C2–OH), 5.06 (d, $J = 6.0$ Hz, 1H, C3–OH), 4.89 (t, $J_{3,8a} = 2.5$ Hz, 1H, H-8a), 4.92 (t, $J_{3,8b} = 2.5$ Hz, 1H, H-8b), 4.52 (d, $J = 7.0$ Hz, 1H, H-5), 4.08 (dd, $J_{1,2} = 4.5$ Hz, $J_{1,7a} = 7.5$ Hz, 1H, H-1), 3.81–3.77 (m, $J_{2,3} = 8.5$ Hz, $J_{3,8} = 2.5$ Hz, 1H, H-3), 3.30–3.26 (m, $J_{1,2} = 4.5$ Hz, $J_{2,3} = 8.5$ Hz, 1H, H-2), 2.00–1.94 (m, 1H, H-7a), 1.88–1.83 (m, 1H, H-6b), 1.70–1.63 (m, 1H, H-7b), 1.58–1.53 (m, 1H, H-6a). ^{13}C NMR (125 MHz, DMSO-d_6): δ 150.0 (C-4), 105.9 (C-8), 79.0 (C-5), 77.3 (C-1), 75.8 (C-2), 70.5 (C-3), 28.8 (C-6), 23.5 (C-7). MS (ESI-TOF, positive, *m*/*z*): 174 $[M+NH_4]^+$, 179 $[M+Na]^+$. HRFAB-MS (*m*/*z*): calcd for $C_8H_{12}O_3H$ $[M+H]^+$, 157.0859; found, 157.0852.

4.8. (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3-Dibenzyloxy-1-benzyloxymethyl-4-iodo-8-oxa-bicyclo[3.2.1]octane 13

To compound **12a**[21] (339 mg, 0.763 mmol) dissolved in CH_2Cl_2 (10 mL) was added NIS (189 mg, 0.839 mmol) in CH_2Cl_2 at 0 °C under argon. The mixture was stirred overnight and warmed to rt and concentrated. The residue was purified on a silica gel column (petroleum ether/EtOAc, 50:1) to give **13** as a white solid (378 mg, 87%). $[\alpha]_D^{20} = -38.8$ (*c* 0.37, CH_2Cl_2), ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37–7.23 (m, 15H, H-arom.), 4.67 (t, $J_{4,5} = 1.0$ Hz, $J_{3,4} = 5.0$ Hz, 1H, H-4), 4.49, 4.39 (dd, $J = 12.0$ Hz, 2H, CH_2Ph), 4.45, 4.36 (dd, $J = 12.0$ Hz, 2H, CH_2Ph), 4.43 (m, 3H, CH_2Ph and H-5), 3.74 (d, $J = 8.5$ Hz, 1H, H-8a), 3.57 (d, $J_{2,3} = 1.5$ Hz, 1H, H-2), 3.49 (dt, $J_{2,3} = 1.5$ Hz, $J_{3,4} = 5.0$ Hz, 1H, H-3), 3.32 (d, $J = 8.5$ Hz, 1H, H-8b), 2.55–2.50 (m, 1H, H-6a), 2.29–2.24 (m, 1H, H-7a), 1.89–1.79 (m, 2H, H-6b and H-7b). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.0, 137.7, 137.5 ($3 \times C_{ipso}$), 128.5–127.6 (aromatic C), 82.9 (C-1), 80.1 (C-5), 77.5 (C-3), 77.0 (C-2), 73.5, 73.2, 72.8 ($3 \times CH_2Ph$), 72.3 (C-8), 33.5 (C-4), 29.4 (C-7), 25.4 (C-6). MS (ESI-TOF, positive, *m*/*z*): 571 $[M+H]^+$, 588 $[M+NH_4]^+$, 593 $[M+Na]^+$. Anal. Calcd for $C_{29}H_{31}IO_4$: C, 61.06; H, 5.48. Found: C, 60.96; H, 5.56.

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