Stereospecific Synthesis of Eight-Membered Polyhydroxy Carbocycles via TIBAL-Promoted Claisen Rearrangement

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Abstract: The stereoselective synthesis of novel eight-membered polyhydroxy carbocycles was achieved from D-glucose via mercuriocyclization and triisobutylaluminum (TIBAL)-promoted Claisen rearrangement. Along with rearrangement, TIBAL also promoted debenzylation and cycloaddition, and a 3,9-dioxa-bicyclo[3.3.1]nonane derivative was formed. The stereoselectivity of mercuriocyclization was attributed to the interaction between mercurio and vinyl moities, and this interaction also assisted the mercurio derivative to exist in an abnormal conformation. The configuration and/or conformation of intermediates and products were identified by NMR spectral analyses.

Key words: carbocycle, carbasugar, mercuriocyclization, TIBAL, Claisen rearrangement, debenzylation

The eight-membered polyfunctional carbocycle structure is present in numerous biologically important molecules and natural products, such as paclitaxel,[1] poitediol,[2] fusicoccin H,[3] and kalmanol,[4] etc. Because of the diverse biological properties, their syntheses have been extensively investigated. Various methods have been developed for the construction of eight-membered polyfunctional carbocycles. They include oxidation and hydroxylation of cyclooctene derivatives,[5] cycloadditions,[6] ring expansions,[7] fragmentations,[8] and intramolecular cross-coupling,[9] etc. The discovery of ring-closing metathesis (RCM) has also greatly advanced the development of the synthesis of eight-membered carbocycles.[10]

The polyhydroxy carbacycle (carbasugar) is a carbocyclic mimic of carbohydrate. Comparing furanose to pyranose, carbasugar are more resistant to hydrolysis because of the absence of acetal moiety and they show inhibition activity to glycosidase and glycosyl transferase.[11] It is a superior method to prepare carbasugars via the conversion of carbohydrate because the configurations of the functional groups could be maintained and the specific spatial distribution of hydroxy groups could be achieved.[12] Five- and six-membered carbasugars can be synthesized in many ways, but only a few methods are available for the formation of seven- and eight-membered carbasugars.[13] In this report, we disclose a synthesis of hydroxymethyl-branched polyhydroxy cyclooctene via triisobutylaluminum (TIBAL) promoted Claisen rearrangement of D-glucose derivative (Figure 1). In the synthesis of compound **1**, stereospecific mercuriocyclization was observed. This study provides a practical approach to synthesize eight-membered polyhydroxy carbocycles. The new method could be used for the synthesis of novel bioactive agents.

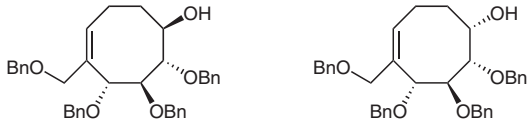
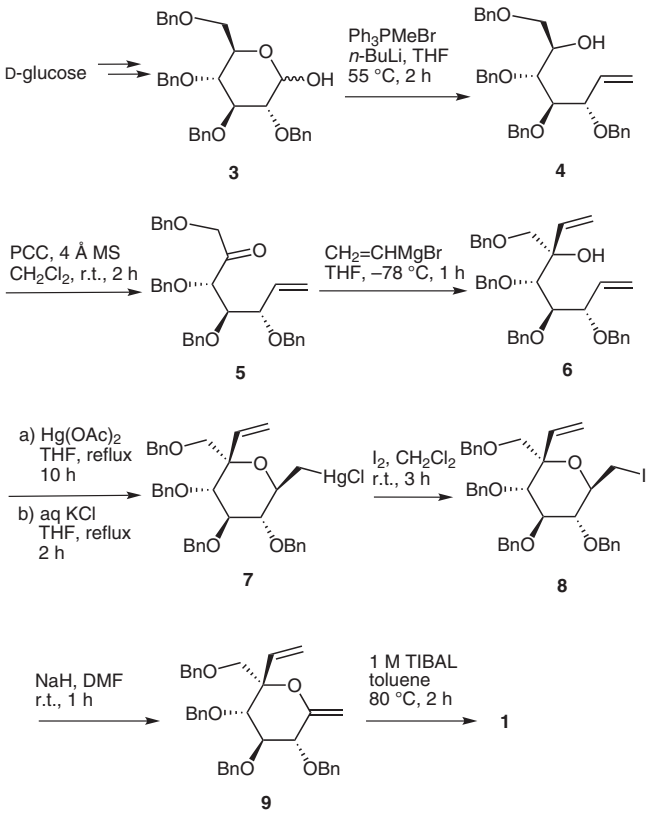


Figure 1 Structures of eight-membered polyfunctional carbocycles



Scheme 1 Synthesis of compound **1**

The synthesis route is presented in Scheme 1. Starting from D-glucose, intermediate **6** could be obtained via hydroxy protection, Wittig olefination,[14] Swern oxidation,[15] and Grignard reaction[15] in an overall yield of 56%. In the

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presence of $Hg(OAc)_2$, stereoselective mercuriocyclization of **6** proceeded to give the mecurio derivative **7**[16] in almost quantitative yield. In this reaction, mercuriocyclization was used for the formation of the six-membered pyran ring. It was noted that iodocyclization generally gives the five-membered furan ring as the major product.[17]

Structural characterization of compound **7** by ^1H NMR spectroscopy showed identical coupling constants of 3 Hz for $J_{2,3}$ and $J_{3,4}$. The result indicated that H-2 and H-3 had the same spatial relationship as H-3 and H-4, which are in *trans* configuration in glucose. Hence, H-2 and H-3 should also be in a *trans* configuration, and C-2 has an *R* absolute configuration. In addition, the small coupling constants indicated that all neighbor protons on the pyran ring of compound **7** should possess an equatorial–equatorial relationship (Figure 2). This conformation is in conflict with the general observation with substituted pyrans, wherein the large group prefers to occupy the equatorial position and the small group the axial position. The result is also different from other organomercurial compounds reported in literature.[17] This unique conformation was attributed to the existence of a vinyl group at C-6. When the vinyl group was located at the axial position, the mercury atom could coordinate to the double bond. The favorable interaction lowers the energy and places the large groups at the axial positions. It is also because of the coordination interaction, the mercuriocyclization proceeded stereoselectively and in high yield. The conformation of compound **7** was further proved by NOE experiments (Figure 2). The existence of a strong NOE between H-8 and H-1 also supported that CH_2HgCl and vinyl group are located at the axial positions.

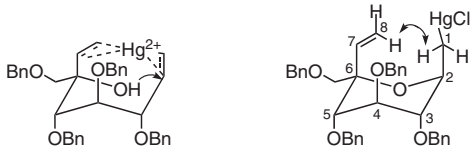


Figure 2 Coordination interaction between vinyl and mercurio afforded stereospecific cyclization (left) and stabilized the unique conformation (right)

After the organomercury functionality in compound **7** was substituted by iodine, compound **8** was obtained in 87% yield. The NMR spectral analysis indicated that compound **8** existed in a similar conformation as compound **7**. Elimination of HI by NaH gave compound **9**[18] in 83% yield. Conversion of compound **9** into the polyhydroxy eight-membered carbocycle **1**[19] was achieved in good stereoselectivity, in 87% yield, via TIBAL-promoted Claisen rearrangement (Scheme 1). The configuration of C-1 of compound **1** was identified by ^1H NMR and 2D NOESY experiments. The coupling constants between H-2 and its neighboring protons ($J_{1,2}$ = 7 Hz, $J_{2,3}$ = 6 Hz) showed that the H-1 had a *trans* relation with H-2, and C-1 was in an *R* configuration. The 2D NOESY NMR spectra also showed strong NOE (Figure 3) interactions between H-1 and H-3 and hence confirming the configuration.

In TIBAL-promoted Claisen rearrangement reaction, besides the formation of compound **1**, an unexpected benzyl elimination byproduct **10**[20] was also isolated. The structure was identified by NMR spectroscopy. The different coupling constants of $J_{5,6}$ and $J_{6,7}$ ($J_{5,6}$ = 5 Hz, $J_{6,7}$ = 9 Hz) indicated that H-5 and H-6 had a *cis* spatial relationship and C-5 is in an *R* configuration. This configuration was further confirmed by the existence of NOE interactions between H-7 and H-2, as well as between H-7 and H-4.

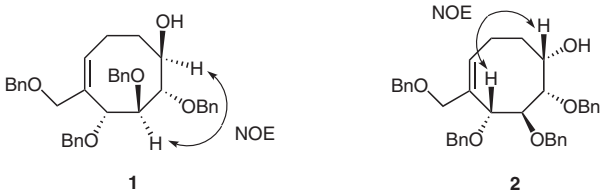
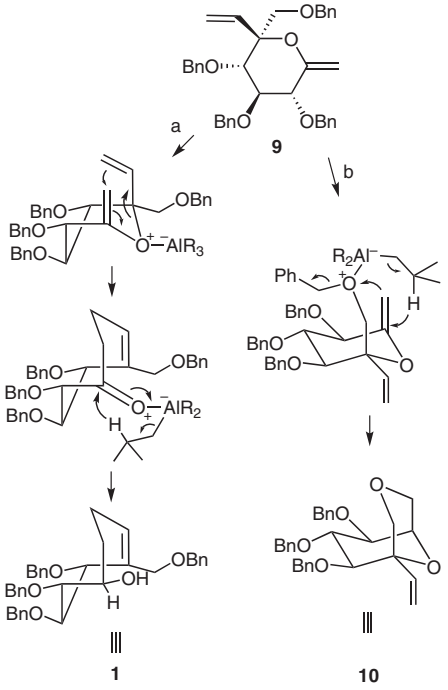


Figure 3 Configurations of compounds **1** and **2** as confirmed by NOESY experiments



Scheme 2 Proposed mechanism for the TIBAL-promoted Claisen rearrangement and debenzylation cycloaddition

The mechanism of the formation of compound **1** and **10** is illustrated in Scheme 2. Triisobutylaluminum bound strongly to the oxygen atom of the benzyloxy group and promoted debenzylation and cycloaddition to form 3,9-dioxabicyclo[3.3.1]nonane (route b). It was also found that the amount of byproduct **10** was increased and even became the main product as the amount of TIBAL decreased (Table 1). This may be resulted from the competition between route a and route b (Scheme 2). Based on the stability of their respective transition states, it appeared that route a should proceed faster because of the less sterically

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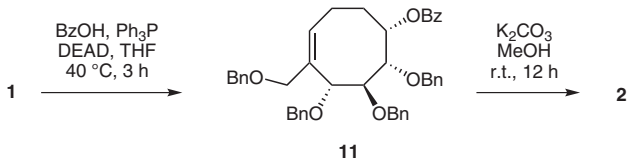
hindered coordination state. At low TIBAL concentration, route b was favored but needed longer reaction time to complete the reaction. At high TIBAL concentration, route a was favored with the increasing opportunity to form a higher sterically hindered coordination state.

Table 1 TIBAL-Promoted Formation of Compounds **1** and **10** under Different Conditions

Entry	**9**/TIBAL (mol:mol)	Solvent	Time (h)	Yield (%) **1**	**10**
1	1:10	toluene	2	87	2
2	1:5	toluene	2	58	26
3	1:2	toluene	6	30	33
4	1:1	toluene	6	14	37

The configuration of C-1 of compound **1** could be easily converted into the *S*-isomer in 97% yield via Mitsunobu reaction. After hydrolysis of the benzoyl group, compound **2**[21] was afforded in 83% yield (Scheme 3). The coupling constants between H-2 and its neighboring protons ($J_{1,2}$ = 2 Hz, $J_{2,3}$ = 8 Hz) indicated that H-1 had a *cis* relation with H-2. Strong NOE (Figure 3) between H-1 and H-4 in 2D NOESY spectra also supported that C-1 of compound **2** has an *S*-configuration.



Scheme 3 Synthesis of compound **2**

In conclusion, we have developed an efficient, highly stereospecific method for the syntheses of hydroxymethyl-branched polyhydroxy cyclooctene compounds. The coordination interaction between mercurio group and vinyl group allowed the mercuriocyclization to proceed stereoselectively and the formed mecurio derivative was found to exist in an all-axial conformation. The hydroxy groups, the side chains, and the double bonds in the carbocycles could be converted into other functional groups. These carbocycles with unique conformations could be used for the synthesis of bioactive compounds and analogues of natural products. The formation of dioxabicyclic compounds also provides a way to build mimics of related natural products.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(16) **Synthesis of 7**
To alkene **6** (1.30 g, 2.30 mmol) dissolved in anhyd THF (20 mL) was added $Hg(OAc)_2$ (0.73 g, 2.31 mmol) under argon. The reaction mixture was stirred and refluxed for 10 h, then sat. aq KCl (1 mL) was added, stirred, and refluxed for another 2 h, quenched by the addition of brine at r.t., and

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extracted three times with EtOAc. Organic extracts were combined, dried by Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography on SiO_2 (PE–EtOAc, 20:1) to give **7** as a colorless oil (1.85 g, 99.9%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.18 (m, 20 H, arom. H), 5.96 (dd, $J_{7,8a}$ = 11.0 Hz, $J_{7,8b}$ = 17.5 Hz, 1 H, H-7), 5.23–5.27 (m, $J_{8a,7}$ = 11.0 Hz, $J_{8b,7}$ = 17.5 Hz, $J_{8a,8b}$ = $J_{8b,8a}$ = 1.5 Hz, 2 H, H-8a, H-8b), 4.66, 4.59 (dd, *J* = 11.5 Hz, 2 H, HCH_2Ph), 4.57, 4.51 (dd, *J* = 12.0 Hz, 2 H, HCH_2Ph), 4.35, 4.23 (dd, *J* = 12.0 Hz, 2 H, HCH_2Ph), 4.42 (m, $J_{2,3}$ = 3.0 Hz, $J_{2,1a}$ = 6.0 Hz, $J_{2,1b}$ = 4.0 Hz, 1 H, H-2), 3.90 (t, $J_{4,3}$ = 3.0 Hz, $J_{4,5}$ = 4.0 Hz, 1 H, H-4), 3.87, 3.41 (dd, *J* = 8.5 Hz, 2 H, H-9a, H-9b), 3.67 (d, $J_{5,4}$ = 4.0 Hz, 1 H, H-5), 3.16 (t, $J_{3,2}$ = 3.0 Hz, $J_{3,4}$ = 3.0 Hz, 1 H, H-3), 1.94 (dd, $J_{1a,2}$ = 6.0 Hz, $J_{1a,1b}$ = 12.0 Hz, 1 H, H-1a), 1.65 (dd, $J_{1b,2}$ = 4.0 Hz, $J_{1b,1a}$ = 12.0 Hz, 1 H, H-1b). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.2 (C-7), 138.5, 138.4, 138.0, 137.3 (4 × C_{ipso}), 129.1–127.5 (arom. C), 114.6 (C-8), 79.6 (C-6), 76.2 (C-3), 76.0 (C-5), 75.9 (C-9), 74.2 (C-4), 73.9, 73.7, 72.5, 72.1 (4 × CH_2Ph), 67.4 (C-2), 31.6 (C-1). MS (ESI-TOF$^+$): *m/z* = 818 $[M + NH_4]^+$, 823 $[M + Na]^+$, 839 $[M + K]^+$. Anal. Calcd for $C_{37}H_{39}O_5HgCl$: C, 55.57; H, 4.92. Found: C, 55.83; H, 5.10.

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(18) **Synthesis of 9**

Compound **8** (559 mg, 0.81mmol) dissolved in anhyd DMF (5 mL) was treated with NaH (60% in oil, 323 mg, 8.10 mmol) under argon. The reaction mixture was stirred for 1 h at r.t., quenched with MeOH, and concentrated. The residue was added H_2O and extracted with CH_2Cl_2. The organic extracts were washed twice with brine, dried by Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography (PE–EtOAc–Et_3N, 15:1:0.02) to yield **9** as a colorless oil (377 mg, 82.7%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.02–6.78 (m, 20 H, arom. H), 5.88 (dd, $J_{7,8a}$ = 17.5 Hz, $J_{7,8b}$ = 11.0 Hz, 1 H, H-7), 5.43 (ss, $J_{8a,7}$ = 17.5 Hz, $J_{8a,8b}$ = 1.5 Hz, 1 H, H-8a), 4.88 (dd, $J_{8b,7}$ = 17.5 Hz, $J_{8b,8a}$ = 1.5 Hz, 1 H, H-8b), 4.70 (d, $J_{1a,1b}$ = 1.5 Hz, 1 H, H-1a), 4.66 (d, $J_{1b,1a}$ = 1.5 Hz, 1 H, H-1b), 4.52 (dd, *J* = 11.5 Hz, 2 H, HCH_2Ph), 4.39 (dd, *J* = 11.5 Hz, 2 H, HCH_2Ph), 4.35 (dd, *J* = 11.5 Hz, 2 H, HCH_2Ph), 4.20 (dd, *J* = 11.5 Hz, 2 H, HCH_2Ph), 3.81 (m, $J_{5,4}$ = 8.0 Hz, $J_{4,5}$ = 8.0 Hz, $J_{4,3}$ = 8.0 Hz, 2 H, H-5, H-4), 3.58 (dd, *J* = 10.0 Hz, 2 H, H-9a, H-9b), 3.34 (d, $J_{3,4}$ = 8.0 Hz, 1 H, H-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.0 (C-2), 139.3 (C-7), 139.0, 138.8, 138.7, 138.5 (4 × C_{ipso}), 128.6–127.7 (arom. C), 115.3 (C-8), 94.7 (C-1), 84.2 (C-6), 82.8 (C-3), 82.2 (C-5), 80.6 (C-4), 75.6 (C-9), 74.7, 73.9, 73.5, 71.1 (4 × CH_2Ph). MS (ESI-TOF$^+$): *m/z* = 585 $[M + Na]^+$, 601 $[M + K]^+$. Anal. Calcd for $C_{37}H_{38}O_5$: C, 78.98; H, 6.81. Found: C, 78.80; H, 7.02.

(19) **Synthesis of 1**

To the solution of compound **9** (660 mg, 1.17 mmol) in toluene (20 mL) was added dropwise 1 M TIBAL (11.7 mL, 11.7 mmol) in toluene at r.t. under argon. The mixture was stirred at 80 °C for 2 h, cooled to 0 °C, and quenched with 20% aq NaOH solution. The mixture was extracted with toluene, and the organic layers were combined, dried with Na_2SO_4, and concentrated. The residue was purified by column chromatography (PE–acetone, 20:1) to give **1** as colorless oil (571 mg, 86.5%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.18 (m, 20 H, arom. H), 6.02 (t, $J_{6,7a}$ = $J_{6,7b}$ = 8 Hz, 1 H, H-6), 4.73 (d, $J_{4,3}$ = 6 Hz, 1 H, H-4), 4.61 (dd, *J* = 12 Hz, 2 H, HCH_2Ph), 4.58 (dd, *J* = 12 Hz, 2 H, HCH_2Ph), 4.48 (dd, *J* = 12 Hz, 2 H, HCH_2Ph), 4.33 (dd, *J* = 12 Hz, 2 H, HCH_2Ph), 4.11 (t, $J_{1,2}$ = 7 Hz, $J_{1,8a}$ = 7 Hz, 1 H, H-1), 4.00 (dd, *J* = 12 Hz, 2 H, H-9), 3.90 (t, $J_{3,2}$ = $J_{3,4}$ = 6 Hz, 1 H, H-3), 3.63 (dd, $J_{2,3}$ = 6 Hz, $J_{2,1}$ = 7 Hz, 1 H, H-2), 3.39 (s, 1 H, OH), 2.42 (br, 1 H, H-7a), 2.22 (br, 1 H, H-7b), 2.04 (t, $J_{8b,8a}$ = 13 Hz, 1 H, H-8b), 1.71 (m, $J_{8a,8b}$ = 13 Hz, $J_{8a,1}$ = 7 Hz, 1 H, H-8a). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.6, 138.4, 138.1, 138.1 (4 × C_{ipso}), 134.2 (C-5), 131.4 (C-6), 128.4-127.4 (arom. C), 84.4 (C-3), 81.3 (C-2), 78.7 (C-4), 74.2, 72.5, 72.2, 71.2 (4 × CH_2Ph), 70.4 (C-1), 32.9 (C-8), 21.3 (C-7). MS (ESI-TOF$^+$): *m/z* = 565 $[M + H]^+$, 582 $[M + NH_4]^+$, 587 $[M + Na]^+$, 603 $[M + K]^{+\cdot}$ Anal. Calcd for $C_{37}H_{40}O_5$: C, 78.69; H, 7.14. Found: C, 78.84; H, 6.91.

(20) Compound **10**: white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26–7.19 (m, 15 H, H-arom.), 5.74 (dd, $J_{10,11a}$ = 18 Hz, $J_{10,11b}$ = 11 Hz, 1 H, H-10), 5.26 (dd, $J_{11a,10}$ = 18 Hz, $J_{11a,11b}$ = 2 Hz, 1 H, H-11a), 5.09 (dd, $J_{11b,10}$ = 11 Hz, $J_{11b,11a}$ = 2 Hz, 1 H, H-11b), 4.87 (dd, *J* = 12 Hz, 2 H, HCH_2Ph), 4.82 (dd, *J* = 12 Hz, 2 H, HCH_2Ph), 4.66 (dd, *J* = 12 Hz, 2 H, HCH_2Ph), 4.58 (t, $J_{7,6}$ = $J_{7,8}$ = 9 Hz, 1 H, H-7), 4.13 (d, $J_{2a,2b}$ = 12 Hz, 1 H, H-2a), 4.02 (d, $J_{4a,4b}$ = 12 Hz, 1 H, H-4a), 3.79 (dd, $J_{6,5}$ = 5 Hz, $J_{6,7}$ = 9 Hz, 1 H, H-6), 3.75 (dd, $J_{5,6}$ = 5 Hz, $J_{5,4b}$ = 3 Hz, 1 H, H-5), 3.54 (dd, $J_{4b,4a}$ = 12 Hz, $J_{4b,5}$ = 3 Hz 1 H, H-4b), 3.39 (d, $J_{8,7}$ = 9 Hz, 1 H, H-8), 3.22 (d, $J_{2b,2a}$ = 12 Hz, 1 H, H-2b). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.0, 138.6, 138.3 (3 × C_{ipso}), 136.8 (C-10), 128.4–127.4 (arom. C), 115.5 (C-11), 84.4 (C-8), 83.7 (C-7), 80.9 (C-6), 75.5, 75.3, 73.2 (3 × CH_2Ph), 74.6 (C-1), 69.6 (C-5), 68.8 (C-2), 63.8 (C-4). MS (ESI-TOF$^+$): *m/z* = 490 $[M + NH_4]^+$, 495 $[M + Na]^+$, 511 $[M + K]^{+\cdot}$ Anal. Calcd for $C_{37}H_{40}O_5$: C, 76.25; H, 6.83. Found: C, 76.50; H, 7.05.

(21) **Synthesis of 2**

To the solution of Ph_3P (296 mg, 1.13 mmol) in anhyd THF (3 mL) previously cooled in an ice bath was added dropwise 2.2 M DEAD in toluene (0.5 mL, 1.13 mmol) under argon. After 30 min, this solution was added dropwise to the solution of compound **1** (254 mg, 0.45 mmol) and benzoic acid (100 mg, 0.82 mmol) in anhyd THF under argon in an ice bath. The mixture was stirred for 30 min at 0 °C, then stirred at 45 °C for 3 h. When the volatiles were removed, the residue was purified by column chromatography (PE–acetone, 40:1) to yield **10** as colorless oil (290 mg, 96.5%). Compound **10** (362 mg, 0.54 mmol) dissolved in MeOH (10 mL) was treated with K_2CO_3 (372 mg, 2.69 mmol) and stirred at r.t. for 12 h. The reaction mixture was subsequently filtered and concentrated, and the residue was purified by column chromatography (PE–acetone, 20:1) to afford **2** as colorless oil (254 mg, 82.7%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31–7.21 (m, 20 H, arom. H), 6.03 (t, $J_{6,7a}$ = $J_{6,7b}$ = 8.5 Hz, 1 H, H-6), 4.67 (dd, *J* = 12.0 Hz, 2 H, HCH_2Ph), 4.62 (dd, *J* = 12.0 Hz, 2 H, HCH_2Ph), 4.47 (dd, *J* = 12.0 Hz, 2 H, HCH_2Ph), 4.43 (dd, *J* = 12.0 Hz, 2 H, HCH_2Ph), 4.41 (m, $J_{2,1}$ = 2.5 Hz, $J_{2,3}$ = 6.0 Hz, 1 H, H-2), 4.07–3.98 (m, 3 H, H-1, H-9a, H-9b), 3.83 (t, $J_{3,2}$ = 6.0 Hz, $J_{3,4}$ = 5.0 Hz, 1 H, H-3), 3.69 (d, $J_{4,3}$ = 5.0 Hz, 1 H, H-4), 2.36 (br, 1 H, H-7a), 2.10 (m, 1 H, H-7b), 2.00 (m, 1 H, H-8a), 1.70 (m, 1 H, H-8b). MS (ESI-TOF$^+$): *m/z* = 565 $[M + H]^+$, 582 $[M + NH_4]^+$, 587 $[M + Na]^+$, 603 $[M + K]^{+\cdot}$ Anal. Calcd for $C_{37}H_{40}O_5$: C, 78.69; H, 7.14. Found: C, 78.64; H, 7.02.

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