[5+3] Cycloaddition of 3-Oxidopyrylium: A Novel Route to Functionalized Cyclooctanoids from Furans

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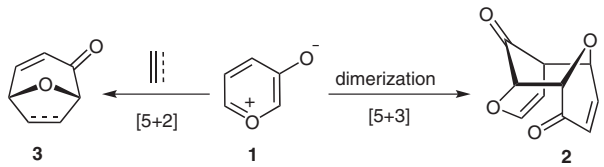
Abstract: We report a facile and efficient synthesis of highly functionalized cyclooctanoid derivatives by employing a dimerization reaction of 3-oxidopyrylium ylides. Different substituents are introduced on the dimer and the stereochemical outcome of the resultant cyclooctanoids is unambiguously established by single-crystal X-ray analysis.

Key words: cyclooctanoids, 3-oxidopyrylium ylides, [5+3] cycloadditions, stereoselectivity, density functional calculations

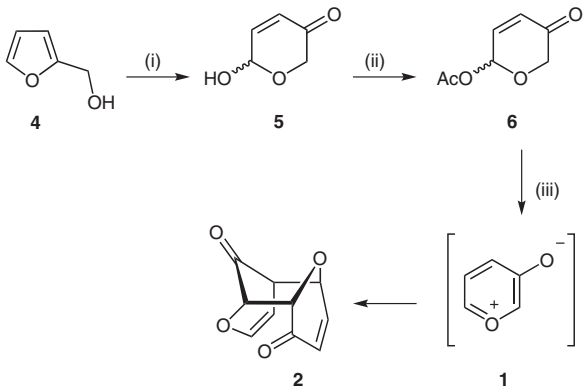
The synthesis of cyclooctanoid systems from acyclic precursors remains a challenging problem, mainly because of the unfavorable entropic and enthalpic factors that preclude ring closure. The difficulty associated with the construction of cyclooctanoids and their ubiquity in numerous diverse natural products have prompted the search for novel methods for their construction.[1–3] 3-Oxidopyrylium ylide (**1**) (Scheme 1), generated by base treatment of acetoxypyranones, readily undergoes cycloadditions with various dienophiles to produce the corresponding cycloadducts. This approach has been proved to be a highly useful method for the synthesis of seven-membered carbocycles and natural products.[4] However, in the absence of suitable dienophiles, the reactive 3-oxidopyrylium ylide readily undergoes self-dimerization and generates the polycyclic structures with excellent regio- and stereoselectivity (Scheme 1). This reaction was first reported by Hendrickson and Farina in 1980, but, surprisingly, no further studies have been reported until we disclosed our investigations on exploring the use of dimer **2** towards the synthesis of functionally rich cyclooctanoid derivatives.[5–7]

In this paper, we wish to present a detailed account of our investigations into the stereocontrolled transformation of cycloadduct **2** into highly functionalized cyclooctanoid[8–13] systems. We demonstrate that different substituents can be introduced onto the cycloadduct **2** in a stereoselective manner by virtue of conformational rigidity imparted by the oxa bridge to the flexible systems. We believe that the results reported herein may be useful for the application of dimerization reactions of oxidopyrylium ions in the total synthesis of cyclooctanoid natural products.



Scheme 1 Cycloaddition reactions of 3-oxidopyrylium

Dimer **2** was readily prepared in three steps by the method reported by Hendrickson et al. (Scheme 2).[6a] Exposure of furfuryl alcohol **4** to Achmatowicz conditions,[14] which involve an oxidative rearrangement of furylcarbinols to hydroxypyranones, provided hemiacetal **5**, which was immediately converted into the corresponding acetoxypyranone by acetylation of the anomeric hydroxy group. Treatment of the acetoxypyranone **6** with triethylamine generated the 3-oxidopyrylium ylide **1**, which readily underwent thermal [5+3] cycloaddition to afford the *endo* cycloadduct **2** as the only observed product (Scheme 2).



Scheme 2 *Reagents and conditions*: (i) NBS, THF–H_2O, NaOAc, 0 °C, 0.5 h; (ii) Ac_2O, pyridine, 0 °C, 59% (two steps); (iii) Et_3N, CH_2Cl_2, r.t., 60%.

With sufficient quantities of **2** in hand, we subjected cycloadduct **2** to reduction of the α,β-unsaturated olefinic double bond under typical hydrogenation conditions (H_2, Pd/C) in ethanol as solvent. However, this reaction did not result in the formation of the expected dihydro product **7**, but instead we ended up with the unanticipated product **8**, in which a new carbon–carbon bond between the enol ether and the ketone had formed (Scheme 3). The ^{1}H NMR spectrum of the product confirmed the solvent participation in the reaction, showing a triplet at δ = 1.15 (3*H*) and a pair of doublets of a quartet centered at δ = 3.8 (1*H*)

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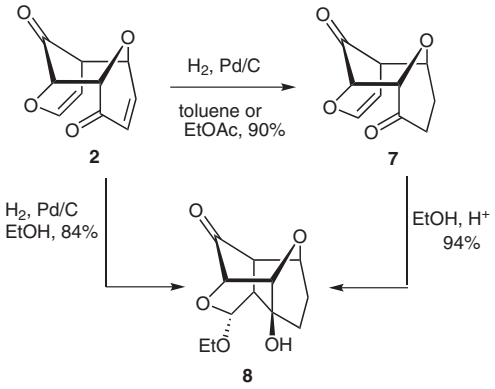
and 3.48 (1*H*), assigned to an ethoxy substituent in the product. The ^{13}C NMR spectrum showed a single carbonyl peak instead of the two initially present in the dimer, thus helping us in ruling out the formation of the expected dihydro product **7** or the corresponding tetrahydro product. Unambiguous evidence for the structure and stereochemistry of the product was obtained by single-crystal X-ray analysis (Figure 1).[15] The structure confirmed the presence of an ethoxy group and the formation of a new carbon–carbon bond (C_4–C_9, X-ray). In view of these observations, the hydrogenation reaction was carried out in nonparticipating, non-nucleophilic solvent systems, so that solvent participation could be avoided. Thus, dimer **2** was subjected to the hydrogenation reaction in ethyl acetate and toluene under similar reaction conditions, and, in both cases, we obtained the desired product **7**, whose identity was confirmed by its spectroscopic data (Scheme 3).

The formation of an intramolecular carbon–carbon bond during hydrogenation is rather unique and unanticipated. Our proposed mechanistic pathway for the formation of the undesired product **8** is shown in Scheme 4. Thereby, the acidic nature of the reaction medium is responsible for the formation of the unexpected product through the transannular cationic cyclization of **7**. The transient carbocation **9** was then trapped by the solvent (ethanol) to yield the observed product. These observations also helped in confirming the relative stereochemistry of the dimer **2**. Recently Lee and co-workers also reported similar observations.[6c]

Next we focused on opening the heavily encumbered pyranyl ether moiety while still maintaining the geometrical rigidity imparted by the oxa bridge to the deeply embedded eight-membered ring in the structure. Since cycloadduct **7** is highly susceptible to acidic conditions, we decided to secure the ketone groups as the corresponding diols to thus eliminate the possibility of intramolecular carbon–carbon bond formation. The ketone groups are reduced under sodium borohydride reduction conditions to yield the diol **10** as the only observed product in a stereoselective manner (Scheme 5). In parallel, an efficient one-step reduction of dimer **2** to the corresponding diol **10** was accomplished under nickel boride ($NiCl_2/NaBH_4$) reduction conditions.[16] The relative stereochemistry of the diol was established by single-crystal X-ray analysis (Figure 2)[15] of the corresponding diacetate (Ac_2O, Et_3N, CH_2Cl_2). The diacetate was characterized as **11**, and hence the stereostructure **10** was assigned to the diol. As shown in Scheme 5, nickel boride was also found to be efficient in the reduction of the α,β-unsaturated double bond of dimer **2** when the reaction was carried out in aqueous methanol.

The hydroxy groups in **10** were protected as benzyl ethers (BnBr, NaH, TBAI), and the resultant bis-benzyl ether **12** was then hydrated with use of acidic resins (Dowex 50W X4) in the presence of water to furnish the aldehyde **13**



Scheme 3 Solvent effects on hydrogenation of dimer **2**

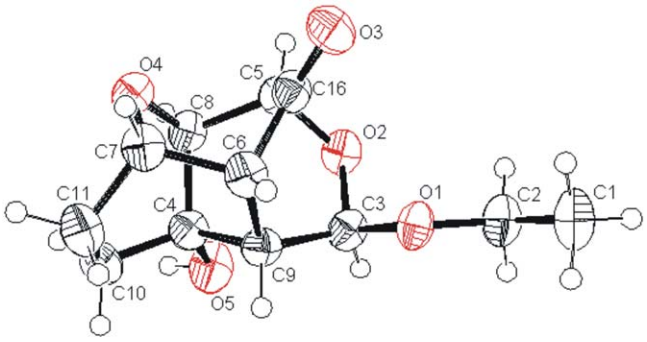


Figure 1 ORTEP drawing of the X-ray crystallographic structure of **8**

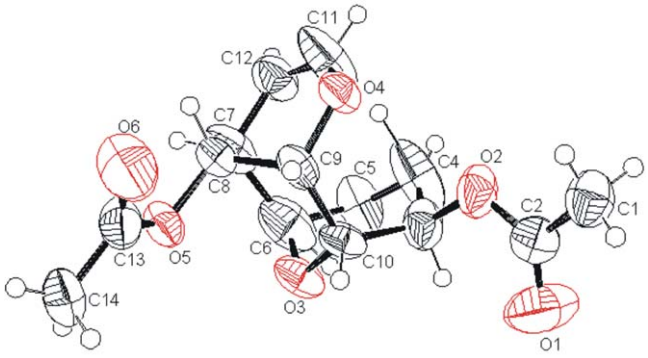
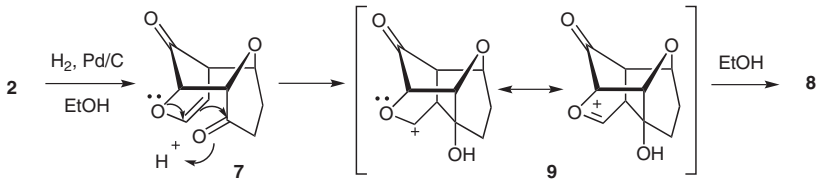
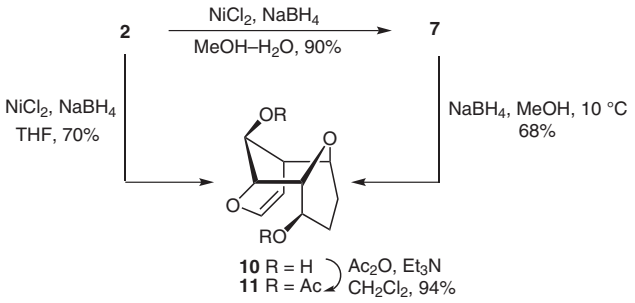


Figure 2 ORTEP drawing of the X-ray crystallographic structure of **11**



Scheme 4 Mechanism of formation of **8**



Scheme 5

(ν_{max} = 1719 cm^{-1}),[17] which was further converted into oxa-bridged cyclooctanoid derivatives **14** and **15** (Scheme 6). The synthesis of ketone **17** was achieved by Wittig olefination of aldehyde **13** (72% yield), followed by Swern oxidation of the resultant hydroxyalkene **16** (Scheme 7). Once again, the stereostructure of the ketone **17** was validated by single-crystal X-ray analysis (Figure 3).[15]

It is evident from these investigations that functionality can be introduced in a stereochemically well-defined manner at many sites on the cycloadduct and, hence, the synthesis of a wide variety of valuable multifunctional skeletons is feasible. After transforming cycloadduct **2** into functionally rich oxa-bridged cyclooctanoids, we examined the possibility of extending the use of these intermediates towards the synthesis of bridged bicyclic systems, as these structures are present in medicinally important natural products.[1,8] Towards this goal, our attention was drawn towards employing the ring-closing metathesis (RCM) strategy, as this method had been used successfully in the construction of eight-membered carbocycles.[18] When ketone **17** reacted with an excess of vinylmagnesium bromide at –40 °C, compound **18** was obtained as the only observed product (Scheme 8). The stereochemistry of diene **18** was rationalized to result from a chelation-controlled approach of the Grignard reagent (*syn* with respect to the oxa bridge). Unfortunately, when compound **18** was subjected to olefin metathesis reaction conditions in the presence of the Grubbs first generation catalyst [benzylidenedichlorobis(tricyclohexylphosphine)ruthenium] under different solvent conditions and temperatures, the desired annulated product **19** was not obtained (Scheme 8). In the search for alternative methods for the construction of bridged bicyclic systems, our attention was drawn towards exploiting the intramolecular aldol condensation reaction. Oxa-bridged cyclooctanone **17** was subjected to Wacker oxidation conditions[19] ($PdCl_2$, DMF) to afford the diketone **20** in 94% yield (Scheme 8). Disappointingly, our efforts to enforce the desired cyclization under various aldol reaction conditions (Scheme 8) have so far been unsuccessful under a variety of reaction conditions [$KN(TMS)_2$, LDA, NaOMe, NaH, *t*-BuOK, DBU]. In all cases, either the starting material was recovered or had decomposed.

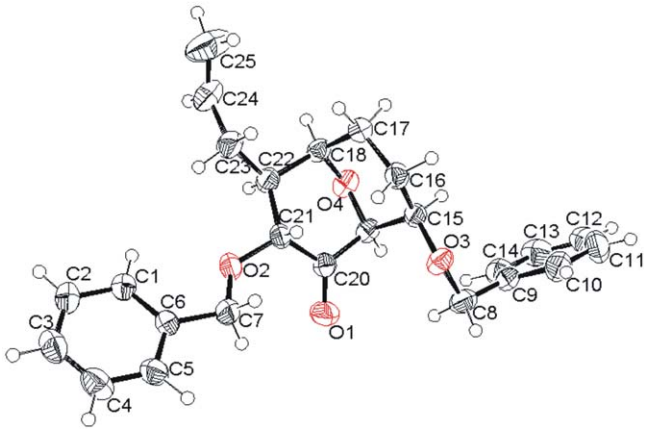
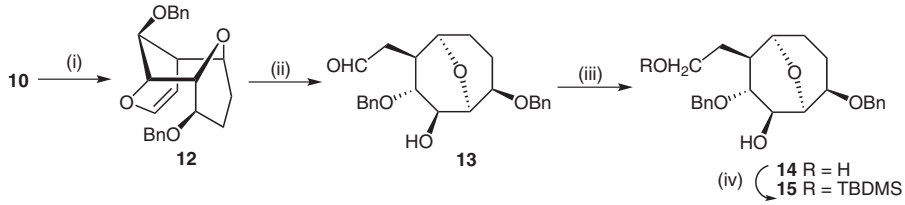
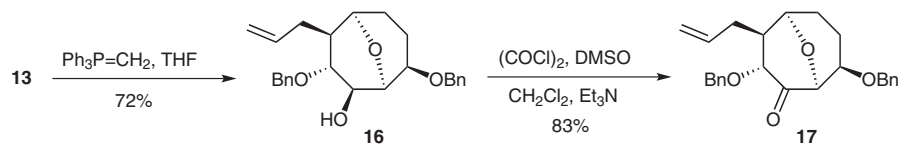


Figure 3 ORTEP drawing of the X-ray crystallographic structure of **17**

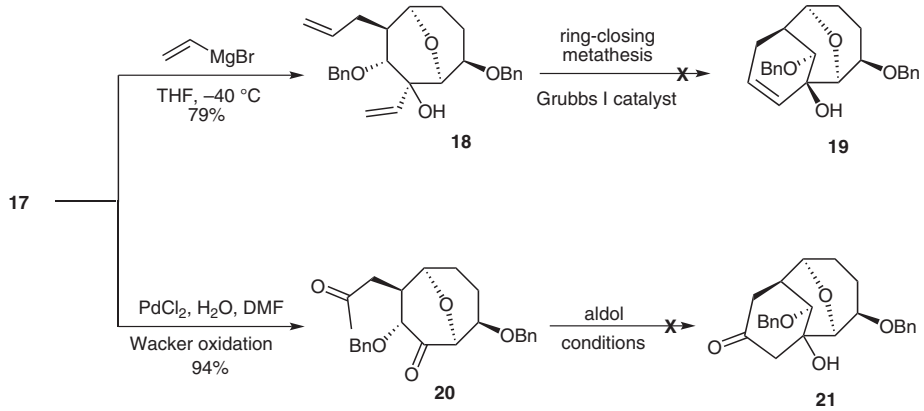
To examine whether stereoelectronic issues are responsible for the problem associated with the ring closure of **20** leading to **21**, we decided to focus on the intramolecular aldol reaction of **20** in the presence of a base. The aldol reaction as shown in Scheme 9 involves two key steps, namely the generation of carbanion **20**-crb and subsequent cyclization involving the nucleophilic addition of the carbanion to the carbonyl group to furnish the aldol product. The computed barriers for these two steps are –17.5 and 13.1 kcal/mol, obtained at the $PCM_{(THF)}$/



Scheme 6 *Reagents and conditions*: (i) NaH, BnBr, TBAI, THF, 77%; (ii) Dowex 50W X4, LiBr, H_2O, MeCN, 88%; (iii) $NaBH_4$, MeOH, 0 °C, 100%; (iv) TBDMSCl, imidazole, THF–DMF, 85%.



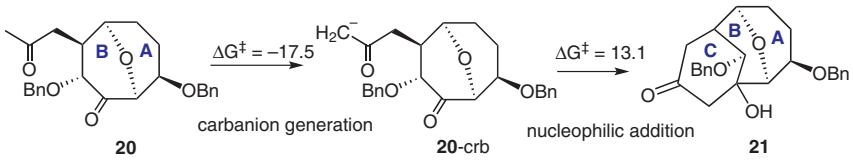
Scheme 7



Scheme 8

B3LYP/6-311G**//B3LYP/6-31G* level of theory. The barriers for the generation of the carbanion and the subsequent nucleophilic addition were computed with respect to **20** and **20**-crb, respectively. This indicates that the intramolecular nucleophilic addition (C–C bond formation) could be the rate-limiting step, and studies directed towards understanding the difficulty associated with the ring closure should therefore focus on this step. The activation barrier for the nucleophilic addition was found to be well within the range of reported barriers for other intramolecular aldol reactions.[20] In such a case, the factor prohibiting the ring closure is either the endothermicity of the reaction (reversibility) or an unfavorable interaction/event that restricts the approach of the two reacting centers along the reaction coordinate prior to reaching the desired transition state.

The computed reaction energies ($\Delta E_{rxn} = 4.6$ kcal/mol) suggest that the reaction is endoergic and the process is likely to be reversible. The geometries of the transition state (**20**-crb→**21**), reactant (**20**-crb), and product (**21**) were examined more closely (Figure 4). For the sake of concise representation, the rings are designated as **A**, **B**,



Scheme 9

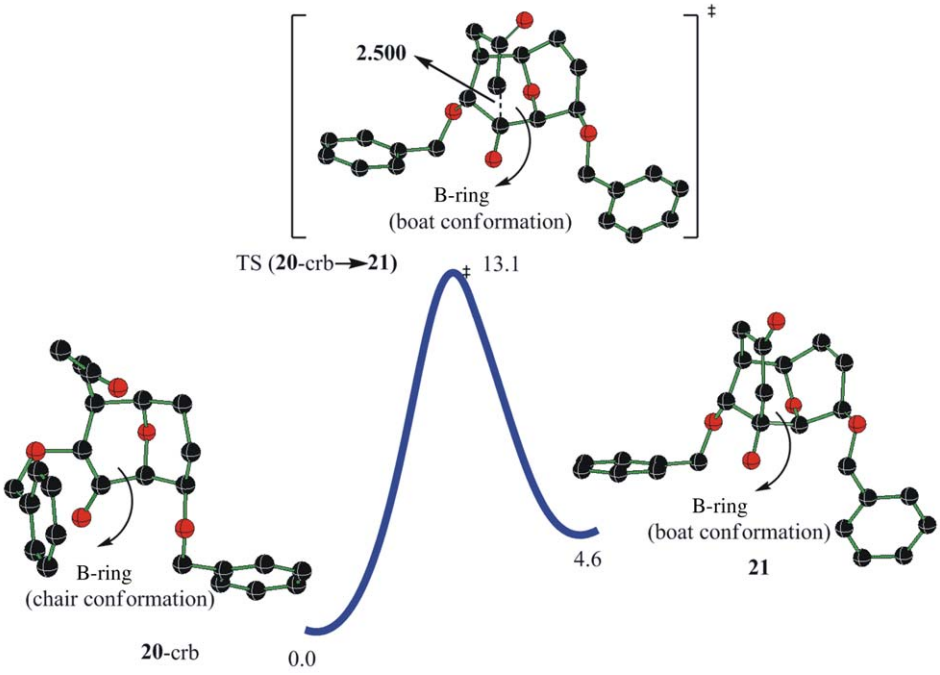


Figure 4 Reaction profile diagram for the conversion of **20**-crb into **21**

and **C** (Scheme 9). It was found that in the transition state (**20**-crb→**21**), rings **A** and **C**, which are being formed, exhibit a chair conformation, whereas ring **B** has a boat conformation. Careful optimization towards reactant and product was performed using intrinsic reaction coordinate (IRC) calculations in order to identify the changes in the conformations of the **A**, **B**, and **C** rings along the reaction pathway. Optimization in the forward direction starting from the transition state geometry leads to the tricyclic product without any major conformational changes in the **A**, **B**, and **C** rings. On the other hand, geometry optimization in the reverse direction exhibits significant changes in the conformation of ring **B** along with the separation of the C–C bond (Figure 4). Interestingly, it has been noticed that the chair form is the preferred conformation for ring **B** in **20**-crb as well as **20**. This evidently suggests that the ring closure of **20** to **21** requires flipping of ring **B**, from chair to boat form, prior to the nucleophilic addition. While the computed low barrier for the nucleophilic addition suggests a feasible bond formation, two crucial factors that can be attributed to the unsuccessful ring closure under various reaction conditions are evident. First, the cyclization could be reversible as the reaction is found to be endoergic.[21] The changes in the conformational features of the **B** ring during cyclization could be the second deterrent. The **B**-ring flip from chair to boat conformation may not be possible owing to the rigidity offered by the oxa bridge.[22]

The present investigations demonstrated that dimerization of 3-oxidopyrylium provides a novel and concise method for the synthesis of highly functionalized cyclooctanoid derivatives. The attractive features of this methodology are (a) a high degree of regioselectivity in the adduct formation and (b) that functionality can be introduced in a stereocontrolled fashion on the cycloadduct, owing to its conformational rigidity imparted by the oxa bridge. Both the density functional theory calculations and experimental results proved that the oxa bridge does, however, impede the conformational changes required for the bridged bicycle formation and thus removal of the oxa bridge is essential for the successful generation of bridged bicyclic systems.[23] Further studies to utilize this methodology towards the synthesis of biologically active cyclooctanoid-bearing natural products will be reported in due course.

Oxygen- and moisture-sensitive reactions were carried out in flame-dried glassware sealed with a rubber septum under a positive pressure of anhyd N_2 or argon. Sensitive liquids and solns were transferred by syringe or cannula through rubber septa through which a positive pressure of N_2 was maintained. Drying of solns was performed with anhyd Na_2SO_4 and concentrating of solns was carried out in a rotary evaporator. Anhyd solvents were prepared following standard procedures. TLC was performed on silica gel plates prepared by coating a thin film of silica gel slurry on glass plates, and the components were visualized by observation under I_2 vapors and UV light. Flash chromatography was performed on silica gel (100–200 mesh). Melting points were determined with a Veego apparatus of Buchi type and are uncorrected. NMR spectra were measured in FT mode on a Varian mercury-400 (^{1}H at 400 MHz, ^{13}C at 100 MHz) and Varian VXR-300s (^{1}H at 300 MHz, ^{13}C at 75 MHz) spectrometer. ^{1}H NMR peaks are referenced to TMS as internal standard (δ = 0.00). IR spectra were recorded on a Nicolet Impact 400 series FT spectrometer.

Theoretical Calculations

The potential energy surfaces were explored by use of the B3LYP/6-31G* level of theory using the GAUSSIAN 03 suite of quantum chemical programs.[24] All geometries were fully optimized and were characterized as stationary points on the potential energy surface at the same level of theory by evaluating corresponding Hessian indices. The single-point energies were calculated at the $PCM_{(THF)}$/B3LYP/6-311G** level of theory using Tomasi's polarized continuum model (PCM).[25] Transition states were characterized by the unique imaginary frequency pertaining to the reaction coordinate. Intrinsic reaction coordinate (IRC) calculations were carried out to authenticate the transition state.[26]

3,11-Dioxatricyclo[5.3.1.1^{2,6}]dodeca-4,8-diene-10,12-dione (2)

A previously reported procedure[6a] was used for the synthesis of dimer **2**. Et_3N (13.2 mL, 95 mmol) was added to a soln of acetoxypyranone **6** (7.8 g, 50 mmol) in CH_2Cl_2 (186 mL) at 0 °C. The resultant mixture was warmed to r.t. and stirred for 2 d. Concentration of the solvent under reduced pressure, followed by purification by flash column chromatography (silica gel, EtOAc–hexanes, 2:3) afforded dimer **2**.

Yield: 5.7 g (60%); white solid; mp 146–148 °C.

IR ($CHCl_3$): 1755, 1702, 1631 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.01 (dd, *J* = 10.6, 4.8 Hz, 1 H), 6.40 (d, *J* = 5.8 Hz, 1 H), 6.39 (d, *J* = 10.6 Hz, 1 H), 5.20 (dd, *J* = 9.5, 4.8 Hz, 1 H), 4.95 (d, *J* = 8.8 Hz, 1 H), 4.71 (dd, *J* = 7.3, 5.8 Hz, 1 H), 4.78 (dd, *J* = 8.8, 2.6 Hz, 1 H), 3.63 (overlapped ddd, *J* = 9.2, 7.3, 2.6 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.5, 189.9, 148.8, 144.8, 128.5, 101.0, 82.6, 77.4, 74.5, 46.3.

GC-MS: *m*/*z* = 192.

3,11-Dioxatricyclo[5.3.1.1^{2,6}]dodec-4-ene-10,12-dione (7)

Method A: A 10% Pd/C mixture (20 mg) was added to a soln of dimer **2** (0.1 g, 0.52 mmol) in either toluene or EtOAc (10 mL), and then the mixture was stirred under a H_2 atmosphere (balloon) at r.t. for 3 h. The reaction mixture was filtered though a pad of Celite and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, EtOAc–hexanes, 2:3) to yield adduct **7**.

Yield: 0.092 g (90%); colorless solid.

Method B: In a 50-mL round-bottom flask fitted with a reflux condenser was placed dimer **2** (0.06 g, 0.312 mmol) in MeOH (4 mL). To this was added $NiCl_2 \cdot 6H_2O$ (0.37 g, 1.56 mmol) followed by distilled H_2O (0.6 mL). $NaBH_4$ (0.024 g, 0.624 mmol) was added to the flask and the reaction mixture was stirred vigorously at r.t. After completion of the reaction (TLC), the reaction mixture was filtered through a pad of Celite and the pad was washed with CH_2Cl_2 (3 × 15 mL). The combined CH_2Cl_2 extracts were dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, EtOAc–hexanes, 2:3) to provide compound **7**.

Yield: 0.055 g (90%); colorless solid; mp 178–180 °C.

IR ($CHCl_3$): 1762, 1722, 1639 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.3 (d, *J* = 5.9 Hz, 1 H), 4.89–4.76 (m, 2 H), 4.85 (d, *J* = 5.9 Hz, 1 H), 4.70 (dd, *J* = 9.5, 2.6 Hz, 1 H), 3.16 (m, 1 H), 2.68–2.49 (m, 3 H), 2.11 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.9, 202.5, 144.9, 98.7, 81.4, 77.6, 73.7, 44.7, 33.3, 23.1.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{10}H_{10}O_4$: 194.0588; found: 194.0579.

Alcohol 8

A 10% Pd/C mixture (10 mg) was added to a soln of dimer **2** (0.05 g, 0.26 mmol) in EtOH (5 mL) and the reaction mixture was stirred under a H_2 atmosphere (balloon) at r.t. for 3 h. The mixture was filtered though a pad of Celite and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, EtOAc–hexanes, 2:3) to provide adduct **8**.

Yield: 0.053 g (84%); colorless crystals; mp 132–134 °C.

IR ($CHCl_3$): 3463, 1764 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.14 (d, *J* = 2.8 Hz, 1 H), 4.15 (m, 2 H), 4.08 (dd, *J* = 7.6, 2.8 Hz, 1 H), 3.78 (dq, *J* = 9.6, 7.2 Hz, 1 H), 3.48 (dq, *J* = 9.6, 7.2 Hz, 1 H), 2.77 (m, 1 H), 2.68 (m, 1 H), 2.35 (s, 1 H), 2.16 (m, 2 H), 1.99 (m, 1 H), 1.72 (m, 1 H), 1.15 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.5, 96.3, 77.7, 75.1, 73.2, 68.9, 63.2, 46.6, 42.2, 28.5, 24.8, 14.7

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{12}H_{16}O_5$: 240.0990; found: 240.0998

3,11-Dioxatricyclo[5.3.1.1^{2,6}]dodec-4-ene-10,12-diol (10)

Method A: $NaBH_4$ (0.85 g, 22.5 mmol) was added in portions to a soln of **7** (1.4 g, 7.1 mmol) in MeOH (50 mL) at 10 °C. The reaction mixture was stirred at the same temperature for 3 h before being quenched by the addition of H_2O and CH_2Cl_2. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried (Na_2SO_4). The crude reaction mixture was filtered and concentrated under reduced pressure. Purification of the resultant residue by flash chromatography (silica gel, EtOAc–hexanes, 3:2) afforded adduct **10**.

Yield: 0.98 g (68%); syrup.

Method B: An excess of $NiCl_2·6H_2O$ (12.6 g, 53.25 mmol) followed by $NaBH_4$ (4 g, 106 mmol) were added to a soln of compound **2** (0.7 g, 3.55 mmol) in THF (50 mL). The reaction mixture was stirred vigorously at r.t. for 0.5 h before the addition of H_2O (20 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 15 mL), dried (Na_2SO_4), and evaporated under reduced pressure. Purification of the resultant residue by flash chromatography (silica gel, EtOAc–hexanes, 3:2) afforded adduct **10**.

Yield: 0.5 g (70%); syrup.

IR ($CHCl_3$): 3490, 1641 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.24 (d, *J* = 5.2 Hz, 1 H), 5.06 (dd, *J* = 8.4, 5.6 Hz, 1 H), 4.85 (m, 1 H), 4.56 (m, 1 H), 4.39 (dd, *J* = 10, 5.2 Hz, 1 H), 3.96 (m, 1 H), 3.81 (dd, *J* = 9.2, 3.6 Hz, 1 H), 3.47 (d, *J* = 12.4 Hz, 1 H, D_2O exch), 2.81 (m, 1 H), 2.24 (d, *J* = 12 Hz, 1 H, D_2O exch), 1.9 (m, 3 H), 1.7 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.9, 101.7, 73.5, 73.3, 70.2, 68.5, 66.7, 33.2, 26.0.

HRMS (FAB): *m/z* $[M + Na]^+$ calcd for $C_{10}H_{14}NaO_4$: 221.0801; found: 221.0790.

3,11-Dioxatricyclo[5.3.1.1^{2,6}]dodec-4-ene-10,12-diyl Diacetate (11)

Et_3N (2.1 mL, 15 mmol), Ac_2O (1.4 mL, 14.8 mmol), and DMAP (cat.) were added to a soln of **10** (1.22 g, 6.2 mmol) in anhyd CH_2Cl_2 (20 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h, and then warmed to r.t. and stirred for a further 3 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and the organic layer was washed with sat. aq $NaHCO_3$ (3 × 10 mL) and brine (20 mL) and dried (Na_2SO_4). The crude reaction mixture was filtered and concentrated under reduced pressure. Purification of the resultant residue by flash chromatography (silica gel, EtOAc–hexanes, 2:3) afforded the desired adduct **11**.

Yield: 1.63 g (94%); white crystalline solid; mp 100–101 °C.

IR ($CHCl_3$): 1731, 1640 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.32 (d, *J* = 5.2 Hz, 1 H), 5.04 (m, 2 H), 4.9 (m, 1 H), 4.78 (m, 1 H), 4.54 (m, 1 H), 4.29 (dd, *J* = 9.6, 6 Hz, 1 H), 2.93 (m, 1 H), 2.08 (s, 3 H), 2.07 (s, 3 H), 2.19–1.94 (m, 2 H), 1.78 (m, 1 H), 1.60 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 170.3, 143.6, 100.1, 70.6, 70.3, 69.8, 68.9, 31.1, 26.0, 21.4, 21.3.

HRMS (FAB): *m/z* $[M + Na]^+$ calcd for $C_{14}H_{18}NaO_4$: 305.1014; found: 305.1001.

10,12-Bis(benzyloxy)-3,11-dioxatricyclo[5.3.1.1^{2,6}]dodec-4-ene (12)

NaH (3.2 g, 60%, prewashed) was added to a soln of compound **10** (1.5 g, 7.6 mmol) in THF (50 mL) at 0 °C. The resultant mixture was stirred for 0.5 h before the addition of BnBr (1.79 mL, 2 equiv, 15 mmol) and TBAI (0.01 equiv) and was then stirred for 24 h. The reaction mixture was quenched by slow addition of cold sat. aq NH_4Cl and extracted several times with Et_2O. The organic phase was washed with H_2O (2 × 20 mL) and brine (20 mL) and dried (Na_2SO_4). The crude reaction mixture was filtered and concentrated under reduced pressure. Purification of the resultant residue by flash chromatography (silica gel, EtOAc–hexanes, 2:3) afforded adduct **12**.

Yield: 2.2 g (77%); viscous liquid.

IR ($CHCl_3$): 1640 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 10 H), 6.29 (d, *J* = 5.5 Hz, 1 H), 4.91 (dd, *J* = 8.2, 5.7 Hz, 1 H), 4.74 (m, 1 H), 4.61 (m, 4 H), 4.43 (dd, *J* = 14, 6.2 Hz, 1 H), 4.27 (dd, *J* = 10, 6.2 Hz, 1 H), 3.8 (m, 1 H), 3.68 (m, 1 H), 2.79–2.72 (m, 1 H), 2.1 (m, 1 H), 1.83 (m, 1 H), 1.71 (m, 1 H), 1.62 (m, 1 H).

^{13}C NMR (300 MHz, $CDCl_3$) δ = 143.9, 139.1, 128.6, 128.5, 128, 127.7, 100.6, 76.0, 74.3, 71.8, 71.4, 69.4, 31.5, 26.6, 22.9.

HRMS (FAB): *m/z* $[M + Na]^+$ calcd for $C_{24}H_{26}NaO_4$: 401.1719; found: 401.1729.

3,8-Bis(benzyloxy)-4-(2-hydroxyethyl)-9-oxabicyclo[3.3.1]nonan-2-ol (14)

Preparation of the acid resin: The commercial Dowex 50W X4 resin (H^+ form, 50 g, 50–100 mesh) was washed with H_2O (3 × 100 mL) until the filtrate was colorless and then with reagent grade MeCN (10 × 70 mL). It was then dried over P_2O_5 in a desiccator under vacuum (0.5 Torr) for 1 d to give the dry resin.

The acidic resin (207 mg) and H_2O (0.45 mL) were added to a soln of **12** (0.5 g, 1.37 mmol) and LiBr (0.357 g) in MeCN (15 mL). The mixture was stirred at r.t. for 0.5 h. The soln was filtered, neutralized with Et_3N, and evaporated to dryness. The residue was dissolved in CH_2Cl_2 (60 mL), washed successively with H_2O (10 mL), ice-cold 1 M aq HCl (10 mL), and sat. aq $NaHCO_3$ (3 × 10 mL), and dried (Na_2SO_4). The crude reaction mixture was filtered and concentrated under reduced pressure. Generally, purification of this compound (**13**) is not necessary, and it was used directly in the next step.

A soln of **13** (0.1 g, 0.25 mmol) in MeOH (5 mL) at 0 °C was treated with $NaBH_4$ (0.015 g, 0.39 mmol) in portions. The reaction mixture was stirred for 1 h and quenched by the addition of H_2O (1 mL) and CH_2Cl_2 (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with brine (5 mL) and dried (Na_2SO_4). The crude reaction mixture was filtered and concentrated under reduced

pressure. Purification of the resultant residue by flash chromatography (silica gel, EtOAc–hexanes, 3:2) afforded adduct **14**.

Yield: 0.1 g (100%); syrup.

IR (neat): 3472 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.26 (m, 10 H), 5.20 (d, *J* = 11 Hz, AB system, 1 H), 4.70 (d, *J* = 11 Hz, AB system, 1 H), 4.67 (d, *J* = 11.7 Hz, AB system, 1 H), 4.61 (d, *J* = 11.7 Hz, AB system, 1 H), 4.30 (m, 1 H), 4.16 (dd, *J* = 8, 6.2 Hz, 1 H), 4.0–3.93 (m, 1 H), 3.79 (m, *J* = 9, 3.6 Hz, 2 H), 3.69–3.56 (m, 2 H), 3.2 (br, 2 H), 2.18–1.4 (m, 7 H).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 138.2, 136.9, 128.6, 128.4, 128.3, 128.2, 127.8, 127.7, 83.5, 78.4, 77.7, 74.6, 71.8, 71.3, 69.3, 61.5, 42.9, 33.6, 26.9, 24.0.

3,8-Bis(benzyloxy)-4-[2-(*tert*-butyldimethylsiloxy)ethyl]-9-oxabicyclo[3.3.1]nonan-2-ol (15)

TBDMSCl (0.023 g, 0.15 mmol) and imidazole (0.022 g, 0.32 mmol) were added to a soln of diol **14** (0.05 g, 0.13 mmol) in THF–DMF (3:1, 5 mL) at 0 °C. After 1 h, the mixture was poured into Et_2O (20 mL) and the Et_2O layer was washed with H_2O (2 × 5 mL) and sat. aq $NaHCO_3$ (5 mL), and dried (Na_2SO_4). The crude reaction mixture was filtered and concentrated under reduced pressure. Purification of the resultant residue by flash chromatography (silica gel, EtOAc–hexanes, 3:7) afforded **15**.

Yield: 0.57 g (85%); oil.

IR (neat): 3491 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.4–7.3 (m, 10 H), 5.11 (d, *J* = 10.9 Hz, AB system, 1 H), 4.68 (d, *J* = 10.9 Hz, AB system, 1 H), 4.66 (d, *J* = 11.7 Hz, AB system, 1 H), 4.67 d, *J* = 11.4 Hz, AB system, 1 H), 4.27 (overlapped dd, *J* = 5.5 Hz, 1 H), 4.11 (overlapped dd, *J* = 7.6 Hz, 1 H), 3.93 (m, 2 H), 3.76–3.53 (m, 3 H), 2.16–1.25 (m, 8 H), 0.86 (s, 9 H), 0.0 (s, 6 H).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 139.2, 137.2, 128.7, 128.4, 128.3, 128.1, 127.9, 127.5, 83.7, 78.4, 77.9, 74.6, 71.7, 70.6, 69.3, 62.4, 43.6, 32.7, 26.9, 26.0, 23.9, 18.3, –5.4.

4-Allyl-3,8-bis(benzyloxy)-9-oxabicyclo[3.3.1]nonan-2-ol (16)

A 15% soln of *n*-BuLi in hexane (0.6 mL, 2 mmol) was added dropwise to a suspension of the phosphonium salt CH_3PPh_3I (0.68 g, 1.67 mmol) in anhyd THF (3.5 mL, 0.5 M) at –20 °C. The mixture was stirred at –20 °C to r.t. until all the solids had disappeared (ca. 0.5–1 h). A soln of **13** [0.48 g, 1.36 mmol, coevaporated with anhyd benzene (3 × 25 mL) before use] in THF (20 mL) was added to the reaction mixture at –20 °C, and the soln was stirred for 16 h while allowed to gradually come to r.t. An excess of reagent grade acetone (10–15 mL) was added and the mixture was stirred for 10 min; then Et_2O (70 mL) was added and the precipitated solid was removed by filtration over Celite. The Celite pad was washed with excess Et_2O, and the combined Et_2O extracts were washed with sat. aq $NaHCO_3$ (3 × 15 mL), H_2O (20 mL), and brine (10 mL). The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the resultant residue by flash chromatography (silica gel, EtOAc–hexanes, 1:3) afforded **16**.

Yield: 0.41 g (72%); pale yellow oil.

IR (neat): 3482, 1640 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.2 (m, 10 H), 5.76–5.63 (m, 1 H), 5.12 (d, *J* = 11.4 Hz, AB system, 1 H), 4.96 (m, 2 H), 4.74 (d, *J* = 11.4 Hz, AB system, 1 H), 4.60 (m, 2 H, benzylic), 4.28 (m, 1 H), 4.20–4.10 (m, 2 H), 3.96 (m, 1 H), 3.82 (m, 1 H), 3.66 (dd, *J* = 10.6, 8 Hz, 1 H), 2.20 (m, 2 H), 2.7 (m, 1 H), 1.87–1.60 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.1, 137.2, 136.3, 128.7, 128.4, 128.2, 127.9, 127.6, 116.3, 83.2, 78.5, 77.8, 74.7, 71.8, 70.0, 69.6, 44.8, 33.8, 26.9, 23.4.

HRMS (FAB): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{30}NaO_4$: 417.2027; found: 417. 2042.

4-Allyl-3,8-bis(benzyloxy)-9-oxabicyclo[3.3.1]nonan-2-one (17)

A soln of DMSO (0.12 mL, 1.6 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise to a soln of oxalyl chloride (0.05 mL, 0.71 mmol) in CH_2Cl_2 (2 mL) at –78 °C. After 5 min, a soln of alcohol **16** (0.225 g, 0.57 mmol) in CH_2Cl_2 (1 mL) was added. Stirring was continued for 20 min at –78 °C and Et_3N (0.4 mL, 2.9 mmol) was added dropwise. The resulting mixture was allowed to warm slowly to r.t. and stirred for 1 h. H_2O (5 mL) was added, and the organic layer was separated and concentrated under reduced pressure. The residue was diluted with Et_2O (50 mL), washed with H_2O (2 × 5 mL) and brine (5 mL), and dried (Na_2SO_4). The crude reaction mixture was filtered and concentrated under reduced pressure to give a residue that was purified by flash column chromatography (silica gel, EtOAc–hexanes, 1:4); this gave ketone **17**.

Yield: 0.19 g (83%); colorless crystals; mp 105 °C.

IR ($CHCl_3$): 1729, 1639 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.26 (m, 10 H), 5.72–5.63 (m, 1 H), 5.11 (d, *J* = 11 Hz, AB system, 1 H), 5.02 (m, 2 H), 4.71 (d, *J* = 11.6 Hz, AB system, 1 H), 4.57 (d, *J* = 11 Hz, AB system, 1 H), 4.52 (d, *J* = 11.6 Hz, AB system, 1 H), 4.45 (d, *J* = 6.4 Hz, 1 H), 4.0 (m, 1 H), 3.79 (d, *J* = 11.2 Hz, 1 H), 3.75 (dd, *J* = 11.2, 6 Hz, 1 H), 2.62–2.50 (m, 2 H), 2.16–1.83 (m, 4 H), 1.42–1.39 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.6, 137.8, 135.4, 128.6, 128.5, 128.4, 128.0, 127.9, 117.0, 82.7, 79.2, 74.3, 71.6, 70.8, 70.1, 48.4, 34.5, 26.3, 22.5.

HRMS (FAB): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{28}NaO_4$: 415.1811; found: 415.1886.

4-Allyl-3,8-bis(benzyloxy)-2-vinyl-9-oxabicyclo[3.3.1]nonan-2-ol (18)

A 1 M soln of vinylmagnesium bromide in THF (6 mL, 6 mmol) was added to a soln of ketone **17** (0.09 g, 0.3 mmol) in THF (20 mL) at –78 °C. After the mixture had stirred for 15 min at –78 °C, it was allowed to warm to 0 °C over 1 h. Sat. aq NH_4Cl was added (5 mL) and the mixture was extracted with Et_2O (3 × 15 mL). The organic layer was washed with brine (5 mL) and dried (Na_2SO_4). The crude reaction mixture was filtered and concentrated under reduced pressure. Purification of the resultant residue by flash column chromatography (silica gel, EtOAc–hexanes, 3:7) afforded **20**.

Yield: 0.076 g (79%); viscous oil.

IR (neat): 3450, 1640 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.26 (m, 10 H), 6.44 (dd, *J* = 17.2, 10.8 Hz, 1 H), 5.73–5.61 (m, 1 H), 5.63 (dd, *J* = 17.2, 2.4 Hz, 1 H), 5.27 (dd, *J* = 10.8, 2.4 Hz, 1 H), 5.06–4.96 (m, 4 H), 4.69–4.57 (m, 3 H), 3.96–3.80 (m, 4 H), 2.70 (m, 1 H), 2.22–1.67 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.8, 138.7, 136.8, 136.0, 128.5, 128.2, 128.0, 127.7, 127.3, 116.3, 113.6, 84.2, 79.6, 77.9, 74.6, 73.9, 71.7, 70.3, 43.5, 33.8, 26.8, 23.6.

HRMS (FAB): *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{32}NaO_4$: 443.2209; found: 443.2199.

3,8-Bis(benzyloxy)-4-(2-oxopropyl)-9-oxabicyclo[3.3.1]nonan-2-one (20)

$PdCl_2$ (0.12 g, 0.68 mmol) was added to a soln of **17** (0.1 g, 0.26 mmol) in DMF (50 mL) and H_2O (7.1 mL) at 0 °C, and the mixture was stirred at r.t. for 3 h. Then phosphate buffer (pH 7) was added at 0 °C. The mixture was diluted with Et_2O (2 × 50 mL), and the organic layer was washed with H_2O (3 × 10 mL) and brine (10 mL), and dried (Na_2SO_4). The crude reaction mixture was filtered and

concentrated under reduced pressure. Purification of the resultant residue by flash chromatography (silica gel, EtOAc–hexanes, 3:2) afforded the diketone **20**.

Yield: 0.098 g (94%); white solid; mp 95 °C.

IR ($CHCl_3$): 1721 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.26 (m, 10 H), 5.04 (d, *J* = 10.8 Hz, 1 H), 4.69 (d, *J* = 12 Hz, 1 H), 4.52–4.45 (m, 3 H), 4.14 (t, *J* = 4.8 Hz, 1 H), 3.89 (d, *J* = 11.6 Hz, 1 H), 3.78–3.75 (m, 1 H), 2.99–2.92 (m, 1 H), 2.65 (dd, *J* = 16, 5.6 Hz, 1 H), 2.26 (dd, *J* = 16, 8.8 Hz, 1 H), 2.16–2.10 (m, 1 H), 2.07 (s, 3 H), 1.94–1.80 (m, 2 H), 1.48–1.41 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.3, 204.3, 137.3, 137.1, 129.6, 128.8, 128.6, 128.3, 127.9, 127.7, 127.6, 81.8, 79, 74, 71.2, 70.7, 69.8, 44.9, 44.4, 29.7, 26, 22.8.

HRMS (FAB): *m/z* $[M + Na]^+$ calcd for $C_{25}H_{28}NaO_5$: 431.1829; found: 431.1835.

Supporting Information for this article is available online at http://www.thieme-connect.de/ejournals/toc/synthesis. It contains the optimized geometries for all the stationary points obtained at the B3LYP/6-31G* levels of theory, total electronic energies, and IRC plots of transition states.

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(15) CCDC 232578 (**8**), 232579 (**11**), and 735916 (**17**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
X-ray crystallographic data for **8**: CCDC 232578, empirical formula $C_{12}H_{16}O_5$, formula weight 240.25, *T* = 293(2) K, λ = 0.70930 Å, crystal system monoclinic, space group *P*21/*n*, unit cell dimensions *a* = 7.4888(5) Å, α = 90.000°, *b* = 15.2345(11) Å, β = 98.888(5)°, *c* = 10.0221(5) Å, γ = 90.000°, *V* = 1129.67(12) $Å^3$, *Z* = 4, D_{calcd} = 1.413 Mg/m^3, absorption coefficient 0.110 mm^{-1}, *F*(000) = 512, crystal size 0.35 × 0.30 × 0.20 mm, data collection θ range 2.45–25.01°, index ranges $0 \le h \le 8$, $0 \le k \le 18$, $-11 \le l \le 11$, reflections collected 1875, unique 1875 [*R*(int) = 0.0000], refinement method full-matrix least-squares on F^2, data/restraints/parameters 1875/0/220, goodness-of-fit on F^2 1.134, final *R* indices [$I > 2\sigma(I)$] *R*1 = 0.0539, *wR*2 = 0.1481, *R* indices (all data) *R*1 = 0.0571, *wR*2 = 0.1524, largest diff. peak and hole 0.249 and –0.394 e·$Å^{-3}$.
X-ray crystallographic data for **11**: CCDC 232579, empirical formula $C_{14}H_{18}O_6$, formula weight 282.28, *T* = 293(2) K, λ = 0.70930 Å, crystal system: monoclinic, space group *P*21/*n*, unit cell dimensions *a* = 10.5020(13) Å,

b = 10.6560(10) Å, c = 12.9850(18) Å, β = 109.664(10)°, V = 1368.4(3) Å^3, Z = 4, D_{calcd} = 1.370 Mg/m^3, absorption coefficient 0.107 mm^{-1}, F(000) = 600, crystal size 0.4 × 0.35 × 0.35 mm, data collection θ range 2.17–24.90°, index ranges $0 \le h \le 12$, $0 \le k \le 12$, $-15 \le l \le 14$, reflections collected 1840, unique 1840 [R(int) = 0.0000], refinement method full-matrix least-squares on F2, data/restraints/parameters 1840/0/253, goodness-of-fit on F^2 1.023, final R indices [$I > 2\sigma(I)$] $R1$ = 0.0711, $wR2$ = 0.1712, R indices (all data) $R1$ = 0.0875, $wR2$ = 0.1823, largest diff. peak and hole 0.339 and –0.283 e·Å^{-3}.

X-ray crystallographic data for **17**: CCDC 735916, empirical formula $C_{25}H_{28}O_4$, formula weight 392.47, T = 293(2) K, λ = 0.70930 Å, crystal system monoclinic, space group $P21/c$, unit cell dimensions a = 7.550(5) Å, b = 24.686(3) Å, c = 11.4950(10) Å, β = 90.116(7)°, V = 2087.1(3) Å^3, Z = 4, D_{calcd} = 1.249 Mg/m^3, absorption coefficient 0.083 mm^{-1}, F(000) = 840, crystal size 0.4 × 0.4 × 0.35 mm, data collection θ range 1.65–24.92°, index ranges $0 \le h \le 8$, $0 \le k \le 29$, $-13 \le l \le 13$, reflections collected 3074, unique 3074 [R(int) = 0.0000], refinement method full-matrix least-squares on F2, data/restraints/parameters 3074/0/375, goodness-of-fit on F^2 1.065, final R indices [$I > 2\sigma(I)$] $R1$ = 0.0423, $wR2$ = 0.0983, R indices (all data) $R1$ = 0.0620, $wR2$ = 0.1107, largest diff. peak and hole 0.183 and –0.162 e·Å^{-3}.

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