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Benzannulated Cyclooctanol Derivatives by Samarium Diiodide Induced Intramolecular Carbonyl–Alkene Coupling – Scope, Limitations, Stereoselectivity

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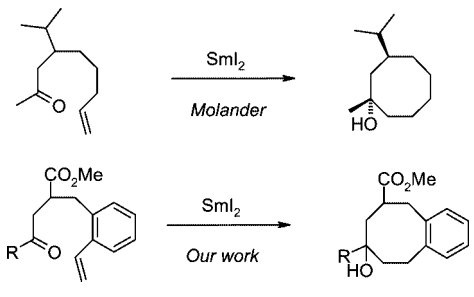
A series of γ-oxo esters **27**–**34** was prepared from methyl 2-silyloxycyclopropanecarboxylates **1**–**9** as key building blocks in a flexible modular synthesis. Their samarium diiodide promoted cyclization to benzannulated cyclooctanol derivatives was systematically investigated. Samarium ketyl compounds derived from aldehydes **27** and **28** mainly provided tricyclic γ-lactones **38** and **39** as a result of a *cis*-selective ring-closure process, whilst the related ketones **29**–**31** underwent *trans*-selective reductive cyclization to furnish the expected benzannulated cyclooctanol derivatives **43**–**45** in moderate to excellent yields. With cyclohexanones **33** and **34** an interesting stereochemical matched/mismatched situation was observed. Whereas diastereomers **33a** and **34a** smoothly afforded tricyclic products **47** and **48** in good yields, compound **33b** with apparently mismatched configuration did not undergo the samarium diiodide promoted ring-closure process. An explanation for this intriguing behaviour is presented, together with an explanation for the *cis*/*trans* selectivity. Tricyclic γ-lactone **38** could be smoothly deprotonated at one bridgehead and the generated lithium enolate was trapped with suitable alkyl halides. Remarkably, a clean α-hydroxylation of **38** and **39** by direct employment of molecular oxygen was possible, providing high yields of the corresponding tertiary alcohols **54** and **55**. These results demonstrate that the cyclization products prepared can easily be converted into higher functionalized benzannulated cyclooctane derivatives.

Introduction

The development of new synthetic methods for the stereoselective creation of eight-membered rings has received considerable attention during the last two decades,[1] this search certainly having been motivated by the occurrence of functionalized cyclooctane moieties in structurally interesting natural products, some of them of particular importance due to their biologically activity (e.g., taxol and related compounds).[2] In general, the formation of eight-membered rings is not very favourable because of the constraints generated during their construction.[3] Despite these obstacles, however, surprisingly efficient and flexible methods have been found.[4] One of the newer reaction modes for the construction of eight-membered rings is the cyclization of samarium ketyl compounds to olefins;[5] pioneering investigations by Molander et al.[6] demonstrated with simple model compounds that 8-*endo*-*trig* cyclizations of samarium ketyl compounds to produce cyclooctanol derivatives in fair yields are possible. One example is depicted in Scheme 1. Because of the occurrence of the bicyclo[6.4.0]-undecane core in taxol we were interested in synthesizing this unit[7] by a samarium ketyl promoted cyclization of styrene-type precursors, which would be expected to gain additional driving force by benzylic stabilization of the intermediates involved during the 8-*endo*-*trig* reaction. We have already reported our preliminary results[8] and now wish to present full details showing the scope and limitations of the method, as well as some intriguing stereochemical features.



Scheme 1.

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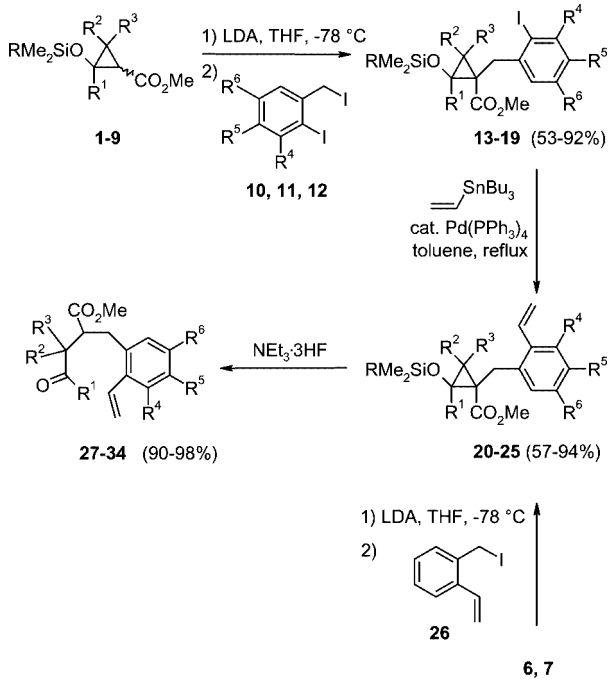
Results

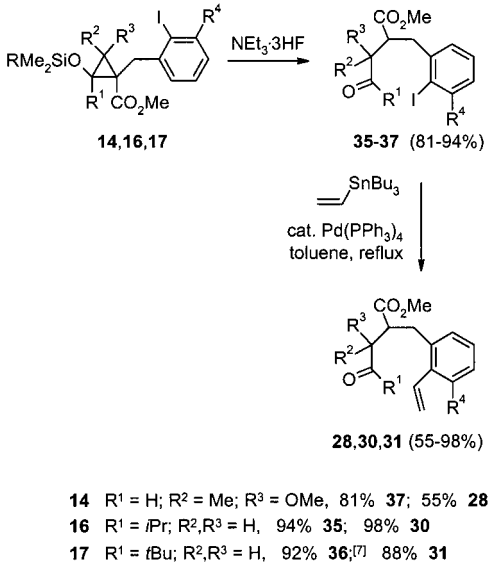
Precursor Synthesis

The model substrates for cyclization studies were prepared by a reliable modular approach employing methyl 2-silyloxycyclopropanecarboxylates **1**–**5** and **8**–**9** as precursors (Scheme 2).[9] Their deprotonation with LDA and subsequent treatment with 1-iodo-2-(iodomethyl)benzene derivatives **10**, **11** or **12** provided the benzyl-substituted cyclopropanes **13**–**19** in moderate to excellent yields. Subsequent Stille coupling with tributylvinylstannane under standard conditions[10] furnished styrene derivatives **20**, **21**, **24** and **25**, and ensuing fluoride-induced ring cleavage afforded the desired cyclization precursors **27**–**34** in excellent yields (for substituents and individual yields see Table 1). Styrene derivatives **22** and **23** were prepared by a shortened reaction sequence by direct alkylation of methyl cyclopropanecarboxylates **6** and **7** with 2-vinylbenzyl iodide (**26**).



Scheme 2. (For R, R^1-R^6 see Table 1.).

Syntheses of precursors **28**, **30** and **31** were accomplished by an inverted sequence in which cyclopropane derivatives **14**, **16** and **17** were first ring-opened to give oxo esters **35**, **36** and **37**, which were then converted into the required styrene derivatives with reasonable overall efficacy by Stille coupling (Scheme 3). In summary, the preparation of the required starting materials by our flexible route via donor/acceptor-substituted cyclopropanes[11] was easy to achieve and smoothly allowed generation of different substitution patterns.



Scheme 3.

Cyclization Experiments

Cyclization reactions were generally performed in THF as solvent with 2.2 equiv. of samarium diiodide (generated from samarium metal with 1,2-diiodoethane) in the presence of 18 equiv. of HMPA and 2 equiv. of *tert*-butyl alcohol. The use of the very strong donor ligand HMPA is required to increase the reduction ability of samarium diiodide[12] – without this additive samarium ketyl formation and couplings are generally not efficient. A search aimed at substitution of this carcinogenic reagent by suit-

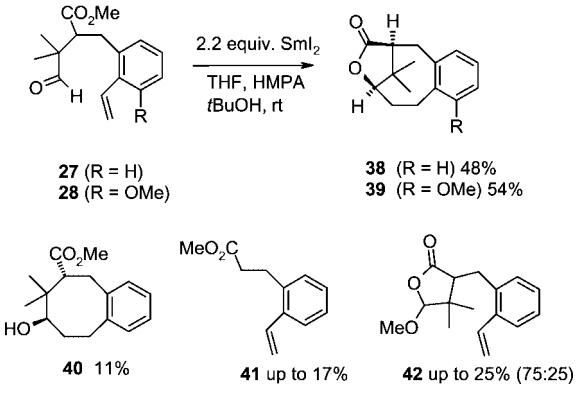
Table 1. Substitution patterns of compounds **1**–**9**, **13**–**19**, **20**–**25** and **27**–**34** (Schemes 2 and 3).

Entry	Starting material	R	R^1	R^2	R^3	Alkylating agent	R^4	R^5	R^6	Products		
1	**1**	Me	H	Me	Me	**10**	H	H	H	**13** 92%[a]	**20** 86%	**27** 98%
2	**2**	Me	H	Me	Me	**11**	OMe	H	H	**14** 78%[a]	–	**28** 55%[b]
3	**3**	*t*Bu	Me	H	H	**10**	H	H	H	**15** 87%[c]	**21** 76%	**29** 97%
4	**4**	Me	*i*Pr	H	H	**10**	H	H	H	**16** 53%	–	**30** 98%[b]
5	**5**	*t*Bu	*t*Bu	H	H	**10**	H	H	H	**17** 52%[c]	–	**31** 88%[b]
6	**6**	*t*Bu	Ph	H	H	**26**	H	H	H	–	**22** 65%	**32** 99%
7	**7**	Me	$-(CH_2)_4-$		H	**26**	H	H	H	–	**23** 57%	**33** 97%[d]
8	**8**	*t*Bu	$-(CH_2)_4-$		H	**10**	H	H	H	**18** 84%	**24** 72%	**33** 90%[d]
9	**9**	Me	$-(CH_2)_4-$		H	**12**	H	OMe	OMe	**19** 88%	**25** 94%	**34** 91%

[a] Mixture of *trans* and *cis* isomers (ca. 75:25). [b] Compound was prepared by an alternative route (see Scheme 3). [c] Result taken from ref.[7] [d] Mixture of 2 diastereomers (1:1).

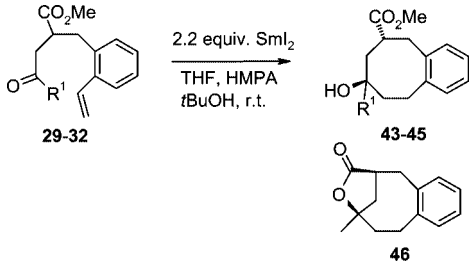
able alternatives has not so far provided a general solution.[13]

Treatment of styryl-substituted aldehydes **27** and **28** under these standard conditions provided tricyclic compounds **38**[14] and **39** in approximately 50% yields. Obviously, the ketyl–olefin coupling to form the eight-membered ring was followed by an intramolecular attack of the samarium alkoxide on the *cis*-positioned methoxycarbonyl group to form the γ-lactone ring (Scheme 4). This treatment of **27** also furnished the diastereomeric cyclization product **40**, which cannot form a γ-lactone ring, as a by-product. In addition, fragmentation product **41** and compound **42** were isolated in varying yields. Reductive cleavages of C–C bonds of 1,4-dicarbonyl compounds are known in the literature[15] and apparently also occur to some extent with the precursor compounds employed in this study, which may be the reason for the moderate mass balances of several cyclization experiments, although fragmentation products such as **41** were not always actually isolated. γ-Methoxy-substituted γ-lactone **42** is probably the result of a Lewis acid catalysed rearrangement of starting material **27**.[16] The acting Lewis acid can either be samarium diiodide or one of the generated samarium(III) compounds. When the cyclization of **27** was attempted with samarium diiodide in the presence of nickel diiodide,[17] compound **42** was isolated in as much as 87% yield.



Scheme 4.

Whereas aldehydes **27** and **28** furnished tricyclic γ-lactones **38** and **39** as major or exclusive products as a result of *cis*-selective cyclization,[18] the stereochemical outcome was different when alkyl ketones **29**–**31** were used as precursors in the samarium ketyl–alkene cyclization process. Methyl ketone **29** furnished the benzannulated cyclooctanol derivative **43** as the major component (Scheme 5), but the tricyclic product **46** originating from the diastereomeric cyclization intermediate was also isolated in 10% yield. With bulkier carbonyl substituents such as isopropyl (precursor **30**) or *tert*-butyl (precursor **31**) the samarium ketyl cyclization was highly *trans*-selective[18] and only products **44** and **45** were found. The conversion of isopropyl ketone **30** into compound **44** was remarkably efficient – the yield of 84% was excellent considering the generally unfavourable nature of the formation of eight-membered rings.[3] The assignment of the *trans* diastereomers is in part based on observed coupling constants in the ^{1}H NMR spectra, but also on the fact that these compounds did not form the corresponding γ-lactones (even under treatment with catalytic amounts of acid).

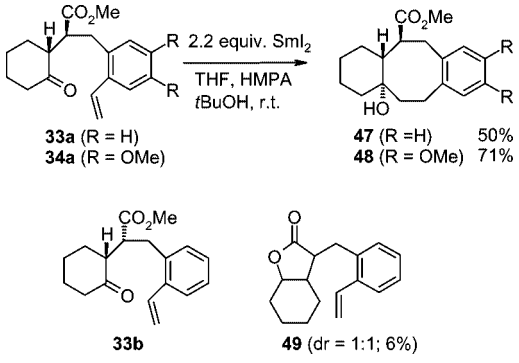


	R^1	Product	Yield
29	Me	**43**, **46**	31%, 10%
30	*i*Pr	**44**	84%
31	*t*Bu	**45**	39%
32	Ph	--	--

Scheme 5.

Phenyl ketone **32**, in contrast, did not undergo cyclization to the expected cyclooctanol derivative under the standard conditions employed, with starting material mainly being recovered instead (Scheme 5). Since the ketyl compound of **32** should actually be formed more easily we have to assume that its higher stability, and thus the lower driving force for cyclization, prevent the formation of a product. This and a similar result with a compound bearing an isopropenyl group instead of the phenyl substituent support our opinion that the ketyl formation and the cyclization step are equilibrium reactions (see discussion below and Scheme 8).[19]

The two diastereomers of cyclohexanone derivatives **33** and **34** were easily separated by chromatography. Interestingly, only the *unlike* diastereomers[20] underwent smooth samarium diiodide promoted cyclization, whilst oxo ester **33a**, with the matching *unlike* configuration, furnished a moderate yield of the desired tricyclic product **47** (Scheme 6). The configuration of **47** was confirmed by an



Scheme 6.

X-ray analysis, which also revealed a boat conformation of the central eight-membered ring (Figure 1).[21] As a by-product a small amount of compound **49** was isolated, apparently formed by simple reduction of the carbonyl group with subsequent lactonization. The mismatched *like* diastereomer **33b** was essentially inert to samarium diiodide and starting material was mainly recovered. We also isolated **41** in 15% yield (see Scheme 4), which is again the result of the reductive fragmentation of 1,4-dicarbonyl compounds discussed above. Dimethoxy-substituted precursor **34a** with the matching *unlike* configuration cyclized very smoothly under standard conditions and provided the expected product **48** in 71% yield (99% yield when recovered **34a** is taken into account).

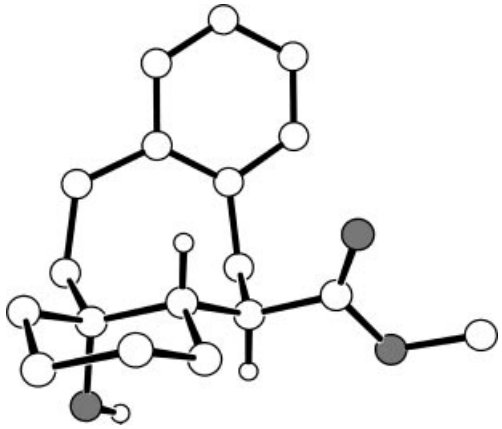
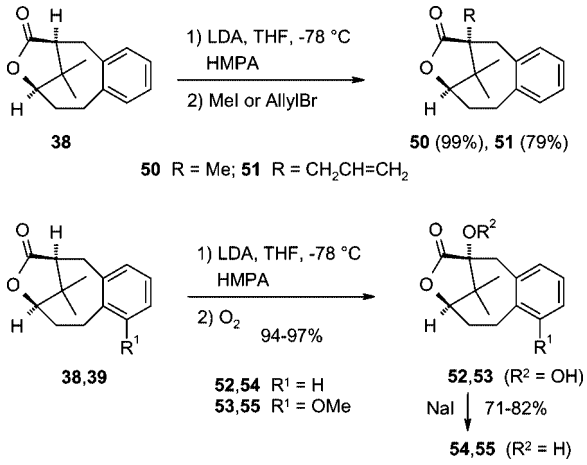


Figure 1. Benzocyclooctanol derivative **47** (only selected hydrogen atoms are depicted).

Subsequent Reactions

Tricyclic compounds **38** and **39** each bear a geminal dimethyl moiety, as present in the taxol structure, and hence served as model substrates for functionalization at the bridgehead position. Deprotonation of **38** with LDA and treatment with electrophiles such as methyl iodide and allyl bromide in the presence of HMPA furnished the alkylation products **50** and **51** in very good yields (Scheme 7). Less reactive alkylating agents could also be used, but the yields of substitution products were disappointingly low.[22] During these experiments we unexpectedly discovered that α-hydroxylation of lactones **38** and **39** occurred in the presence of traces of oxygen. This observation proved to be exploitable, with this synthetically valuable hydroxylation process being performed intentionally[23] by generating the lithium enolates of **38** and **39** and subsequent treatment with dry oxygen. The resulting hydroperoxides **52** and **53** were smoothly converted into the desired α-hydroxy-γ-lactones **54** and **55** by reduction with sodium iodide. These experiments demonstrate that substitution and functionalization at the bridgehead positions in compounds such as **38** are easily performed with reactive electrophiles although the intermediate enolates formally break Bredt's rule.[24]

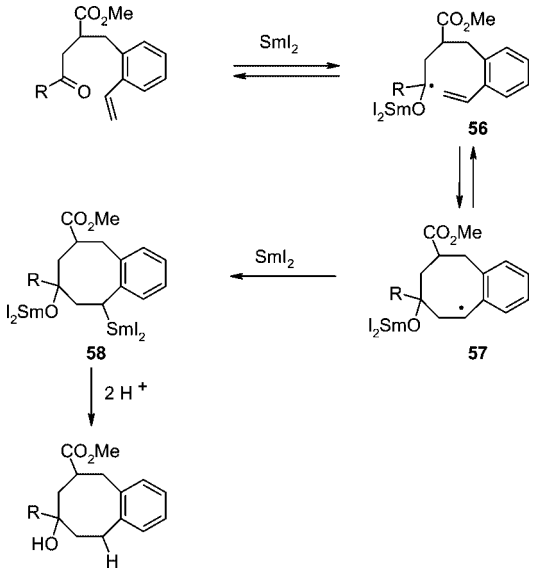


Scheme 7.

Discussion

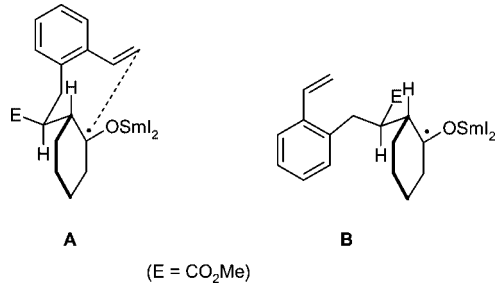
The mechanism of the 8-*endo*-*trig* cyclizations of styrene derivatives as described above is straightforward in light of related reactions.[5,6] Formation of samarium ketyl **56** is followed by its attack at the terminal carbon atom of the styrene unit to provide a benzyl radical **57**, which accepts an electron from the second equivalent of samarium diiodide to generate the benzylic samarium species **58**. Protonation by *tert*-butyl alcohol (and during aqueous workup) provides the isolated benzannulated cyclooctanol derivative (Scheme 8). We assume that the first two steps of this sequence are reversible, a hypothesis supported by the recovery of starting material when the cyclization is unfavourable (e.g., substrate **32**). Although we have no real proof for this suggestion, the stabilities of the two intermediates **56** and **57** should be fairly similar and so an equilibrium can reasonably be assumed. Even the formation of samarium species **58** from radical **57** may be reversible according to literature precedence,[25] although we regard this as less likely in our system.

The reactivity of cyclohexanone derivatives **33** and **34** demonstrates that conformative prerequisites must be fulfilled to allow a successful formation of eight-membered rings. The matching configuration of **33a** and the resulting samarium ketyl may prefer a conformation with a pseudo-equatorially positioned methoxycarbonyl group, in which the proximity of the carbonyl group and the ethenyl group easily allows cyclization (**A** in Scheme 9). In contrast, the energetically most favourable conformation of mismatching diastereomer **33b** should arrange the carbonyl group and the accepting styrene unit into a *transoid* relationship, essentially preventing cyclization (**B** in Scheme 9). For the proposed transition structures we have sketched out some boat-like arrangements with respect to the forming eight-membered ring, which reflects the preferred conformation of product **47** as established by the X-ray analysis (see Figure 1).[21] This may also be valid in the transition structure leading to this compound. A similar dependence on the relative configuration of the cyclohexanone precursors has



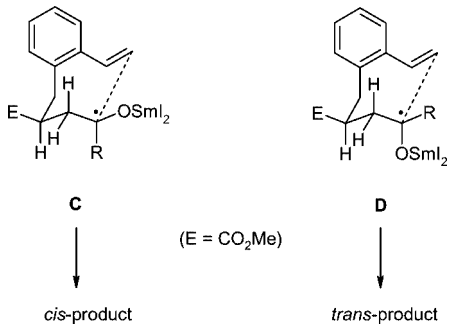
Scheme 8.

been observed during the samarium ketyl triggered cyclizations of related benzyl-substituted oxo esters to afford dearomatized hexahydronaphthalene derivatives.[26]



Scheme 9.

The *cis*/*trans* selectivity observed with respect to the methoxycarbonyl substituent and the generated hydroxy group can be interpreted in terms of a similar model. If the group R at the carbonyl carbon atom is small (hydrogen or methyl) the bulky samarium(III)oxy substituent can still occupy the preferred pseudoequatorial position in an eight-membered transition structure (**C** in Scheme 10) to afford a *cis* product. As R becomes bulkier, this group prefers the pseudoequatorial position and the samarium(III)oxy group is forced into a pseudoaxial position (**D** in Scheme 10). This arrangement would deliver products with *trans*-positioned functional groups. Unfortunately, we were unable to prepare the aldehyde analogous to **27** but without a geminal dimethyl system, which would allow a more unambiguous comparison of results. Nevertheless, the sequence of diastereoselectivities observed during cyclizations of **27**, **29**, **30** and **31**, showing high *cis* selectivity with **27** and exclusive *trans* product formation with **31**, is consistent with the suggested transition structure model.



Scheme 10.

Conclusions

In this report we have been able to demonstrate that a series of styryl-substituted oxo esters can be cyclized with samarium diiodide to provide benzannulated cyclooctanol derivatives in moderate to good yields. These results nicely supplement our investigations of alkynyl-substituted compounds that provided the corresponding cyclooctenols fused to a benzene ring.[27] Furthermore, certain stereochemical features were discovered and interpreted by transition structure models taking into account the preferred conformations of the precursors and the samarium ketyl compounds derived from them. Particularly interesting results have been obtained with the pair of diastereomers containing the cyclohexanone moiety. The products are suitable for further synthetic manipulations providing higher substituted benzannulated cyclooctane derivatives. With tricyclic γ-lactones **38** and **39** as starting materials we were able to easily perform enolate chemistry at the bridgehead carbon atoms, introducing new alkyl substituents or a hydroxy group. Future investigations will deal with the role of additional substituents at the alkenyl moiety of the precursor molecules, which may not only steer the regioselectivity (formation of seven-membered vs. eight-membered rings) but also the diastereoselectivity.[28]

Experimental Section

General: All reactions were performed under argon in flame-dried flasks, and the components were added by syringe. All solvents were dried by standard methods. Thin layer chromatography (TLC) was carried out on commercial Polygram Sil G/UV_{254} or Polygram Alox N/UV_{254} (Macherey & Nagel). Column chromatography was performed with 70–230 mesh silica gel (Merck) or neutral aluminium oxide (activity grade III; Fluka or Merck). Unless stated otherwise, ^1H NMR and ^{13}C NMR spectra were determined with Bruker AC 200, AC 300, DRX 500 or Jeol Eclipse 500 instruments in $CDCl_3$ solution. The chemical shifts are related to TMS or to the $CDCl_3$ signal (δ_H = 7.26 ppm; δ_C = 77.0 ppm). IR spectra were measured with a Nicolet 205 FT-IR spectrometer and gas-phase IR spectra were measured with an HP5965B FT-IRD spectrometer (Hewlett–Packard). Melting points are uncorrected. Boiling points of compounds obtained in small-scale experiments refer to the temperature in a Büchi Kugelrohrofen. MS and HRMS analyses were performed with Finnigan MAT 711 (EI = 80 eV, 8 kV), MAT 95 (EI = 70 eV), MAT CH7A (EI = 80 eV, 3 kV) and CH5DF (FAB

= 80 eV, 3 kV) instruments. The GC-MS data were recorded with a Hewlett–Packard HP 5890 (series II) and a HP 5972 MS-selective detector. Operating conditions were as follows: start temperature 70 °C, programmed to 310 °C at 10 °C min^{-1}. Compounds **10**, **11** and **26** were prepared according to known or analogous procedures.[29] Preparation of starting materials and intermediates **12**–**31** is described in the Supporting Information.

SmI_2-Induced Intramolecular Cyclization. General Procedure 1: Samarium metal (2.4 equiv.) was placed under a flow of argon in a flame-dried, two-necked round-bottomed flask containing a magnetic stirring bar and a septum inlet. The flask and the Sm were flame-dried. THF (12 mL/mmol of 1,2-diiodoethane) was added to the metal, followed by the addition of 1,2-diiodoethane (2.2 equiv.). The mixture was stirred at room temperature for 1 h. HMPA (18 equiv.) was added to this solution of SmI_2 (2.2 equiv.), and argon was bubbled through the solution for 10 min. A solution of the styrene derivative (1 equiv.) and *t*BuOH (2 equiv.) in THF (40 mL/mmol of substrate) was added over 1.5 h. The mixture was stirred at room temperature for 16 h. The mixture was quenched with satd. aqueous $NaHCO_3$ solution (20 mL/mmol of substrate), the phases were separated, and the aqueous layer was extracted with diethyl ether (3 × 15 mL/mmol of substrate). The combined organic layers were washed with water and brine (10 mL/mmol of substrate) and dried (Na_2SO_4).

SmI_2-Induced Intramolecular Cyclization of 27. a) The reaction was performed as described in General Procedure 1, with **27** (0.600 g, 2.29 mmol), SmI_2 (7.51 mmol), HMPA (10.7 mL, 60.9 mmol) and *t*BuOH (0.339 g, 4.58 mmol). The crude product was purified by column chromatography (alumina, ethyl acetate/hexane 10%) to furnish **41** (0.008 g, 2%), **42** (0.069 g, 11%, mixture of two diastereomers = 3:1), **38** (0.252 g, 48%) and finally **40** (0.063 g, 11%). **b)** In the presence of NiI_2.[17] The reaction was performed as described in General Procedure 1, with **27** (0.403 g, 1.55 mmol), SmI_2 (3.75 mmol), NiI_2 (5 mg, 0.016 mmol) and *t*BuOH (0.251 g, 3.39 mmol). The crude product was purified by column chromatography (alumina, ethyl acetate/hexane 10%) to furnish **42** (0.351 g, 87%, mixture of two diastereomers = 75:25).

14,14-Dimethyl-12-oxatricyclo[9.2.1.0^{3,8}]tetradeca-3(8),4,6-trien-13-one (38): Colourless crystals, m.p. 115–116 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.25–7.08 (m, 4 H, Ar), 4.27 (t, J = 3.5 Hz, 1 H, 11-H), 3.21 (dd, J = 2.1, 14.8 Hz, 1 H, 2-H), 3.09 (dd, J = 9.5, 14.8 Hz, 1 H, 2-H), 2.98 (dt, J = 3.4, 13.5 Hz, 1 H, 9-H), 2.68–2.60 (m, 2 H, 1-H, 9-H), 2.34–2.22 (m, 1 H, 10-H), 2.02 (qd, $J \approx$ 3.8, 15.2 Hz, 1 H, 10-H), 1.31, 1.20 (br s, s, 3 H each, Me) ppm. ^{13}C NMR ($CDCl_3$, 126.9 MHz): δ = 177.3 (s, C-13), 139.9, 136.6, 132.1, 129.4, 127.7, 126.5 (2 × s, 4 × d, Ar), 88.6 (d, C-11), 52.1 (d, C-1), 41.8 (s, C-14), 33.1, 31.2, 29.8 (3 × t, C-2, C-9, C-10), 33.3, 18.0 (2 × q, Me) ppm. IR (neat): $\tilde{\nu}$ = 3100–2850 (=C–H, C–H), 1765 (C=O) cm^{-1}. MS (EI = 70 eV): *m*/*z* (%) = 230 (84) [M]$^+$, 186 (52), 169 (27), 143 (42), 129 (45), 115 (51), 105 (41), 91 (26), 83 (100), 77 (14), 41 (19). $C_{15}H_{18}O_2$ (230.3): calcd. C 78.23, H 7.88; found C 78.62, H 8.27.

Methyl *trans*-8-Hydroxy-7,7-dimethyl-5,6,7,8,9,10-hexahydrobenzocyclooctene-6-carboxylate (40): ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.19–7.07 (m, 4 H, Ar), 3.69 (s, 3 H, CO_2Me), 3.41, 3.02–2.58 (m_c, m, 1 H, 3 H, 5-H, 6-H, 8-H), 1.79–1.22 (m, 5 H, 9-H, 10-H, OH), 0.92, 0.89 (2 × s, 6 H, 2 × Me) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 173.5, 51.6 (s, q, CO_2Me), 140.2, 138.2, 129.3, 128.9, 126.6, 126.2 (2 × s, 4 × d, Ar), 76.7 (d, C-8), 40.5 (s, C-7), 35.6, 33.7, 27.8 (3 × t, C-5, C-9, C-10), 35.3 (d, C-6), 18.8, 13.6 (2 × q, 2 × Me) ppm. IR (neat): $\tilde{\nu}$ = 3500 (O–H), 3100–2880 (=C–H, C–H), 1735 (C=O) cm^{-1}. MS (EI = 70 eV): *m*/*z* (%) = 262 (2) [M]$^+$, 216 (10), 198 (20), 145 (100), 91 (36), 42 (31). HRMS (80 eV): calcd. for $C_{16}H_{22}O_3$ 262.1569, found 262.1590.

Methyl 3-(2-Vinylphenyl)propanoate (41): ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.51–7.45, 7.26–7.10 (2 × m, 1 H, 3 H, Ar), 6.98, 5.66, 5.33 (ABX system, J_{AX} = 17.3 Hz, J_{BX} = 11 Hz, J_{AB} = 1.5 Hz, 1 H each, CH=CH_2), 3.68 (s, 3 H, CO_2Me), 3.06–2.98, 2.61–2.53 (2 × m, 2 H each, 2-H, 3-H) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 173.2, 51.6 (s, q, CO_2Me), 137.7, 136.5, 129.3, 127.9, 126.8, 126.0 (2 × s, 4 × d, Ar), 134.1, 116.1 (d, t, CH=CH_2), 35.1, 28.4 (2 × t, C-2, C-3) ppm. IR (neat): $\tilde{\nu}$ = 3100–2850 (=C–H, C–H), 1740 (C=O) cm^{-1}. $C_{12}H_{14}O_2$ (190.2): calcd. C 75.76, H 7.42; found C 75.53, H 7.57.

5-Methoxy-4,4-dimethyl-3-(2-vinylbenzyl)dihydrofuran-2(3*H*)-one (42): Mixture of diastereomers = 75:25. ^{1}H NMR ($CDCl_3$, 200 MHz): major diastereomer: δ = 7.49–7.45, 7.30–7.18 (2 × m, 1 H, 3 H, Ar), 6.99, 5.64, 5.35 (ABX system, J_{AX} = 17.3 Hz, J_{BX} = 10.9 Hz, J_{AB} = 1.5 Hz, 1 H each, CH=CH_2), 4.75 (s, 1 H, 5-H), 3.43 (s, 3 H, OMe), 3.22 (dd, J = 5.6, 14.1 Hz, 1 H, CH_2Ar), 2.91 (dd, J = 5.6, 8.5 Hz, 1 H, 3-H), 2.73 (dd, J = 8.5, 14.1 Hz, 1 H, CH_2Ar), 1.09, 0.81 (2 × s, 3 H each, 3-Me) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 177.9 (s, C-2), 136.7, 136.2, 134.4, 130.5, 127.0, 126.3 (2 × s, 4 × d, Ar), 127.6, 116.4 (d, t, CH=CH_2), 109.7 (d, C-5), 56.6 (q, OMe), 47.8 (d, C-3), 43.6 (s, C-4), 28.1 (t, *C*H_2Ar), 21.4, 20.5 (2 × q, 4-Me) ppm. Additional signals for the minor diastereomer: δ = 4.87 (s, 1 H, 5-H), 3.56 (s, 3 H, OMe), 3.28 (dd, J = 9.1, 14.0 Hz, 1 H, CH_2Ar), 1.03, 0.89 (2 × s, 3 H each, 3-Me) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 175.6 (s, C-2), 136.65, 136.0, 134.5, 130.5, 126.95, 126.4 (2 × s, 4 × d, Ar), 127.7, 116.3 (d, t, CH=CH_2), 110.3 (d, C-5), 58.3 (q, OMe), 51.5 (d, C-3), 43.7 (s, C-4), 29.1 (t, *C*H_2Ar), 23.9, 15.7 (2 × q, 4-Me) ppm. IR (neat): $\tilde{\nu}$ = 3100–2850 (=C–H, C–H), 1810 (C=O) cm^{-1}. MS (EI = 70 eV): *m*/*z* (%) = 260 (6) [M]$^+$, 229 (6), 129 (59), 115 (27), 99 (17), 86 (100), 71 (13). HRMS (80 eV): calcd. for $C_{16}H_{20}O_3$ 260.1412, found 260.1409.

SmI_2-Induced Intramolecular Cyclization of 28: The reaction was performed as described in General Procedure 1, with **28** (0.060 g, 0.206 mmol), SmI_2 (0.495 mmol), HMPA (0.65 mL, 3.71 mmol) and *t*BuOH (0.040 g, 0.540 mmol). The crude product was purified by column chromatography (alumina, ethyl acetate/hexane 10%) to furnish **39** (0.029 g, 54%) as a colourless solid, m.p. 128–132 °C.

7-Methoxy-14,14-dimethyl-12-oxatricyclo[9.2.1.0^{3,8}]tetradeca-3(8),4,6-trien-13-one (39): ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.09 (t, J = 8.1 Hz, 1 H, Ar), 6.75 (d, J = 8.1 Hz, 2 H, Ar), 4.26 (t, J = 3.3 Hz, 1 H, 11-H), 3.79 (s, 3 H, OMe), 3.19 (dd, J = 1.8, 14.7 Hz, 1 H, 2-H), 3.11–2.97, 2.75–2.67 (2 × m, 2 H, 1 H, 1-H, 2-H, 9-H), 2.63 (br dd, $J \approx$ 2, 10 Hz, 1 H, 9-H), 2.32–2.23 (m, 1 H, 10-H), 1.89 (dq, J = 3.9, 15.4 Hz, 1 H, 10-H), 1.33, 1.18 (br s, s, 3 H each, Me) ppm. ^{13}C NMR ($CDCl_3$, 126.9 MHz): δ = 157.0 (s, C-13), 138.3, 132.0, 128.0, 126.7, 124.2, 109.3 (3 × s, 3 × d, Ar), 89.0 (d, C-11), 55.4 (q, OMe), 52.3 (d, C-1), 41.8 (s, C-14), 33.4, 31.4, 30.9 (3 × t, C-2, C-9, C-10), 33.4, 18.0 (2 × q, Me) ppm. IR (neat): $\tilde{\nu}$ = 3065–2850 (=C–H, C–H), 1775 (C=O) ppm. MS (EI = 80 eV): *m*/*z* (%) = 260 (100) [M]$^+$, 216 (35), 199 (22), 173 (18), 159 (15), 147 (11), 135 (14), 115 (12), 91 (8), 83 (31). HRMS (80 eV): calcd. for $C_{16}H_{20}O_3$ 260.1412; found 260.1429.

SmI_2-Induced Intramolecular Cyclization of 29: The reaction was performed as described in General Procedure 1, with **29** (0.204 g, 0.830 mmol), SmI_2 (1.84 mmol), HMPA (2.65 g, 14.8 mmol) and *t*BuOH (0.120 g, 1.64 mmol). The crude product was purified by column chromatography (alumina, ethyl acetate/hexane 10%) to furnish **46** (17 mg, 10%), followed by **43** (64 mg, 31%).

Methyl *trans*-8-Hydroxy-8-methyl-5,6,7,8,9,10-hexahydrobenzocyclooctene-6-carboxylate (43): ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.18–7.03 (m, 4 H, Ar), 3.71 (s, 3 H, CO_2Me), 3.30–2.29 (m, 4 H, 5-H, 6-H, 10-H), 2.71 (ddd, J = 3.6, 8.9, 14.1 Hz, 1 H, 10-H), 2.01–1.54 (m, 5 H, 7-H, 9-H, OH), 1.21 (s, 3 H, Me) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 176.1, 51.7 (s, q, CO_2Me), 141.6, 137.2, 130.0, 129.3, 127.1, 126.7 (2×s, 4×d, Ar), 71.9 (s, C-8), 46.3, 38.6, 34.1, 29.3 (4×t, C-5, C-7, C-9, C-10), 42.7 (d, C-6), 34.6 (q, Me) ppm. IR (neat): $\tilde{\nu}$ = 3490 (O–H), 3100–2850 (=C–H, C–H), 1730 (C=O) cm^{-1}. MS (EI = 70 eV): m/z (%) = 248 (3) $[M]^+$, 230 (10) $[M^+ - H_2O]$, 215 (8), 197 (17), 170 (32), 154 (23), 144 (100), 129 (26), 115 (42), 91 (29), 42 (28). $C_{15}H_{20}O_3$ (248.3): calcd. C 72.55, H 8.12; found C 72.39, H 7.91.

11-Methyl-12-oxatricyclo[9.2.1.0^{3,8}]tetradeca-3(8),4,6-trien-13-one (46): ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.25–7.12, 7.04 (m, d, J = 8 Hz, 3 H, 1 H, Ar), 3.30–3.16 (m, 3 H, 1-H, 2-H), 2.81–2.48, 2.32–2.09, 2.03–1.52 (3×m, 2 H, 1 H, 3 H, 9-H, 10-H, 14-H), 1.40 (s, 3 H, Me) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz) shows temperature-dependent spectrum at room temp.; all signals except δ = 136.6 (s), 129.8 (d), 127.7 (d), 126.8 (d), 86.3 (s) appear as very broad signals; measurement in [D$_6$]DMSO as solvent at 80 °C showed all the signals clearly: δ = 178.4 (s, C-13), 141.1, 136.5, 130.5, 129.3, 127.0, 125.9 (2×s, 4×d, Ar), 85.5 (s, C-11), 41.7, 35.2, 34.7, 28.2 (4×t, 4×CH_2), 29.3 (d, C-1) ppm. IR (gas-phase): $\tilde{\nu}$ = 3100–2850 (=C–H, C–H), 1795 (C=O) cm^{-1}. MS (EI = 70 eV): m/z (%) = 216 (100) $[M]^+$, 159 (82), 129 (62), 115 (53), 115 (53), 104 (37), 91 (27), 43 (39). $C_{14}H_{16}O_2$ (216.3): calcd. C 77.75, H 7.46; found C 77.68, H 7.31.

SmI$_2$-Induced Intramolecular Cyclization of 30: The reaction was performed as described in General Procedure 1, with **30** (0.210 g, 0.780 mmol), SmI_2 (1.73 mmol), HMPA (2.53 g, 14.2 mmol) and *t*BuOH (0.120 g, 1.64 mmol). The crude product was purified by column chromatography (silica gel, ethyl acetate/hexane 10%) to furnish **44** as a colourless oil (0.180 g, 84%).

Methyl *trans*-8-Hydroxy-8-isopropyl-5,6,7,8,9,10-hexahydrobenzocyclooctene-6-carboxylate (44): ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.22–7.11, 7.10–7.02 (2×m, 3 H, 1 H, Ar), 3.70 (s, 3 H, CO_2Me), 3.29 (dd, J = 5.5, 13.7 Hz, 1 H, 5-H), 3.08 (dd, J = 5.2, 13.7 Hz, 1 H, 5-H), 3.05–2.92 (m, 2 H, 10-H), 2.77–2.66 (m, 1 H, 6-H), 1.86–1.73 (m, 4 H, 7-H, 9-H, OH), 1.55 (sept, J = 6.8 Hz, 1 H, C*H*Me$_2$), 1.39 (dd, J = 12.3, 14.7 Hz, 1 H, 7-H), 0.86, 0.85 (2×d, J = 6.8 Hz, 3 H each, Me) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 176.3, 51.5 (s, q, CO_2Me), 142.1, 137.3, 130.1, 129.2, 127.0, 126.5 (2×s, 4×d, Ar), 75.0 (s, C-8), 42.6, 42.1 (2×d, C-6, *C*HMe$_2$), 40.7, 34.5 (2×t, C-5, C-10), 34.5, 28.7 (2×t, C-7, C-9), 17.0, 16.5 (2×q, CH*Me*$_2$) ppm. IR (neat): $\tilde{\nu}$ = 3520 (br., O–H), 3060–2880 (=C–H, C–H), 1730 (C=O) cm^{-1}. $C_{17}H_{24}O_3$ (276.4): calcd. C 73.88, H 8.75; found C 73.02, H 8.63.

SmI$_2$-Induced Intramolecular Cyclization of 31: The reaction was performed as described in General Procedure 1, with **31** (0.190 g, 0.660 mmol), SmI_2 (1.45 mmol), HMPA (2.12 g, 11.9 mmol) and *t*BuOH (0.097 g, 1.32 mmol). The crude product was purified by flash chromatography (silica gel, ethyl acetate/hexane 7%) to furnish **45** (75 mg, 39%) as colourless crystals (m.p. 86–88 °C).

Methyl *trans*-8-*tert*-Butyl-8-hydroxy-5,6,7,8,9,10-hexahydrobenzocyclooctene-6-carboxylate (45): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.20–7.11, 7.08–7.05 (2×m, 3 H, 1 H, Ar), 3.71 (s, 3 H, CO_2Me), 3.22 (dd, J = 4.8, 13.8 Hz, 1 H, 5-H), 3.08 (dd, J = 6.7, 13.8 Hz, 1 H, 5-H), 2.95–2.74 (m, 3 H, 6-H, 10-H), 2.12 (dd, J = 2.5, 15.0 Hz, 1 H, 7-H), 1.91–1.86 (m, 2 H, 9-H), 1.41 (dd, J = 12.1, 15.0 Hz, 1 H, 7-H), 0.87 (s, 9 H, *t*Bu) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 176.6, 51.7 (s, q, CO_2Me), 141.9, 137.8, 130.1, 129.1, 127.2, 126.7 (2×s, 4×d, Ar), 76.6 (s, C-8), 42.8 (d, C-6), 40.1, 24.6 (s, q, *t*Bu), 39.2, 35.3, 33.0, 28.9 (4×t, 4×CH_2) ppm. IR (KBr): $\tilde{\nu}$ = 3500 (br., O–H), 3060–2860 (=C–H, C–H), 1715 (C=O) cm^{-1}. $C_{18}H_{26}O_3$ (290.4): calcd. C 74.45, H 9.02; found C 74.17, H 9.42.

SmI$_2$-Induced Intramolecular Cyclization of 33a: The reaction was performed as described in General Procedure 1, with **33a** (0.220 g, 0.760 mmol), SmI_2 (1.66 mmol), HMPA (2.42 g, 13.6 mmol) and *t*BuOH (0.115 g, 1.55 mmol). The crude product was purified by column chromatography (silica gel, ethyl acetate/hexane 10%) to furnish **49** (12 mg, 6%, mixture of 2 diastereomers = 1:1), followed by **47** (0.110 g, 50%) as colourless crystals (m.p. 80–81 °C).

Methyl (4a*SR*,5*SR*,12a*RS*)-12a-Hydroxy-1,2,3,4,4a,5,6,11,12,12a-decahydrodibenzo[*a*,*e*][8]annulene-5-carboxylate (47): ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.18–7.10, 6.97–6.96 (2×m, 3 H, 1 H, Ar), 3.75 (dd, J = 6.6, 14.9 Hz, 1 H, 6-H), 3.65 (s, 3 H, CO_2Me), 3.18 (ddd, J = 3.5, 6.4, 17.3 Hz, 1 H, 11-H), 2.99 (ddd, J = 2.8, 6.6, 10.5 Hz, 1 H, 5-H), 2.91 (ddd, J = 3.6, 12.6, 17.3 Hz, 1 H, 11-H), 2.80 (dd, J = 2.8, 14.9 Hz, 1 H, 6-H), 2.57 (ddd, J = 3.5, 12.6, 15.0 Hz, 1 H, 12-H), 1.80 (ddd, J = 3.6, 6.4, 15.0 Hz, 1 H, 12-H), 1.72–1.60, 1.59–1.47, 1.39–1.25, 1.19–1.07 (4×m, 3 H, 3 H, 2 H, 1 H, CH, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 175.8, 51.0 (s, q, CO_2Me), 139.6, 135.5, 132.3, 129.7, 126.6, 125.5 (2×s, 4×d, Ar), 74.0 (s, C-12a), 48.1 (d, C-5), 42.5 (t, C-12), 41.1 (d, C-4a), 39.9 (t, C-1), 35.7 (t, C-6), 30.8 (t, C-11), 27.1, 24.9, 21.0 (3×t, 3×CH_2) ppm. IR (KBr): $\tilde{\nu}$ = 3510 (br., O–H), 3060–2860 (=C–H, C–H), 1730 (C=O) cm^{-1}. MS (EI = 70 eV): m/z (%) = 270 (84) $[M^+ - 18]$, 238 (50), 209 (44), 196 (100), 129 (81), 117 (65), 104 (45), 91 (47), 55 (26), 41 (23). $C_{18}H_{24}O_3$ (288.4): calcd. C 74.97, H 8.39; found C 74.97, H 8.65.

3-(2-Vinylbenzyl)hexahydro-1-benzofuran-2(3*H*)-one (49): Mixture of two diastereomers (1:1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.49–7.45, 7.25–7.04 (2×m, 1 H, 3 H, Ar), 6.97, 5.60, 5.29 (ABX system: J_{AX} = 17.3 Hz, J_{BX} = 10.9 Hz, J_{AB} = 1.4 Hz, 1 H each, CH=CH$_2$), 4.55 (dd, J = 6.3, 10.6 Hz, 1 H, 4-H), 3.75–3.58, 3.46–3.12, 2.69–2.45, 2.30–1.05 (4×m, 12 H, 2×CH, 5×CH_2) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 174.0, 164.0, 141.4, 137.7, 137.0 (5×s, C=O, Ar), 135.4, 134.7, 130.2, 129.6, 129.5, 127.8, 127.0, 126.5, 122.2 (2×s, 7×d, Ar, =CH), 116.1, 101.5 (2×t, =CH_2), 80.1, 49.7, 42.0 (3×d, CH), 39.4, 38.2, 34.3, 33.3, 28.0, 27.4, 27.1, 26.2, 26.0, 23.3, 22.8, 22.6 (12×t, CH_2) ppm. IR (neat): $\tilde{\nu}$ = 3100–2850 (=C–H, C–H), 1795 (C=O) cm^{-1}. MS (EI = 70 eV): m/z (%) = 256 (82) $[M]^+$, 238 (38), 183 (28), 159 (100), 129 (74), 117 (72), 104 (43), 91 (38), 41 (25).

Methyl 12a-Hydroxy-8,9-dimethoxy-1,2,3,4,4a,5,6,11,12,12a-decahydrodibenzo[*a*,*e*][8]annulene-5-carboxylate (48): The reaction was performed as described in General Procedure 1, with **34a** (35 mg, 0.100 mmol), SmI_2 (0.220 mmol), HMPA (0.330 g, 1.81 mmol) and *t*BuOH (15 mg, 0.200 mmol). The crude product was purified by flash chromatography (silica gel, ethyl acetate/hexane 15%) to furnish **48** (25 mg, 71%) as a colourless oil and starting material **34a** (10 mg, 28%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.59, 6.45 (2×s, 1 H each, Ar), 3.84, 3.82 (2×s, 3 H each, ArO*Me*), 3.63 (s, 3 H, CO_2Me), 3.10 (ddd, J = 3.5, 6.4, 17.2 Hz, 1 H, 5-H), 2.95–2.77 (m, 2 H, 11-H), 2.71 (dd, J = 2.9, 15.1 Hz, 1 H, 6-H), 2.53 (td, J = 3.5, 15.1 Hz, 1 H, 6-H), 1.81–1.09 (m, 12 H, 4a-H, 11-H, OH, CH, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 176.0, 51.2 (s, q, CO_2Me), 147.4, 146.5, 131.5, 127.5, 115.5, 112.9 (4×s, 2×d, Ar), 74.1 (s, C-12a), 55.8, 55.7 (2×q, ArO*Me*), 48.4 (d, C-5), 42.3 (t, CH_2), 41.2 (d, C-4a), 39.9 (t, CH_2), 35.4 (t, C-12), 30.6, 27.2, 24.9, 21.0 (4×t, 4×CH_2) ppm. IR (neat): $\tilde{\nu}$ = 3525 (br., O–H), 2995–2835 (=C–H, C–H), 1730 (C=O) cm^{-1}. $C_{20}H_{28}O_5$ (348.4): calcd. C 68.94, H 8.10; found C 68.71, H 8.42.

Deprotonation of Lactones 38 and 39 and Treatment with Electrophiles. General Procedure 2: A mixture of lactone derivative and HMPA in THF was added at –78 °C to a solution of 2 equiv. of LDA (generated in situ from diisopropylamine and *n*-butyllithium in THF at –78 °C, 20 min). The mixture was stirred for 2 h and then 10 equiv. of the electrophile in THF was added. The mixture was stirred overnight (12–16 h), allowed to warm slowly to 10 °C during this period and quenched with satd. aqueous NH_4Cl solution. The two phases were separated and the aqueous phase was repeatedly extracted with diethyl ether. The combined organic phases were washed with water and brine and dried (Na_2SO_4). After removal of the solvent, the crude product was purified by column chromatography (alumina, ethyl acetate/hexane 10–30%).

1,14,14-Trimethyl-12-oxatricyclo[9.2.1.0^{3,8}]tetradeca-3(8),4,6-trien-13-one (50): The reaction was performed as described in General Procedure 2. LDA (0.610 mmol), **38** (70 mg, 0.300 mmol), methyl iodide (433 mg, 3.05 mmol), HMPA (218 mg, 1.22 mmol) in THF (4 mL) were used. The crude product was purified by column chromatography (alumina, ethyl acetate/hexane 10%) to give **50** as colourless crystals (73 mg, 99%), m.p. 123–125 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.19–7.05 (m, 4 H, Ar), 4.23 (t, J = 3.5 Hz, 1 H, 11-H), 3.43 (d, J = 14.3 Hz, 1 H, 2-H), 3.06 (dt, J = 4.8, 13.7 Hz, 1 H, 9-H), 2.71–2.60 (m, 1 H, 9-H), 2.57 (d, J = 14.3 Hz, 1 H, 2-H), 2.37–2.17 (m, 1 H, 10-H), 2.06 (qd, J = 4.8, 15.7 Hz, 1 H, 10-H), 1.40, 1.33, 1.11 (3×s, 3 H each, Me) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 178.5 (s, C-13), 139.7, 136.7, 132.3, 128.7, 127.8, 126.5 (2×s, 4×d, Ar), 87.9 (d, C-11), 52.1 (s, C-1), 44.2 (s, C-14), 41.3, 32.8, 30.4 (3×t, C-2, C-9, C-10), 31.2, 20.9, 17.4 (3×q, 3×Me) ppm. IR (KBr): $\tilde{\nu}$ = 3100–2850 (=C–H, C–H), 1755 (C=O) cm^{-1}. $C_{16}H_{20}O_2$ (244.3): calcd. C 78.65, H 8.25; found C 78.42, H 8.70.

1-Allyl-14,14-dimethyl-12-oxatricyclo[9.2.1.0^{3,8}]tetradeca-3(8),4,6-trien-13-one (51): The reaction was performed as described in General Procedure 2. LDA (0.610 mmol), **38** (70 mg, 0.300 mmol), allyl bromide (370 mg, 3.06 mmol), HMPA (218 mg, 1.22 mmol) and THF (4 mL) were used. The crude product was purified by column chromatography (alumina, ethyl acetate/hexane 10%) to give **51** (65 mg, 79%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.18–7.11 (m, 3 H, Ar), 7.07 (d, J = 7.4 Hz, 1 H, Ar), 6.14–6.06 (m, 1 H, 2′-H), 5.29–5.23 (m, 2 H, 3′-H), 4.15 (t, J = 3.4 Hz, 1 H, 11-H), 3.38 (d, J = 14.4 Hz, 1 H, 2-H), 3.03 (dt, J = 4.4, 14.2 Hz, 1 H, 1′-H), 2.84 (d, J = 14.4 Hz, 1 H, 2-H), 2.70 (dd, J = 6, 14.7 Hz, 1 H, 9-H), 2.64 (dt, J = 4.6, 14.2 Hz, 1 H, 1′-H), 2.50 (dd, J = 8.5, 14.7 Hz, 1 H, 9-H), 2.27–2.19 (m, 1 H, 10-H), 2.05 (dq, J = 3.8, 15.8 Hz, 1 H, 10-H), 1.43, 1.21 (br s, s, 3 H each, Me) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 177.8 (s, C-13), 139.9, 136.7, 132.2, 128.7, 127.7, 126.5 (2×s, 4×d, Ar), 133.1, 118.9 (d, t, C-2′, C-3′), 87.8 (d, C-11), 53.7 (s, C-1), 44.8 (s, C-14), 40.5, 38.0, 32.6, 30.4 (4×t, C-2, C-10, C-9, C-1′), 30.1, 18.7 (2×q, Me) ppm. IR (neat): $\tilde{\nu}$ = 3100–2850 (=C–H, C–H), 1760 (C=O), 1640 (C=C) cm^{-1}. $C_{18}H_{22}O_2$ (270.4): calcd. C 79.96, H 8.20; found C 79.74, H 8.29.

1-Hydroxy-14,14-dimethyl-12-oxatricyclo[9.2.1.0^{3,8}]tetradeca-3(8),4,6-trien-13-one (54): A mixture of lactone **38** (0.374 g, 1.62 mmol) and HMPA (1.16 g, 6.52 mmol) in THF (10 mL) was added at –78 °C to a solution of LDA (3.24 mmol, generated in situ from diisopropylamine and *n*-butyllithium, in 10 mL of THF at –78 °C, 20 min). The mixture was stirred for 2 h and then dry oxygen gas was bubbled through the mixture (1 h), which was stirred overnight and allowed to warm slowly to 10 °C during this period. The mixture was quenched with satd. aqueous NH_4Cl solution, the phases were separated, and the aqueous phase was repeatedly extracted with diethyl ether. The combined organic phases were washed with water and brine and dried (Na_2SO_4). Removal of the solvent furnished product **52** (0.412 g, 97%), which was then treated with NaI (0.500 g, 3.33 mmol) in THF (10 mL) and stirred overnight. After the usual workup, purification by column chromatography (alumina, ethyl acetate/hexane 30%) provided compound **54** as a colourless oil (0.328 g, 82%).

14,14-Dimethyl-1-perhydroxy-12-oxatricyclo[9.2.1.0^{3,8}]tetradeca-3(8),4,6-trien-13-one (52): Colourless crystals, m.p. 127–128 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 10.25 (s, 1 H, OOH), 7.20–7.09 (m, 4 H, Ar), 4.29 (t, J = 4 Hz, 1 H, 11-H), 3.86, 3.51 (2×d, J = 14.5 Hz, 1 H each, 2-H), 3.13 (dt, J = 5, 14 Hz, 1 H, 9-H), 2.73–2.60 (m, 1 H, 9-H), 2.43–2.03 (m, 2 H, 10-H), 1.48, 1.24 (2×s, 3 H each, Me) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 176.1 (s, C-13), 139.8, 134.4, 132.2, 129.1, 128.2, 127.1 (2×s, 4×d, Ar), 88.7 (d, C-11), 87.6 (s, C-1), 46.0 (s, C-14), 33.3, 32.3, 30.0 (3×t, C-2, C-10, C-9), 27.2, 17.1 (2×q, Me) ppm. IR (KBr) $\tilde{\nu}$ = 3515–3330 (O–H), 3060–2935 (=C–H, C–H), 1750 (C=O) cm^{-1}. HRMS (80 eV): calcd. for $C_{15}H_{18}O_4$ [M]$^+$ 262.1205, found 262.1204.

1-Hydroxy-14,14-dimethyl-12-oxatricyclo[9.2.1.0^{3,8}]tetradeca-3,5,7-trien-13-one (54): ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.20–7.11 (m, 4 H, Ar), 4.31 (t, J = 3.5 Hz, 1 H, 11-H), 3.79 (d, J = 14.5 Hz, 1 H, 2-H), 3.07 (dt, J = 4.9, 14.1 Hz, 1 H, 9-H), 2.87 (d, J = 14.5 Hz, 1 H, 2-H), 2.68 (dt, J = 5.8, 14.1 Hz, 1 H, 9-H), 2.39–2.20 (m, 1 H, 10-H), 2.10 (qd, J = 4.4, 15.5 Hz, 1 H, 10-H), 1.47, 1.19 (2×s, 3 H each, Me) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 177.3 (s, C-13), 139.6, 134.6, 132.4, 128.9, 128.1, 126.9 (2×s, 4×d, Ar), 87.6 (d, C-11), 81.1 (s, C-1), 44.9 (s, C-14), 43.1, 32.2, 30.1 (3×t, C-2, C-10, C-9), 28.5, 16.9 (2×q, Me) ppm. IR (KBr): $\tilde{\nu}$ = 3450 (O–H), 3100–2850 (=C–H, C–H), 1755 (C=O) cm^{-1}. $C_{15}H_{18}O_3$ (246.3): calcd. C 73.15, H 7.37; found C 73.15, H 7.93.

1-Hydroxy-7-methoxy-14,14-dimethyl-12-oxatricyclo[9.2.1.0^{3,8}]tetradeca-3,5,7-trien-13-one (55): LDA (0.514 mmol), **39** (0.067 g, 0.257 mmol) and HMPA (0.184 g, 1.03 mmol) in THF (3 mL), analogously to the preparation of **54**, gave hydroperoxide **53** as a pale yellow oil (0.071 g, 94%). Subsequent treatment of **53** with NaI (0.077 g, 0.514 mmol) in THF (2 mL) overnight and purification by column chromatography (alumina, ethyl acetate/hexane 30%) gave **55** (0.052 g, 71%) as colourless crystals (m.p. 189–192 °C).

7-Methoxy-14,14-dimethyl-1-perhydroxy-12-oxatricyclo[9.2.1.0^{3,8}]-tetradeca-3,5,7-trien-13-one (53): ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 10.28 (s, 1-H, OOH), 7.10 (t, $J \approx$ 8 Hz, 1 H, Ar), 6.80, 6.77 (2×d, $J \approx$ 8 Hz, 1 H each, Ar), 4.26 (t, J = 3.3 Hz, 1 H, 11-H), 3.78, 3.43 (2×d, J = 14.6 Hz, 1 H each, 2-H), 3.74 (s, 3 H, OMe), 3.20–3.08 (m, 1 H, 9-H), 2.65 (dd, J = 3.6, 13.7 Hz, 1 H, 9-H), 2.32–2.15, 2.00–1.87 (2×m, 1 H each, 10-H), 1.41, 1.17 (br s, s, 3 H each, Me) ppm.

1-Hydroxy-7-methoxy-14,14-dimethyl-12-oxatricyclo[9.2.1.0^{3,8}]-tetradeca-3,5,7-trien-13-one (55): ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.07 (t, J = 8 Hz, 1 H, Ar), 6.76, 6.74 (2×d, J = 8 Hz, 1 H each, Ar), 4.27 (t, J = 3.3 Hz, 1 H, 11-H), 3.78 (s, 3 H, OMe), 3.75 (d, J = 14.7 Hz, 1 H, 2-H), 3.20–3.06 (m, 1 H, 9-H), 2.85 (d, J = 14.7 Hz, 1 H, 2-H), 2.75–2.67, 2.38–2.20, 1.55–1.43 (3×m, 1 H each, 9-H, 10-H), 1.23, 1.16 (br s, s, 3 H each, Me) ppm. ^{13}C NMR ($CDCl_3$, 126.9 MHz): δ = 177.4 (s, C-13), 156.6, 136.1, 127.8, 127.0, 124.5, 109.6 (3×s, 3×d, Ar), 88.0 (d, C-11), 81.3 (s, C-1), 55.5 (q, OMe), 45.0 (s, C-14), 43.3, 30.1, 28.5 (3×t, C-2, C-9, C-10), 21.7, 16.9 (2×q, Me) ppm. IR (KBr): $\tilde{\nu}$ = 3420 (O–H), 3005–2835 (=C–H, C–H), 1760 (C=O) cm^{-1}. MS (EI = 80 eV): *m/z* (%) = 276 (100) [M]$^+$, 179 (39), 161 (25), 160 (29), 159 (15), 135 (63), 134 (68), 104 (19), 28 (11). HRMS (80 eV): calcd. for $C_{16}H_{20}O_4$ [M]$^+$ 276.1362, found: 276.1336.

Supporting Information (see footnote on the first page of this article): Full experimental and analytical details for syntheses of starting materials **12**–**31**.

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