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Pentacyclic Compounds by Samarium Diiodide-Induced Cascade Cyclizations of Naphthyl-Substituted 1,3-Diones

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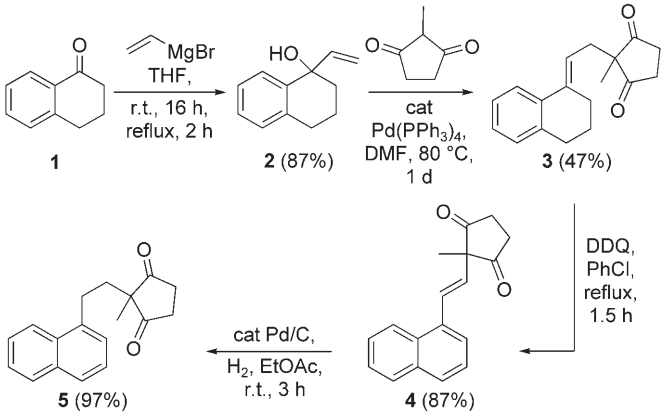
Abstract: Treatment of naphthyl-substituted cyclopentane-1,3-diones with the samarium diiodide-hexamethylphosphoramide (HMPA) complex in the presence of *tert*-butyl alcohol provided the expected tetracyclic diols with steroid-like structures. Surprisingly, reactions without the proton source led to the efficient formation of a new pentacyclic diol. In this case the toxic additive HMPA could be substituted by a combination of lithium bromide (*in situ* generation of samarium dibromide) and *N*,*N*-dimethylimidazolidone. The styrene-like alkene moiety of this product was used to prepare an ensemble of highly substituted pentacyclic steroid-like compounds.

Keywords: electron transfer; ketyl-aryl coupling; polycycles; radical reactions; samarium diiodide; steroids

In earlier communications we have reported that γ-aryl ketones undergo novel samarium diiodide-induced cyclizations leading to synthetically useful hexahydronaphthalene derivatives.[1] The closely related reaction of simple cyclic γ-naphthyl-substituted ketones furnished tetracyclic compounds with steroid-like constitution, but "unnatural" *cis/cis* annulation of rings B/C/D.[2] Here we describe our experiments with cyclic 1,3-diones as precursors for the crucial samarium ketyls,[3] which were performed to generate steroid analogous products with additional functionality in ring D.

The required naphthyl-substituted 1,3-diketones were prepared by a straightforward four-step synthesis following the Torgov approach to steroids as exemplified for compound **5** (Scheme 1).[4] Dione **3** was obtained by addition of vinylmagnesium bromide to tetralone **1** followed by a Pd-catalyzed allylic alkylation.[4d] Oxidation of **3** with DDQ[4e] and subsequent reduction[5] of the alkene moiety furnished dione **5** in

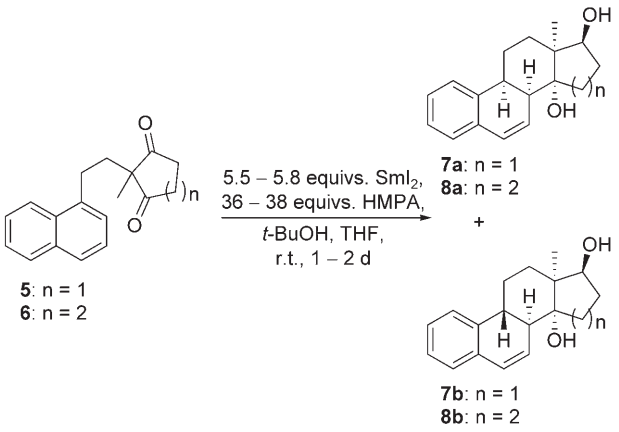


Scheme 1.

35% overall yield. Analogously, **6** and **13** were prepared from the corresponding precursors.

Cyclopentane-1,3-dione derivative **5** was treated with an excess of samarium diiodide in the presence of HMPA[6] and *tert*-butyl alcohol and provided the expected diols **7a**/**7b** in yields varying between 67–74%. The ratio of diastereomers **7a**/**7b** strongly depends on the amount of the proton source (Table 1, entries 1–4). Standard conditions (8 equivs.) led to an unselective reaction (entry 1), whilst use of only 1 equiv. of *tert*-butyl alcohol (entry 4) induced a highly diastereoselective formation of tetracyclic diol **7a**.[7] The relative configurations of **7a** and **7b** were unequivocally proven by X-ray analyses.[8] The conversion of cyclohexane-1,3-dione derivative **6** into tetracyclic diol **8** is rather slow and even after a reaction time of two days 25% of **6** was recovered (entry 5). We assume a mechanism for these cyclizations as proposed before,[2] but here a subsequent stereoselective reduction of the remaining cycloalkanone carbonyl group by the excess of samarium diiodide generates the second hydroxy group. This step affords products **7** and **8** with *trans*-arranged hydroxy groups. However, the protonation at the carbon adjacent to the benzene ring proceeds with varying stereoselectivity, being strongly dependent on the amount of *tert*-butyl alcohol in the case of **5**→**7**.[9]

Table 1. Cyclizations of 1,3-diones **5** and **6** with samarium diiodide.

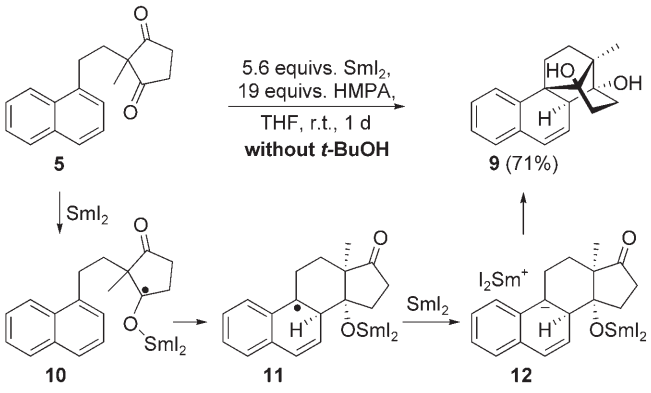


Entry	1,3-Dione	*t*-BuOH (equivs.)	Product	Ratio	Yield [%]
1	**5**	8	**7a**:**7b**	56:44[a]	74[c]
2	**5**	4	**7a**:**7b**	64:36[a]	74[c]
3	**5**	2	**7a**:**7b**	83:17[a]	67[c]
4	**5**	1	**7a**:**7b**	91:9[a]	70[c]
5	**6**	4	**8a**:**8b**	62:38[b]	53[d]

[a] Determined by NMR spectroscopy of the crude product.
[b] Ratio of purified isomers **8a** (33%) and **8b** (20%).
[c] Yield refers to isolated material of purified mixtures of **7a**/**7b**.
[d] Combined yield of separated isomers **8a**/**8b**; 25% of **6** was recovered.

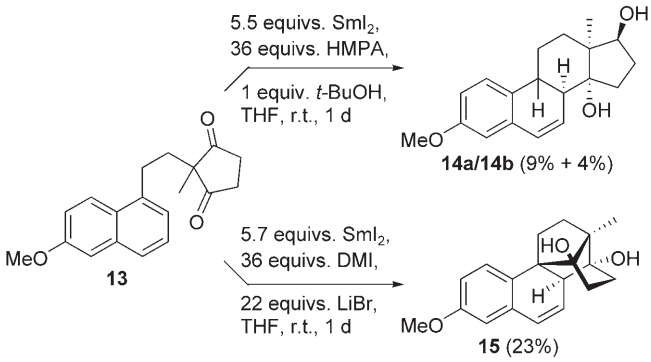
Most surprisingly, reaction of precursor **5** with an excess of samarium diiodide-HMPA *without proton source* furnished the novel pentacyclic diol **9** in good yield (Scheme 2). The constitution and configuration of compound **9** was also determined by X-ray analysis.[8]

As mechanism for this unexpected cascade cyclization we suggest a sequence with intermediates **10** (samarium ketyl), **11** (benzylic radical), and **12** (carbanion). However, in the absence of *tert*-butyl alcohol, **12** is not rapidly protonated to provide the precursor of **7**, but undergoes the second cyclization involving the carbanionic centre and the remaining carbonyl group of the cyclopentane ring (Scheme 2).[10] This conversion could also be performed replacing HMPA by DMI (1,3-dimethyl-2-imidazolidinone, 36 equivs.) and lithium bromide (22 equivs.). The desired cyclization product **9** was obtained in *ca.* 50% yield under these conditions even in the presence of *tert*-butyl alcohol![11] Unfortunately, a similar reaction cascade was not successful with **6** as a homologue precursor, which was entirely unreactive under these conditions and reisolated.



Scheme 2.

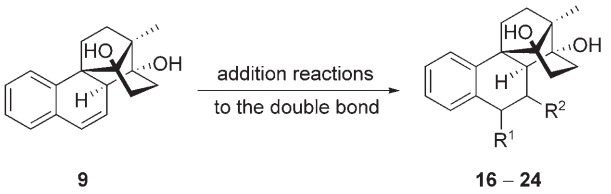
To obtain products with an even closer similarity to steroids we introduced the 3-methoxy group into the precursor. Compound **13** underwent analogous, but less efficient cyclizations giving tetracyclic diol **14a**/**14b** in the presence of *tert*-butyl alcohol or pentacyclic diol **15** in 23% yield, if no proton source was added (Scheme 3). In the last transformation we could again work with the HMPA substitute DMI. Starting material **13** was completely consumed in both cases, but the reduction of the carbonyl moieties was the major process. Due to the electron-donating methoxy group the cyclizations to the naphthalene unit were considerably less efficient as already observed for other γ-aryl ketones.[1b,2b]



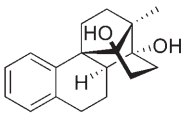
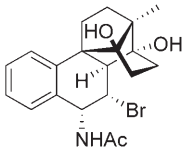
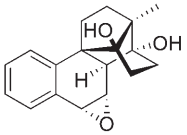
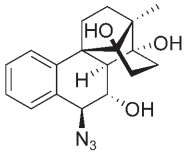
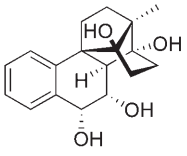
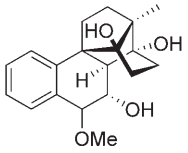
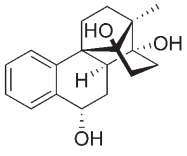
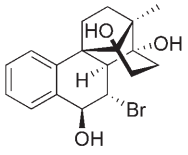
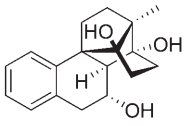
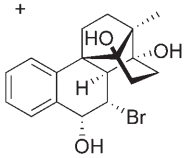
Scheme 3.

Having established a fast route to the rigid, and yet steroid-related pentacyclic scaffold we prepared an ensemble of highly substituted derivatives exploiting the reactive styrene-type alkene moiety of compound **9** (Table 2). The resulting products should be of interest because of potential biological activity. Many transformations proceeded nicely to furnish reduced compounds such as **16** (entry 1) or oxidized products like **17**, **18**, **19**, and **20** (entries 2–4) by stereoselective epoxidation, dihydroxylation and hydroboration. The latter transformation was only moderately regioselective; alternative borane derivatives did not react with **9**. Conversion of **9** into amide **21** could be achieved

Table 2. Addition reactions of pentacyclic compound **9**.



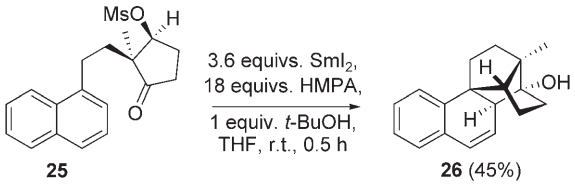
9 **16 – 24**

Entry	Product	Entry	Product
1[a]	 **16** (quant.)	5[e]	 **21** (77%)
2[b]	 **17** (quant.)	6[f]	 **22** (66%)
3[c]	 **18** (85%)	7[g]	 **23a/b** (65%, *cis*:*trans* 63:37)
	 **19** (64%)		 **24a** (32%)
4[d]	+  **20** (29%)	8[h]	+  **24b** (25%)

[a] Cat Pd/C, H_2, EtOAc, r.t., 5 h.
[b] *m*-CPBA, CH_2Cl_2, r.t., 22 h.
[c] Cat $K_2OsO_2(OH)_4$, cat quinuclidine, $K_3Fe(CN)_6$, K_2CO_3, methylsulfonamide, *t*-BuOH/H_2O 1:1, r.t., 45 h.
[d] BH_3·THF, THF, 0 °C, 2.5 h, r.t., 2 h; NaOH, 30% H_2O_2, r.t., 2 h.
[e] $CH_3C(=O)NHBr$, BF_3·OEt_2, H_2O, CH_3CN, 0 °C, 2 h.
[f] a) *m*-CPBA, CH_2Cl_2, r.t., 22 h; b) NaN_3, NH_4Cl, acetone/H_2O 4:1, 54 °C, 3 d.
[g] a) *m*-CPBA, CH_2Cl_2, r.t., 22 h; b) Cat $InCl_3$, MeOH, 0 °C, 2.5 h, r.t., 15 h.
[h] NBS, H_2O, THF, 0 °C, 4.5 h, r.t., 15.5 h.

by a recently published method[12] (entry 5). Its configuration was proven by an X-ray analysis.[8] Azide **22** (entry 6) was prepared regio- and stereoselectively *via* epoxide **17** as intermediate.[13] Similarly, opening of this epoxide in methanol with a catalytic amount of indium trichloride[14] provided the diastereomeric methoxy-substituted compounds **23a/b** (entry 7). The two bromohydrins **24a** and **24b** were also formed unselectively (entry 8).[14]

Finally, we converted 1,3-dione **5** into mesylate **25** by selective reduction of one carbonyl group followed by sulfonylation.[15] Treatment of this compound with the samarium diiodide-HMPA complex and *tert*-butyl alcohol furnished pentacyclic alcohol **26** in 45% yield (Scheme 4). The yield of this reaction was not improved when no *tert*-butyl alcohol was present. This product is related to **9**, but it bears only one bridgehead hydroxy group. We assume that the first cyclization occurs analogously to the process described in Scheme 2. The second cyclization should involve a nucleophilic displacement of the mesylate by the intermediate carbanion. According to NOE measurements the depicted configuration of precursor **25** is very likely, which excludes an S_N2 process for the second cyclization step. An S_N1-type reaction [triggered by the Lewis acidic samarium(III) and samarium(II) species present] seems to be more likely.[16]



25 **26** (45%)

Scheme 4.

In conclusion, we found that samarium diiodide also promotes the reductive cyclizations of naphthyl-substituted cycloalkane-1,3-diones, stereoselectively leading to tetracyclic diols or in the absence of proton sources to novel pentacyclic steroid-like compounds. These products are suitable scaffolds for installing additional substituents and functional groups. Mechanistic details of the reported cascade cyclizations and further functionalizations of the products in order to increase their steroid similarity will be reported in due time.

Experimental Section

General Methods

Reactions were generally performed under argon in flame-dried flasks. Solvents and reagents were added by syringes. Solvents were dried using standard procedures. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone under argon. Hexamethylphosphoramide was distilled from calcium hydride, 1,2-diiodoethane was dried at 50 °C for 3 h under vacuum. SmI_2 was either freshly prepared (see

typical procedure) or taken from a previously prepared 0.1 M stock solution. Other reagents were purchased and were used as received without further purification unless otherwise stated. Unless otherwise stated, products were purified by flash chromatography on silica gel (230–400 mesh, Merck or Fluka) or HPLC (Nucleosil 50–5). Unless otherwise stated, yields refer to analytical pure samples. NMR spectra were recorded on Bruker (AC 250, AM 270, AC 500) and JOEL (Eclipse 500) instruments. Chemical shifts are reported relative to TMS (^{1}H: $\delta = 0.00$ ppm), $CDCl_3$ (^{13}C: $\delta = 77.0$ ppm), or CD_3OD (^{1}H: $\delta = 3.31$ ppm, ^{13}C: $\delta = 49.0$ ppm). Integrals are in accordance with assignments; coupling constants are given in Hz. All ^{13}C spectra are proton-decoupled. For detailed peak assignments 2D spectra were measured (COSY and HMQC for all steroid-like compounds, NOESY and NOE if necessary). IR spectra were measured with an FT-IRD spectrometer Nicolet 5 SXC. MS and HR-MS analyses were performed with Finnigan MAT 711 (EI, 80 eV, 8 kV), MAT CH7A (EI, 80 eV, 3 kV), CH5DF (FAB, 3 kV) and Varian Ionspec QFT-7 (ESI-FT ICRMS) instruments. Elemental analyses were carried out with a CHN-Analyzer 2400 (Perkin–Elmer), Vario EL or Vario EL III (Elementar). Melting points were measured with a Reichert apparatus Thermovar and are uncorrected.

Typical Procedure for the Preparation of Steroid Analogues

(8*S,9*S**,13*S**,14*R**,17*S**)-Estra-1(10),2,4,6-tetraene-14,17-diol (7a) and (8*S**,9*R**,13*S**,14*R**,17*S**)-Estra-1(10),2,4,6-tetraene-14,17-diol (7b):** Sm (325 mg, 2.16 mmol, 6.0 equivs.) and ICH_2CH_2I (503 mg, 1.98 mmol, 5.5 equivs.) were suspended in THF (30 mL) at room temperature and vigorously stirred until the deep blue color of SmI_2 appeared (1–4 h); then HMPA (2.3 mL, 2.3 g, 13 mmol, 36 equivs.) was added. Dione **5** (95 mg, 0.36 mmol) and *t*-BuOH (0.26 mL, 0.21 g, 2.9 mmol, 8.0 equivs.) were dissolved in THF (10 mL) and argon was bubbled through the solution for 30 min. This solution of **5** was added *via* syringe to the SmI_2-HMPA solution. The mixture was stirred at room temperature overnight. Saturated aqueous $NaHCO_3$ solution (50 mL) was added, the organic layer was separated and the aqueous layer was extracted with Et_2O (3×50 mL). The combined organic layers were washed with water (2×10 mL) and brine (1×5 mL) and dried with Na_2SO_4. The solvents were removed under reduced pressure. Column chromatography on silica gel (hexane/EtOAc 2:1) afforded a 56:44 mixture of isomers **7a** and **7b** as a colorless solid; yield: 72 mg (74%). Analytically pure samples of **7a** and **7b** were obtained by HPLC.

7a: mp 167–169 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.12$–1.21 (m, 2H, 16-H^1, OH), 1.16 (s, 3H, CH_3), 1.26* (ddd, J = 4.5, 10.1, 14.7 Hz, 1H, 15-H^1), 1.26* (s, 1H, OH), AB-signal ($\delta_A = 1.38$, $\delta_B = 1.42$, $J_{A,B} = 13.8$ Hz, additional couplings of A, $J = 3.1$, 13.8 Hz, and of B $J = 3.6$, 3.6 Hz, 1 H each, 12-H$_2$), 1.53 (ddd, $J = 5.9$, 12.5, 14.7 Hz, 1H, 15-H^2), 1.87–2.01 (m, 2H, 16-H^2, 11-H^1), 2.43 (qd, $J \approx 3$, 14.6 Hz, 1H, 11-H^2), 2.52 (dd, $J = 6.1$, 6.9 Hz, 1H, 8-H), 3.34 (br. dd, $J = 6.0$, 6.9 Hz, 1H, 9-H), 4.17 (t, $J = 8.5$ Hz, 1H, 17-H), 6.14 (dd, $J = 6.1$, 9.8 Hz, 1H, 7-H), 6.59 (d, $J = 9.8$ Hz, 1H, 6-H), 7.02 (dd, $J = 1.2$, 7.4 Hz, 1H, 4-H), 7.14 (br. t, $J = 7.4$ Hz, 1H, 3-H), 7.19 (dt, $J = 1.2$, 7.4 Hz, 1H, 2-H), 7.26 (br. d, $J = 7.4$ Hz, 1H, 1-H), (*overlapping signals); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 16.5$ (q, CH_3), 19.9 (t, C-11), 24.6 (t, C-12) 28.3 (t, C-16), 31.4 (t, C-15), 36.3 (d, C-9), 41.5 (d, C-8), 47.2 (s, C-13), 80.9 (d, C-17), 83.8 (s, C-14), 123.5 (d, C-1), 126.1 (d, C-3), 126.5 (d, C-4), 127.7 (d, C-2), 129.1 (d, C-7), 129.8 (d, C-6), 134.1, 136.3 (2 s, C-5, C-10); IR (KBr): $\nu = 3325$ (O–H), 3060–2830 (=CH, C–H), 1655–1570 (C=C) cm^{-1}; MS (EI, 80 eV, 90 °C): m/z (%) = 270 (82) [M]$^+$, 156 (31), 154 (72), 142 (40), 141 (55), 129 (59), 128 (100), 28 (51); HR-MS: $m/z = 270.16256$, calcd. for $C_{18}H_{22}O_2$: 270.16199.

7b: mp 176–178 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.07$ (s, 3H, CH_3), 1.41 (dt, $J = 3.8$, 13.6 Hz, 1H, 12-H^1), 1.56–1.72 (m, 6H, 11-H^1, 12-H^2, 15-H^1, 15-H^2, 16-H^1, OH), 2.16–2.34 (m, 4H, 8-H, 11-H^2, 16-H^2, OH), 2.63 (ddd, $J = 3.7$, 11.9, 15.4 Hz, 1H, 9-H), 4.32 (t, $J = 8.6$ Hz, 1H, 17-H), 6.17 (dd, $J = 2.0$, 9.7 Hz, 1H, 7-H), 6.57 (dd, $J = 2.9$, 9.7 Hz, 1H, 6-H), 7.08 (dd, $J = 1.6$, 7.1 Hz, 1H, 4-H), 7.17–7.21 (m, 1H, 3-H), 7.22 (dt, $J = 1.6$, 6.9 Hz, 1H, 2-H), 7.25–7.29 (m, 1H, 1-H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 16.6$ (q, CH_3), 23.2 (t, C-11), 28.4 (t, C-12), 28.8 (t, C-15), 30.0 (t, C-16), 39.3 (d, C-9), 44.9 (d, C-8), 47.7 (s, C-13), 80.9 (d, C-17), 83.1 (s, C-14), 123.5 (d, C-1), 126.0 (d, C-4), 126.4 (d, C-3), 127.3 (d, C-2), 129.0 (d, C-6), 129.4 (d, C-7), 134.1, 138.4 (2 s, C-5, C-10); IR (KBr): $\nu = 3315$ (O–H), 3060–2830 (=CH, C–H), 1660–1600 (C=C) cm^{-1}; MS (EI, 80 eV, 150 °C): m/z (%) = 270 (81) [M]$^+$, 157 (73), 155 (75), 142 (87), 141 (100), 129 (59), 128 (95), 115 (30), 97 (60), 43 (41), 41 (32), 28 (69); HR-MS: $m/z = 270.16114$, calcd. for $C_{18}H_{22}O_2$: 270.16199.

(8*S,9*S**,13*R**,14*R**,17*S**)-3-Methoxy-9,17-cycloestra-1(10),2,4,6-tetraene-14,17-diol (15):** LiBr (774 mg, 8.91 mmol, 22 equivs.) was dissolved in THF (5 mL), 1,3-dimethyl-2-imidazolidinone (1.6 mL, 1.7 g, 15 mmol, 36 equivs.) was added and argon was bubbled through the solution for 20 min. The solution was added to a solution of SmI_2 in THF (0.1 M, 23 mL, 2.3 mmol, 5.7 equivs.). Dione **13** (120 mg, 0.405 mmol) was dissolved in THF (5 mL), argon was bubbled through the solution for 25 min, and the solution was added to the $SmBr_2$ solution and stirred at room temperature for 1 day. Saturated aqueous $NaHCO_3$ solution (30 mL) was added, the organic layer was separated and the aqueous layer was extracted with Et_2O (3×30 mL). The combined organic layers were washed with brine (6×3 mL) and dried with Na_2SO_4. The solvent was removed under reduced pressure. Column chromatography on silica gel (hexane/EtOAc, 2:1) afforded **15** as a colorless solid; yield: 28 mg (23%); mp 144 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.01$ (s, 3H, 13-CH_3), 1.26 (dt, $J = 2.6$, 12.3 Hz, 1H, 16-H^1), 1.45–1.52 (m, 3H, 16-H^2, 11-H^1, OH), 1.54 (ddd, $J = 2.2$, 11.1, 13.4 Hz, 1H, 12-H^1), 1.65 (br. s, 1H, OH), 1.72 (ddt, $J = 2.8$, 6.4, 12.3 Hz, 1H, 15-H^1), 1.85–1.92 (m, 2H, 12-H^2, 15-H^2), 2.40 (q, $J \approx 2.5$ Hz, 1H, 8-H), 2.51 (dt, $J = 7.0$, 11.1 Hz, 1H, 11-H^2), 3.78 (s, 3H, OCH_3), 5.91 (dd, $J = 3.0$, 9.9 Hz, 1H, 7-H), 6.31 (dd, $J = 2.3$, 9.9 Hz, 1H, 6-H), 6.63 (d, $J = 2.7$ Hz, 1H, 4-H), 6.71 (dd, $J = 2.7$, 8.4 Hz, 1H, 2-H), 7.25 (d, $J = 8.4$ Hz, 1H, 1-H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 11.0$ (q, CH_3), 26.0, 26.1 (2 t, C-12, C-16), 31.1 (t, C-15), 37.4 (t, C-11), 50.9 (d, C-8), 51.2, 52.1 (2 s, C-9, C-13), 55.2 (q, OCH_3), 83.0, 86.4 (2 s, C-14, C-17), 112.1 (d, C-2), 113.1 (d, C-4), 124.9 (s, Ar), 127.0 (d, C-6), 127.1 (d, C-1), 127.8 (d, C-7), 134.6, 158.6 (2 s, Ar); IR (KBr): $\nu = 3460$, 3410 (O–H), 3025–2830 (=CH, C–H, OCH_3), 1600, 1500 (C=C) cm^{-1}; anal. calcd. for $C_{19}H_{22}O_3$ (298.4): C 76.48, H 7.43; found: C 76.58, H 7.48.

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[7] For entries 3 and 4 (Table 1) it is important to add *tert*-butyl alcohol to the SmI_2-HMPA complex before addition of precursor **5**; when the standard sequence was applied the yields were lower.

[8] Crystallographic data for **7a**: U. K. Wefelscheid, I. Brüdgam, H. Hartl, H.-U. Reissig, *Z. Kristallogr. NCS* **2007**, *222*, in press; for **7b**: CCDC 659637; for **9**: U. K. Wefelscheid, I. Brüdgam, H.-U. Reissig, *Z. Kristallogr. NCSZ.* **2007**, *222*, in press; for **21**: CCDC 659638; the data for **7b** and **21** can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[9] This dependency was not observed in cyclizations of monoketones (ref.[2]) and requires further investigations.

[10] The detailed mechanistic features of these cyclization reactions are still unclear and have to be investigated. Actually, 2 equivs. of samarium diiodide should be sufficient for conversion of compound **5** into **9**, however, if 2.75 equivs. of SmI_2 were used only reduction of one of the two carbonyl groups of **5** was observed.

[11] Monocyclization product **7** was not detected under these conditions.

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