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Selective Reductions of Cyclic 1,3-Diesters by Using SmI_2 and H_2O

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Abstract: SmI_2/H_2O reduces cyclic 1,3-diesters to 3-hydroxyacids with no over reduction. Furthermore, the reagent system is selective for cyclic 1,3-diesters over acyclic 1,3-diesters, and esters. Radicals formed by one-electron reduction of the ester carbonyl group have been exploited in intramolecular additions to alkenes. The ketal unit and the reaction temperature have a marked impact on the diastereoselectivity of the cyclizations. Cyclization cascades are possible when two alkenes are present in the starting cyclic diester and lead to the formation of two rings and four stereocenters with excellent stereocontrol.

Keywords: chemoselectivity · cyclization · radical reactions · reduction · samarium

Introduction

The re-routing of fundamental chemical transformations through less-conventional intermediates opens up unexplored reaction space where new selectivity and reactivity may be found. For example, our recent studies on the use of SmI_2[1] as a reductant for the carbonyl group, led us to identify SmI_2/H_2O as a reagent system that not only differentiates between the carbonyl groups of esters and lactones, but also shows ring-size selectivity for six-membered lactones.[2] Experimental and computational studies suggested this new selectivity arose from optimal anomeric stabilization of a radical anion intermediate in the reduction of six-membered lactones.[2]

Here we report in full our studies on the mono-reduction of cyclic 1,3-diesters with SmI_2/H_2O.[3] The reagent system is selective for cyclic 1,3-diesters over acyclic 1,3-diesters, lactones and esters and experimental and computational studies have been used to understand the selectivity. The radical intermediates formed by one electron reduction of the ester carbonyl group have been exploited in intramolecular additions to alkenes.

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Results and Discussion

In our search for selective reductions using SmI_2/H_2O we found the reagent system reduces cyclic 1,3-diesters to the corresponding 3-hydroxy acids. Cyclic 1,3-diesters, in particular Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione), are versatile building blocks for synthesis.[4] Cyclic 1,3-diesters **1a**–**h** are reduced with SmI_2/H_2O to give the corresponding hydroxy acids **2a**–**h** in good yield (Table 1). No over-reduction is seen even in the presence of excess reagent (see below). As many cyclic 1,3-diesters are conveniently prepared by Knoevenagel condensation followed by conjugate reduction,[4] we have carried out the sequential reduction of condensation products **1i** and **1j** obtaining the expected products **2f** and **2d** in good yield. Finally, reduction of cyclopropane derivative **1k** results in sequential fragmentation/carbonyl reduction to give **2k**. To our knowledge, these are the first examples of the mono-reduction of such systems. The transformation is normally achieved in multiple steps (e.g. conversion to the monoacid, activation of the acid as a mixed anhydride, reduction using $NaBH_4$, and hydrolysis).[5]

The H_2O cosolvent is essential for the reactivity observed in our study. This observation is in line with Curran's finding that SmI_2 is activated by H_2O.[6] Flowers has since shown that the reduction potential of SmI_2 (-1.3 V) increases to a maximum of -1.9 V on the addition of up to 500 equivalents

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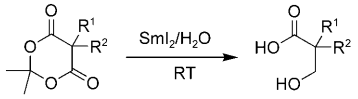
Table 1. Reduction of cyclic 1,3-diesters with SmI_2/H_2O.



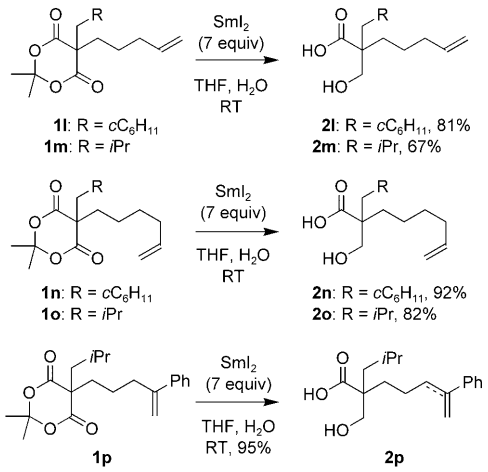
1 2

Substrate	R^1	R^2	Product	R^1	R^2	Yield [%
1a	Bn	Bn	**2a**	Bn	Bn	88[a]
1b		$-(CH_2)_4-$	**2b**		$-(CH_2)_4-$	81[a]
1c	H	Bn	**2c**	H	Bn	68[a]
1d	H	$CH_2C_6H_4$-4-OMe	**2d**	H	$CH_2C_6H_4$-4-OMe	78[a]
1e	H	$CH_2C_6H_4$-4-Br	**2e**	H	$CH_2C_6H_4$-4-Br	77[a]
1f	H	*i*Bu	**2f**	H	*i*Bu	94[a]
1g	Me	Bn	**2g**	Me	Bn	98[a]
1h	H	Ph	**2h**	H	Ph	72[a]
1i		=CH*i*Pr	**2f**	H	*i*Bu	87[b]
1j		$=CHC_6H_4$-4-OMe	**2d**	H	$CH_2C_6H_4$-4-OMe	69[b]
1k		$-CH_2CH_2-$	**2k**	H	Et	75[c]

[a] Conditions: SmI_2 (7 equiv), THF, H_2O, 2-12 h. [b] Conditions: SmI_2 (9 equiv), THF, H_2O, 6-12 h. [c] Conditions: SmI_2 (10 equiv), THF, H_2O, 1 h.

of H_2O.[7] As in the reduction of lactones with SmI_2/H_2O,[2] the cyclic nature of the substrate is essential for reaction. Collapse of the cyclic ketal after carbonyl reduction appears to account for the highly selective mono-reduction of cyclic 1,3-diesters.

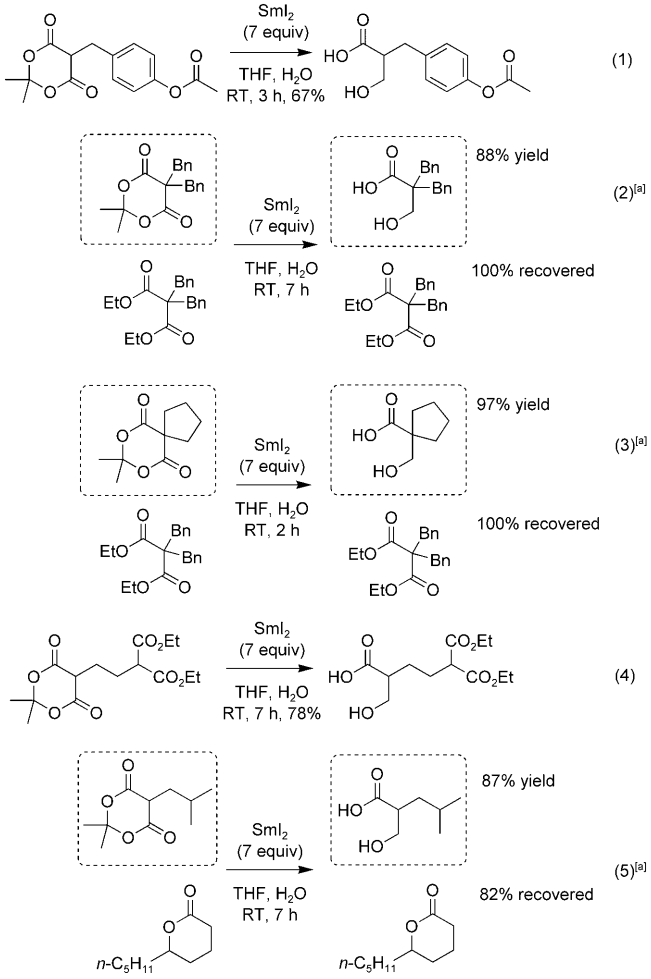
In some cases, cyclic 1,3-diesters bearing alkenes can also be reduced smoothly to the corresponding 3-hydroxy acids (Scheme 1). In the reduction of **1p**, 1,5-hydrogen atom abstraction by the radical intermediate (cf. **3** in Scheme 3) results in partial isomerization of the alkene (2:1, terminal to internal).



Scheme 1. Selective reductions of cyclic 1,3-diesters bearing alkenes with SmI_2/H_2O.

Competition experiments have been carried out to illustrate the selectivity of SmI_2/H_2O for cyclic 1,3-diesters over esters [Scheme 2, Eq. (1)] and acyclic 1,3-diesters [Scheme 2, Eqs. (2), (3) and (4)]. Further competition experiments have shown that, in some cases, SmI_2/H_2O can reduce cyclic 1,3-diesters in the presence of six-membered lactones [Scheme 2, Eq. (5)] although more reactive six-membered lactones are reduced at comparative rates to cyclic 1,3-diesters.[2]

The reduction of **1a** with SmI_2/D_2O gave [D,D]-**2a** (see Scheme 3) suggesting that anions are generated and protonated by H_2O during a series of electron transfer steps. A possible mechanism for the transformation is given in Scheme 3. Activation of the ester carbonyl by coordination to Sm^{II} and electron transfer generates radical anion **3** that is then protonated. A second electron transfer generates carbanion **5** that is quenched by H_2O. Hemiacetal **6** is in equilibrium with hydroxy aldehyde **7**, which is reduced by a third



Scheme 2. Selective reductions of cyclic 1,3-diesters with SmI_2/H_2O. [a] 1:1 mixture of substrates.

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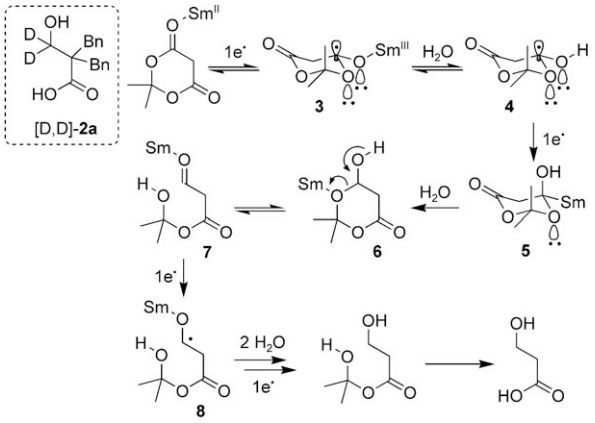
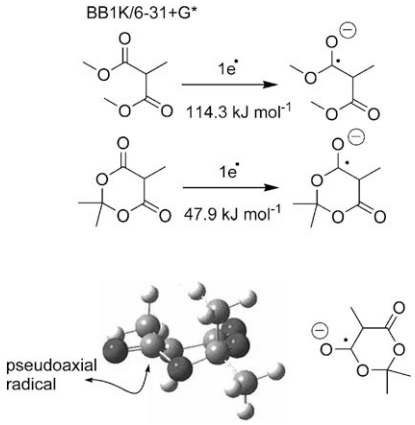
electron transfer from Sm^{II} to give a ketyl-radical anion **8**. A final electron transfer from Sm^{II} gives an organosamarium that is protonated. The amount of SmI_2 (approx. 7 equiv) required experimentally is consistent with a mechanism that requires 4 electrons (4 equiv of SmI_2). It is also important to note that one equivalent of acetone is generated during the reduction and it is likely that this is also reduced (a further 2 equiv of SmI_2) (Scheme 3).



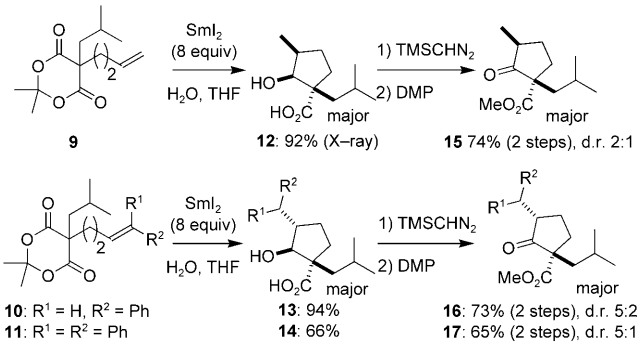
Scheme 3. Mechanism of the mono-reduction of cyclic 1,3-diesters using SmI_2/H_2O.

We propose that the observed selectivity has its origin in the rate of the initial electron transfer to the carbonyl of cyclic 1,3-diesters and that, as for six-membered lactones,[2] anomeric stabilization of the radical anion intermediate **3** is crucial for promoting the initial reduction step.[8] Calculations support this and suggest that electron transfer to the ester carbonyl in cyclic 1,3-diesters is endothermic (relative reaction energy ~50 kJ mol^{-1}) in all cases.[9] The relative reaction energy of this step for substituted dimethyl malonates, however, is calculated to be ~102–114 kJ mol^{-1}, significantly higher than those for cyclic systems (Scheme 4). The second electron transfer is predicted to be more facile, suggesting that the first reduction is rate-determining. Calculations also predict that the radical anions **3** derived from cyclic 1,3-diesters adopt a half-chair conformation with the radical in a pseudoaxial conformation, enjoying anomeric stabilization.[8] Activation of the cyclic 1,3-diesters by coordination to Sm^{II} and electrostatic stabilization of the product radical-anion by coordination to Sm^{III}[10] is likely to render these reductions more favorable than the calculated, relative reaction energies suggest.

The radical intermediates (cf. **3**) can be exploited in radical cyclizations to form five-membered rings: cyclic 1,3-diesters **9**–**11** undergo efficient radical cyclization upon treatment with SmI_2/H_2O to give cyclopentanones **15**–**17**, respectively, after esterification and oxidation (Scheme 5). The reduction of **10** with less SmI_2 resulted in the isolation of cyclopentanone byproducts thus confirming that products **12**–**14** result from cyclization of the first radical intermediate (cf. **3**) followed by reduction of the cyclopentanone intermediates that are prone to decarboxylation (see below). The addition of radicals formed by the one electron reduction of the ester carbonyl group to alkenes has little precedent in organic synthesis.[2b,11]



Scheme 4. Theoretical studies on the origin of the selectivity.



Scheme 5. Preliminary studies on radical cyclization reactions of cyclic 1,3-diesters.

Unfortunately, the stereoselectivity observed in the cyclizations was only moderate (5:1 dr) even when a bulky alkene was used (cf. substrate **11**) (Scheme 5).[3] We proposed that the diastereoselectivity of the radical cyclization of cyclic 1,3-diesters could be improved by variation of the ketal unit. To explore this idea, cyclization substrates **18**–**21** bearing different ketal units were prepared (Table 2). Treatment of cyclic 1,3-diesters **18**–**21** with SmI_2 in THF/H_2O gave cyclopentanol **22** in good yield. As the cyclopentanol product **22** was obtained as a mixture of four diastereoisomers, an esterification/oxidation sequence was again used to prepare cyclopentanone **23** and thus simplify the diastereoisomeric mixture. Diastereoisomeric ratios were then obtained by ^{1}H NMR spectroscopy. We were pleased to find that the nature of the ketal unit in the cyclic 1,3-diesters did have an effect on the diastereoselectivity of the cyclization with the acetophenone ketal giving the best stereoselectivity (dr 7:1). The relative stereochemistry of **20**, **22** (and therefore **23**) was confirmed by X-ray crystallographic analysis.[12]

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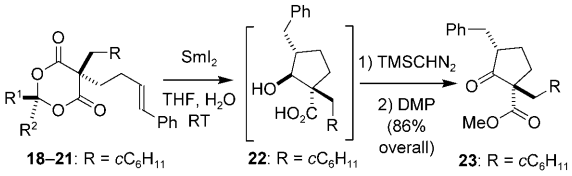
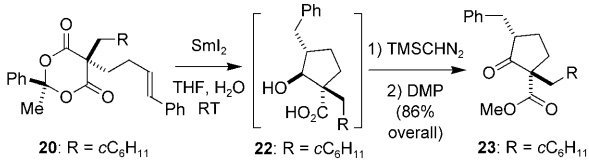
Table 2. Effect of the ketal unit on the diastereoselectivity of radical cyclizations of a cyclic 1,3-diesters.



substrate	R^1	R^2	Yield [%] **22**	d.r. (of **23**)
18	Me	Me	93	3:1
19	Et	Et	75	2:1
20	Ph	Me	79	7:1
21	-$(CH_2)_5$-		77	5:1

We next investigated the effect of temperature on the diastereoselectivity of the SmI_2-mediated cyclization and were surprised to find that improved selectivity was observed at higher temperature: cyclization of **20** at 50 °C gave **23** with greater diastereoselectivity (dr 12:1) (Table 3). (The cyclization of the dimethylacetal substrate **18** at 50 °C gave **23** in an enhanced diastereoisomeric ratio of 5:1 and an overall yield of 70 %).

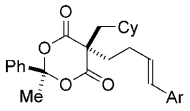
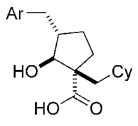
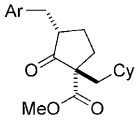
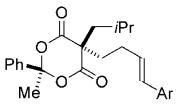
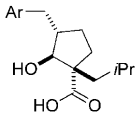
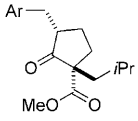
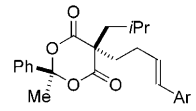
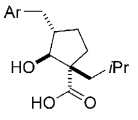
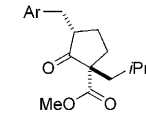
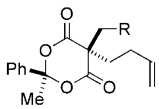
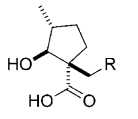
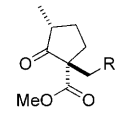
Table 3. Effect of temperature on the diastereoselectivity of radical cyclizations of cyclic 1,3-diester.



T [°C]	Yield [%] **22**	d.r. (of **23**)
0	81	3:1
RT	78	7:1
50	89	12:1

With optimized cyclization conditions in hand, we synthesized a range of cyclic 1,3-diesters from malonic acid and acetophenone, varying the substituent on the cyclic 1,3-diester and on the alkene (**20** and **24**–**30**). In all cases, treatment with SmI_2/H_2O in THF at 50 °C gave good yields of cyclopentanol product (72–90 %, **22** and **31**–**37**). Moderate diastereoselectivity (8:1 dr to 3:1 dr) was also observed in the ketone reduction step (Table 4). Again, an esterification/oxidation sequence was used to simplify the diastereoisomeric mixture and give cyclopentanones (60–86 %, **23** and **38**–**44**) in moderate to excellent diastereoisomeric excess (3:1 to 33:1 dr) (Table 4). The relative stereochemistry of **40** was determined by X-ray crystallographic analysis of a derivative.[12] The cyclization of substrates **29** and **30**, bearing unactivated, terminal alkenes, was also efficient although diastereoselectivities were lower. The relative stereochemistry of **37** was confirmed by comparison to a related compound whose structure was determined by X-ray crystallographic analysis.[3]

Table 4. Cyclizations of cyclic 1,3-diesters mediated by SmI_2/H_2O.

Substrate	Cyclopentanol product[a,b]	Cyclopentanone
 **20**: Ar = Ph **24**: Ar = 4-BrC_6H_4	 **22**: Ar = Ph, 89 %, d.r. 6:1 X-ray **31**: Ar = 4-BrC_6H_4, 74 %, d.r. 7:1	 **23**: Ar = Ph, 88 %, d.r. 12:1 **38**: Ar = 4-BrC_6H_4, 73 %, d.r. 33:1
 **25**: Ar = Ph **26**: Ar = 4-BrC_6H_4	 **32**: Ar = Ph, 83 %, d.r. 5:1 **33**: Ar = 4-BrC_6H_4, 80 %, d.r. 4:1	 **39**: Ar = Ph, 81 %, d.r. 10:1 **40**: Ar = 4-BrC_6H_4, 60 %, d.r. 24:1
 **27**: Ar = 1-naphthyl **28**: Ar = 3-Br-6-MeO phenyl	 **34**: Ar =1-naphthyl, 81 %, d.r. 7:1 **35**: Ar = 3-Br-6-MeO phenyl, 72 %, d.r. 8:1	 **41**: Ar = 1-naphthyl, 81 %, d.r. 7:1 **42**: Ar = 3-Br-6-MeO phenyl, 70 %, d.r. 5:1
 **29**: R = cC_6H_{11} **30**: R = *i*Pr	 **36**: R = cC_6H_{11}, 90 %, d.r. 3:1 **37**: R = *i*Pr, 82 %, d.r. 3:1	 **43**: R = cC_6H_{11}, 81 % d.r. 3:1 **44**: R = *i*Pr, 83 %, d.r. 3:1

[a] Reaction conditions: SmI_2 (8 equiv) was added dropwise (over 30 min) to a solution of the substrate (1 equiv) in THF and H_2O (1200 equiv) at 50 °C. [b] Diastereoisomeric ratios for cyclopentanols refer to the ratio of the major diastereoisomer to the sum of the other diastereoisomers.

Although it is possible that the cyclizations proceed by an anionic path,[13] to our knowledge the addition of organosamariums derived from carbonyls to alkenes is without precedent. In addition, the presence of a large excess of H_2O in the reactions would appear to rule out an anionic reaction, particular as it has been shown that anions are protonated very quickly in H_2O as the proton source coordinates to the Sm center of the organosamarium intermediates and protonation is intramolecular in nature.[14] We therefore suggest that the cyclizations follow a radical pathway.

The preference for the formation of axial radicals in the reduction[8] leads to possible radicals **45**/**46** and **47**/**48**. In the case of dimethyl acetals (R^1 = Me), we believe both axial radicals are accessible due to the similarity in energy between the two radicals (**45** and **47**) and the conformations of the starting material that give rise to them. However, only axial radical **45** can undergo cyclization through an electronically favored *anti* transition structure[15] to give the major product observed.[16] Axial radical **47** may undergo radical interconversion[13b] to give an equatorial radical that then cy-

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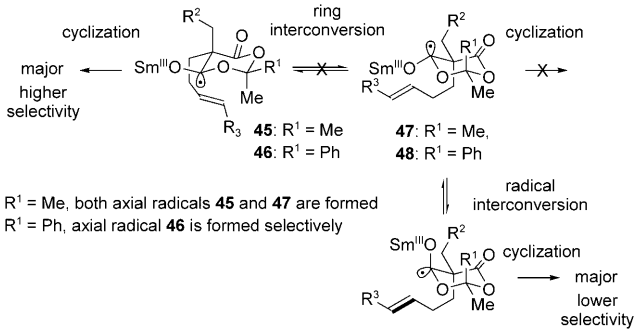
clizes in a less selective fashion. Ring interconversion between **47** and **45** may also occur but this would be expected to have a higher energy barrier than radical interconversion.[13b] We therefore believe that the use of the acetophenone ketal ($R^1 = Ph$) leads to improved diastereoselectivity in the cyclizations by exerting greater conformational control over the substrates and the intermediate radical anions and thus axial radical **46** is formed selectively (Scheme 6).

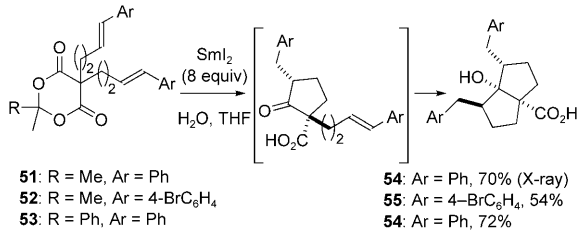


Scheme 6. Possible origin of selectivity in the cyclizations.

It is not clear why higher diastereoselectivities are obtained at increased temperature. Although most radical cyclizations are irreversible, cyclizations of stable radicals can be reversible.[17] Although unlikely, it is therefore possible that the cyclizations of these unusual radical anions may in some cases be reversible with thermodynamic control leading to higher selectivity. However, this does not explain, why the selectivity of cyclizations involving terminal alkenes does not improve with increased temperature (see Table 4). The absence of a group to stabilize the radical formed upon cyclization make these substrates the most likely to undergo reversible cyclizations. Another possibility is that the cyclopentanol products formed in the reaction undergo epimerization by a retroaldol/aldol process upon heating. However, this explanation is not consistent with the observation that different acetals of otherwise identical substrates give different diastereoisomeric ratios at higher temperatures. Studies aimed at understanding this intriguing temperature effect are continuing in our laboratory.

We have also shown that radical anions generated from cyclic-1,3-diesters can be exploited in transannular cyclizations:[18] treatment of cycloheptene **49** with SmI_2/H_2O gave bicyclic alcohol **50** as a single diastereoisomer in 55% yield (Scheme 7).

Finally, the intermediacy of cyclopentanones in the reaction sequence led us to speculate that the presence of a second alkene would result in a second radical cyclization event. To evaluate the feasibility of such cyclization cascades we prepared substrates **51**-**53**. Pleasingly, treatment of bis-alkene substrates **51** and **52** with SmI_2/H_2O gave the expected bicyclic products **54** and **55**, respectively, in moderate yield and with good diastereocontrol[19] (Scheme 8).

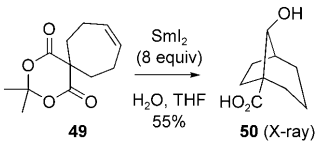


Scheme 8. Cyclization cascades of cyclic 1,3-diesters.

The relative stereochemistry of **54** was confirmed by X-ray crystallographic analysis.[12] Bicyclic alcohol **54** was also obtained from the cyclization of the acetophene-derived ketal **53**, thus confirming that ketoacids are also intermediates in the cyclizations of such substrates.

Conclusion

In summary, H_2O activation of SmI_2 allows the first reduction of cyclic 1,3-diesters using the reagent. The deconstruction of the cyclic system upon reduction ensures that no over reduction occurs and 3-hydroxyacids are obtained in good yield. The reagent system is selective for cyclic 1,3-diesters over acyclic 1,3-diesters, lactones, and esters. In addition to the selectivity of the reagent system, SmI_2 is commercially available, or convenient to prepare, easy to handle, operates at ambient temperature, and does not require toxic cosolvents or additives. Finally, the radicals formed by one electron reduction of the ester carbonyl group can be exploited in highly diastereoselective intramolecular additions to alkenes. The nature of the ketal unit and the reaction temperature have a significant effect on the selectivity of the reactions. Finally, cyclization cascades are possible when two alkenes are present in the starting cyclic diester. The cascades result in the formation of two rings and four stereocenters with good stereocontrol.



Scheme 7. Transannular cyclization of a cyclic 1,3-diester.

Experimental Section

For general experimental procedures and experimental procedures and characterisation data pertaining to Table 1 and Scheme 2 and 5, please see our preliminary report.[3] Please see Supporting Information for additional experimental details, characterization data and ^1H and ^{13}C NMR spectra for all new compounds, X-ray crystal structures for **20**, **22**, **50**, **54** and a derivative of **40** and CCDC numbers.

General procedure A (GP A): SmI_2-mediated reductions in THF/H_2O

2-Cyclohexylmethyl-2-(hydroxymethyl)hept-6-enoic acid (21): To a stirred solution of **11** (30 mg, 0.098 mmol, 1 equiv) in THF (2.0 mL) and H_2O

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(2.1 mL, 117 mmol, 1200 equiv) was added SmI_2 (0.1 M in THF, 8.0 mL, 0.800 mmol, 8 equiv) dropwise using a syringe pump over 30 min. After decolorization of the reaction mixture, the reaction was opened to air and saturated aqueous sodium chloride (15 mL) and tartaric acid (25 mg) were added. The aqueous phase was extracted with ethyl acetate (3× 20 mL) and the combined organic phases dried (Na_2SO_4 or $MgSO_4$) and concentrated in vacuo. Purification by column chromatography on silica gel, eluting with 50% CH_2Cl_2 in petroleum ether (40–60 °C) and 1% acetic acid gave **2l** (20 mg, 0.079 mmol, 81%) as a white solid. M.p. 88–90 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89–1.03 (m, 2H, 2H from Cy), 1.05–1.30 (m, 3H, 3H from Cy), 1.30–1.45 (m, 3H, 2H from CH_2, 1H from CH_2CH), 1.49 (dd, 1H, J=14.4, 5.5 Hz, 1H from CH_2CH), 1.54–1.77 (m, 7H, 5H from Cy, 2H from CH_2), 1.58 (dd, 1H, J=14.4, 6.6 Hz, 1H from CH_2CH), 2.06 (q, 2H, J=7.1 Hz, $CH_2CH{=}CH_2$), 3.65 (d, 1H, J=11.3 Hz, 1H from CH_2OH), 3.81 (d, 1H, J=11.3 Hz, 1H from CH_2OH), 4.97 (d, 1H, J=10.2 Hz, 1H from $CH_2{=}CH$), 5.02 (dd, 1H, J=17.0, 1.4 Hz, 1H from $CH_2{=}CH$), 5.78 ppm (ddt, 1H, J=17.0, 10.2, 6.7 Hz, $CH_2{=}CH$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.3 (CH_2), 26.2 (CH_2 from Cy), 26.4 (2 × CH_2 from Cy), 33.6 (CH_2), 33.8 (CH_2CH), 34.1 (CH_2), 34.2 (CH_2 from Cy), 34.9 (CH_2 from Cy), 41.3 (CH_2CH), 50.0 (C^q), 64.7 (CH_2OH), 114.9 ($CH_2{=}CH$), 138.3 ($CH_2{=}CH$), 183.1 ppm (C=O); IR (neat): ν_{max} = 3376 (br, OH), 2922, 2850, 1691 (C=O), 1640, 1448, 1257, 1235, 1217, 1034, 905, 827, 663 cm^{-1}; MS (ES+): m/z (%): calcd for $C_{15}H_{26}O_3Na$: 277.1774; found: 277.1782 $[M+Na]^+$.

2-Hydroxymethyl-2-isobutylhept-6-enoic acid (2m): As for GP A, reaction of **1m** (30 mg, 0.112 mmol, 1 equiv) in THF (2.0 mL) and H_2O (2.4 mL, 134 mmol, 1200 equiv) with SmI_2 (0.1 M in THF, 9.0 mL, 0.90 mmol, 8 equiv) after column chromatography on silica gel, eluting with 30% ethyl acetate in petroleum ether (40–60 °C) gave **2m** (16 mg, 0.074 mmol, 67%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (d, 6H, J=6.6 Hz, 2 × CH_3CH), 1.31–1.47 (m, 2H, CH_2), 1.49–1.66 (m, 3H, 3H from CH_2), 1.66–1.77 (m, 2H, 1H from CH_2, 1H from CH_2CH), 2.06 (q, 2H, J=7.1 Hz, $CH_2CH{=}CH_2$), 3.65 (d, 1H, J=11.3 Hz, 1H from CH_2OH), 3.82 (d, 1H, J=11.3 Hz, 1H from CH_2OH), 4.97 (ddt, 1H, J=10.3, 1.8, 1.0 Hz, 1H from $CH_2{=}CH$), 5.02 (ddt, 1H, J=17.2, 1.8, 1.8 Hz, 1H from $CH_2{=}CH$), 5.79 ppm (ddt, 1H, J=17.2, 10.3, 6.6 Hz, $CH_2{=}CH$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.2 (CH_2), 23.6 (CH_2CH), 24.3 (CH_3CH), 24.4 (CH_3CH), 33.4 (CH_2), 34.1 (CH_2), 42.6 (CH_2CH), 50.1 (C^q), 64.7 (CH_2OH), 114.9 ($CH_2{=}CH$), 138.3 ($CH_2{=}CH$), 183.1 ppm (C=O); IR (neat): ν_{max} = 3376 (br, OH), 3076, 2952, 2869, 2360, 1697 (C=O), 1640, 1460, 1388, 1367, 1234, 1038, 909 cm^{-1}; MS (ES+): m/z: calcd for $C_{12}H_{22}O_3Na$: 237.1461; found: 237.1455 $[M+Na]^+$.

2-Cyclohexylmethyl-2-(hydroxymethyl)oct-7-enoic acid (2n): As for GP A, reaction of **1n** (30 mg, 0.093 mmol, 1 equiv) in THF (2.0 mL) and H_2O (2.0 mL, 112 mmol, 1200 equiv) with SmI_2 (0.1 M in THF, 7.5 mL, 0.75 mmol, 8 equiv) after column chromatography on silica gel, eluting with 30% ethyl acetate in petroleum ether (40–60 °C) gave **2n** (23 mg, 0.086 mmol, 92%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90–1.02 (m, 2H, 2H from Cy), 1.05–1.45 (m, 8H, 3H from Cy, 4H from CH_2, 1H from CH_2CH), 1.49 (dd, 1H, J=14.4, 5.5 Hz, 1H from CH_2CH), 1.53–1.75 (m, 7H, 5H from Cy, 2H from CH_2), 1.58 (dd, 1H, J=14.4, 6.3 Hz, 1H from CH_2CH), 2.07 (q, 2H, J=7.0 Hz, $CH_2CH{=}CH_2$), 3.65 (d, 1H, J=11.3 Hz, 1H from CH_2OH), 3.80 (d, 1H, J=11.3 Hz, 1H from CH_2OH), 4.95 (ddt, 1H, J=10.3, 1.8, 1.0 Hz, 1H from $CH_2{=}CH$), 5.01 (ddt, 1H, J=17.2, 1.8, 1.8 Hz, 1H from $CH_2{=}CH$), 5.80 ppm (ddt, 1H, J=17.2, 10.3, 6.6 Hz, $CH_2{=}CH$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.3 (CH_2), 26.1 (CH_2 from Cy), 26.3 (CH_2 from Cy), 29.3 (CH_2 from Cy), 29.7 (CH_2), 33.5 (CH_2), 33.8 (CH_2CH, CH_2), 34.2 (CH_2 from Cy), 34.8 (CH_2 from Cy), 41.2 (CH_2CH), 50.0 (C^q), 64.7 (CH_2OH), 114.5 ($CH_2{=}CH$), 138.7 ($CH_2{=}CH$), 183.2 ppm (C=O); IR (neat): ν_{max} = 3376 (br, OH), 3076, 2920, 2850, 2360, 1694 (C=O), 1640, 1448, 1254, 1214, 1036, 988, 907, 732 cm^{-1}; MS (ES+): m/z: calcd for $C_{16}H_{28}O_3Na$: 291.1931291; found: 291.1932 $[M+Na]^+$.

2-Hydroxymethyl-2-isobutyloct-7-enoic acid (2o): As for GP A, reaction of **1o** (31 mg, 0.111 mmol, 1 equiv) in THF (2.0 mL) and distilled water (2.3 mL, 133 mmol, 1200 equiv) with SmI_2 (0.1 M in THF, 8.5 mL, 0.85 mmol, 8 equiv) after column chromatography on silica gel, eluting with 30% ethyl acetate in petroleum ether (40–60 °C) gave **2o** (18.3 mg, 0.080 mmol, 82%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (d, 6H, J=6.6 Hz, 2 × CH_3CH), 1.21–1.35 (m, 2H, CH_2), 1.35–1.45 (m, 2H, CH_2), 1.49–1.65 (m, 3H, 3H from CH_2), 1.66–1.78 (m, 2H, 1H from CH_2, 1H from CH_2CH), 2.06 (q, 2H, J=7.0 Hz, $CH_2CH{=}CH_2$), 3.66 (d, 1H, J=11.3 Hz, 1H from CH_2OH), 3.81 (d, 1H, J=11.3 Hz, 1H from CH_2OH), 4.95 (ddt, 1H, J=10.1, 1.8, 1.0 Hz, 1H from $CH_2{=}CH$), 5.00 (ddt, 1H, J=17.2, 1.8, 1.8 Hz, 1H from $CH_2{=}CH$), 5.79 ppm (m, 1H, J=17.2, 10.1, 6.8 Hz, $CH_2{=}CH$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.3 (CH_2), 23.6 (CH_2CH), 24.3 (CH_3CH), 24.4 (CH_3CH), 29.3 (CH_2), 33.5 (CH_2), 33.7 (CH_2), 42.6 (CH_2), 50.2 (C^q), 64.6 (CH_2OH), 114.5 ($CH_2{=}CH$), 138.7 ($CH_2{=}CH$), 183.1 ppm (C=O); IR (neat): ν_{max} = 3376 (br, OH), 3076, 2926, 2868, 2360, 1694 (C=O), 1640, 1462, 1387, 1367, 1238, 1037, 908 cm^{-1}; MS (ES+): m/z: calcd for $C_{13}H_{25}O_3$: 229.1798; found: 229.1798 $[M+H]^+$.

2-Hydroxymethyl-2-isobutyl-6-phenyl-hept-5-enoic acid and 2-hydroxymethyl-2-isobutyl-6-phenyl-hept-6-enoic acid (2p): As for GP A, reaction of **1p** (75 mg, 0.227 mmol, 1 equiv) in THF (3.0 mL) and distilled water (4.5 mL, 250 mmol, 1100 equiv) with SmI_2 (0.1 M in THF, 18.2 mL, 1.82 mmol, 8 equiv) after column chromatography on silica gel, eluting with 60% ethyl acetate in petroleum ether (40–60 °C) gave **2p** (2:1, terminal alkene/internal alkene) (59 mg, 0.216 mmol, 95%) as a colorless oil. *Major regioisomer*: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.76 (d, 3H, J=6.6 Hz, $CHCH_3$), 0.78 (d, 3H, J=6.6 Hz, $CHCH_3$), 1.36 (m, 1H, CH), 1.41 (dd, 2H, J=6.0, 2.6 Hz, CCH_2CH_2), 1.45–1.78 (m, 4H, 2 × CH_2), 2.32–2.55 (m, 2H, $CH_2{=}CCH_2$), 3.49 (d, 1H, J=11.5 Hz, 1H from CH_2OH), 3.65 (d, 1H, J=11.5 Hz, 1H from CH_2OH), 4.97 (d, 1H, J=1.7 Hz, $C{=}CH_2$) 5.21 (d, 1H, J=1.7 Hz, $C{=}CH_2$), 7.06–7.37 ppm (m, 5H, 5 × Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.7 (CH), 24.2 ($CHCH_3$), 24.3 ($CHCH_3$), 29.7 (CH_2), 33.0 (CH_2), 35.6 ($CH_2{=}CCH_2$), 42.4 (CCH_2CH_2), 50.1 (C^q), 64.7 (CH_2OH), 112.7 ($C{=}CH_2$), 126.1 (2 × ArCH), 127.4 (ArCH), 128.3 (2 × ArCH), 141.1 (C^q), 147.9 (ArC^q), 182.8 ppm (C=O); *minor regioisomer*: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (d, 6H, J=6.6 Hz, $CHCH_3$), 1.45–1.84 (m, 5H, CH and 2 × CH_2), 1.95 (d, 3H, J=1.3 Hz, $CH{=}CCH_3$), 2.04–2.21 (m, 2H, $CH_2CH{=}C$), 3.64 (d, 1H, J=11.6 Hz, 1H from CH_2OH), 3.79 (d, 1H, J=11.6 Hz, 1H from CH_2OH), 5.66 (td, 1H, J=7.1, 1.4 Hz, CH=C), 7.01–7.35 ppm (m, 5H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.8 ($CH{=}CCH_3$), 23.5 (CH_2), 23.7 ($CHCH_3$), 24.4 ($CHCH_3$), 24.4 (CH), 33.7 (CH_2), 42.7 (CH_2), 50.2 (C^q), 64.7 (CH_2OH), 125.6 (2 × ArCH), 126.63 (ArCH), 127.4 ($C{=}CH$), 128.2 (2 × ArCH), 135.4 (C^q), 143.7 (C^q), 182.7 ppm (C=O); IR (evap. film): ν_{max} = 3409 (OH), 2954, 2927, 2868, 1698 (C=O), 1493, 1447, 1367, 1226, 1135, 1056, 1027, 919 cm^{-1}; MS (ES−): m/z: calcd for $C_{11}H_{14}O_5Na$: 289.1804; found: 289.1807 $[M-H+Na]^+$.

General procedure B (GP B): SmI_2-mediated cyclizations in THF/H_2O

rac-(1*R*,2*S*,3*S*)-3-Benzyl-1-cyclohexylmethyl-2-hydroxy-cyclopentanecarboxylic acid (22): To a stirred solution of **18** (100 mg, 0.280 mmol, 1 equiv) in THF (1.0 mL) and H_2O (6.0 mL, 336 mmol, 1200 equiv) was added SmI_2 (0.1 M in THF, 22.5 mL, 2.25 mmol, 8 equiv) dropwise using a syringe pump over 30 min. After decolorization of the reaction mixture, the reaction was opened to air and saturated aqueous sodium chloride (15 mL) and tartaric acid (50 mg) were added. The aqueous phase was extracted with ethyl acetate (3×20 mL) and the combined organic phases dried (Na_2SO_4 or $MgSO_4$) and concentrated in vacuo. Purification by column chromatography on silica gel, eluting with 20% ethyl acetate in petroleum ether (40–60 °C) gave 3-benzyl-1-cyclohexylmethyl-2-hydroxy-cyclopentanecarboxylic acid (82 mg, 0.260 mmol, 93%) as a white solid. The product was obtained as a mixture of four diastereoisomers of which **22** was the major diastereoisomer (3:1 (others)). M.p. 43–45 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85–1.07 (m, 2H, 2H from CH_2), 1.07–1.42 (m, 6H, 6H from CH_2), 1.57–1.71 (m, 7H, 7H from CH_2), 1.84–1.93 (m, 1H, 1H from CH_2), 2.11–2.18 (m, 1H, $ArCH_2CH$), 2.18–2.24 (m, 1H, 1H from CH_2), 2.50 (dd, 1H, J=13.4, 9.6 Hz, 1H from $ArCH_2$), 3.03 (dd, 1H, J=13.4, 4.8 Hz, 1H from $ArCH_2$), 3.84 (d, 1H, J=8.8 Hz, CHOH), 7.17–7.24 (m, 3H, 3 × ArH), 7.26–7.33 ppm (m, 2H, 2 × ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.0 (CH_2), 25.2 (CH_2), 25.3 (CH_2), 25.4 (CH_2), 27.7 (CH_2), 32.4 (CH_2), 33.3 (CH from Cy), 34.1 (CH_2), 37.4 (HO_2CCCH_2), 38.8 ($ArCH_2$), 44.9 ($ArCH_2CH$), 53.6 (C^q), 81.6 (CHOH), 125.0 (ArCH), 127.3 (2 × ArCH), 127.9 (2 × ArCH), 139.7 (ArC^q),

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182.8 ppm (C=O); IR (neat): ν_{max} = 3395, 2920, 2849, 1693 (C=O), 1445, 1209, 1062, 748, 698 cm^{-1}; MS (ES+): *m/z*: calcd for $C_{20}H_{28}O_3Na$: 339.1931; found: 339.1934 $[M+Na]^+$.

***rac*-(1*R*,2*S*,3*S*)-3-(4-Bromobenzyl)-1-cyclohexylmethyl-2-hydroxycyclopentanecarboxylic acid (31)**: As for GP B, with the exception that reaction was warmed to 50 °C prior to addition of SmI_2 and that the temperature was maintained until the reaction was quenched. Reaction of **24** (75 mg, 0.147 mmol, 1 equiv) in THF (2.0 mL) and H_2O (2.9 mL, 161 mmol, 1100 equiv) with SmI_2 (0.1 M in THF, 11.7 mL, 1.17 mmol, 8 equiv) after column chromatography on silica gel, eluting with 10% ethyl acetate in hexane gave 3-(4-bromobenzyl)-1-cyclohexylmethyl-2-hydroxy-cyclopentanecarboxylic acid (46 mg, 0.109 mmol, 74%) as a white solid. The product was obtained as a mixture of four diastereoisomers of which **31** was the major diastereoisomer (7:1 (others)). Characterization was undertaken on the product of subsequent esterification and oxidation **38**.

***rac*-(1*R*,2*S*,3*S*)-3-Benzyl-2-hydroxy-1-isobutylcyclopentanecarboxylic acid (32)**: As for general procedure B, with the exception that reaction was warmed to 50 °C prior to addition of SmI_2 and that the temperature was maintained until the reaction was quenched. Reaction of **25** (76 mg, 0.243 mmol, 1 equiv) in THF (2.0 mL) and H_2O (4.9 mL, 272 mmol, 1100 equiv) with SmI_2 (0.1 M in THF, 19.4 mL, 1.94 mmol, 8 equiv) after column chromatography on silica gel, eluting with 10% ethyl acetate in hexane gave 3-benzyl-2-hydroxy-1-isobutylcyclopentanecarboxylic acid (43 mg, 0.202 mmol, 83%) as a colorless oil. The product was obtained as a mixture of four diastereoisomers of which **32** was the major diastereoisomer (6:1 (others)). Characterization was undertaken on the product of subsequent esterification and oxidation **39**.

***rac*-(1*R*,2*S*,3*S*)-3-(4-Bromobenzyl)-2-hydroxy-1-isobutylcyclopentanecarboxylic acid (33)**: As for general procedure B, with the exception that reaction was warmed to 50 °C prior to addition of SmI_2 and that the temperature was maintained until the reaction was quenched. Reaction of **26** (62 mg, 0.130 mmol, 1 equiv) in THF (2.0 mL) and H_2O (2.9 mL, 158 mmol, 1200 equiv) with SmI_2 (0.1 M in THF, 10.5 mL, 1.05 mmol, 8 equiv) after column chromatography on silica gel, eluting with 10% ethyl acetate in hexane gave 3-(4-bromobenzyl)-2-hydroxy-1-isobutyl-cyclopentanecarboxylic acid (37 mg, 0.104 mmol, 80%) as a colorless oil. The product was obtained as a mixture of four diastereoisomers of which **33** was the major diastereoisomer (4:1 (others)). Characterization was undertaken on the product of subsequent esterification and oxidation **40**.

***rac*-(1*R*,2*S*,3*S*)-2-Hydroxy-1-isobutyl-3-naphthalen-1-ylmethylcyclopentanecarboxylic acid (34)**: As for general procedure B, with the exception that reaction was warmed to 50 °C prior to addition of SmI_2 and that the temperature was maintained until the reaction was quenched. Reaction of **27** (55 mg, 0.124 mmol, 1 equiv) in THF (2.0 mL) and H_2O (2.7 mL, 272 mmol, 1200 equiv) with SmI_2 (0.1 M in THF, 10 mL, 1.0 mmol, 8 equiv) after column chromatography on silica gel, eluting with 10% ethyl acetate in hexane gave 2-hydroxy-1-isobutyl-3-naphthalen-1-ylmethylcyclopentanecarboxylic acid (33 mg, 0.202 mmol, 82%) as a colorless oil. The product was obtained as a mixture of four diastereoisomers of which **34** was the major diastereoisomer (7:1 (others)). Characterization was undertaken on the product of subsequent esterification and oxidation **41**.

***rac*-(1*R*,2*S*,3*S*)-3-(5-Bromo-2-methoxybenzyl)-2-hydroxy-1-isobutylcyclopentanecarboxylic acid (35)**: As for general procedure B, with the exception that reaction was warmed to 50 °C prior to addition of SmI_2 and that the temperature was maintained until the reaction was quenched. Reaction of **28** (33 mg, 0.070 mmol, 1 equiv) in THF (2.0 mL) and H_2O (1.4 mL, 79.2 mmol, 1200 equiv) with SmI_2 (0.1 M in THF, 5.3 mL, 0.53 mmol, 8 equiv) after column chromatography on silica gel, eluting with 10% ethyl acetate in hexane gave 3-(5-bromo-2-methoxybenzyl)-2-hydroxy-1-isobutylcyclopentanecarboxylic acid (18.2 mg, 0.202 mmol, 72%) as a colorless oil. The product was obtained as a mixture of four diastereoisomers of which **35** was the major diastereoisomer (8:1 (others)). Characterization was undertaken on the product of subsequent esterification and oxidation **42**.

***rac*-(1*R*,2*S*,3*S*)-1-Cyclohexylmethyl-2-hydroxy-3-methylcyclopentanecarboxylic acid (36)**: As for general procedure B, with the exception that reaction was warmed to 50 °C prior to addition of SmI_2 and that the temperature was maintained until the reaction was quenched. Reaction of **29** (75 mg, 0.210 mmol, 1 equiv) in THF (2.0 mL) and H_2O (4.2 mL, 233 mmol, 1100 equiv) with SmI_2 (0.1 M in THF, 16.8 mL, 1.68 mmol, 8 equiv) after column chromatography on silica gel, eluting with 10% ethyl acetate in hexane gave 1-cyclohexylmethyl-2-hydroxy-3-methylcyclopentanecarboxylic acid (45 mg, 0.189 mmol, 90%) as a colorless oil. The product was obtained as a mixture of four diastereoisomers which **36** was the major diastereoisomer (3:1 (others)). Characterization was undertaken on the product of subsequent esterification and oxidation **43**.

***rac*-(1*R*,2*S*,3*S*)-2-Hydroxy-1-isobutyl-3-methylcyclopentanecarboxylic acid (37)**: As for general procedure B, with the exception that reaction was warmed to 50 °C prior to addition of SmI_2 and that the temperature was maintained until the reaction was quenched. Reaction of **30** (60 mg, 0.189 mmol, 1 equiv) in THF (2.0 mL) and H_2O (4.1 mL, 228 mmol, 1200 equiv) with SmI_2 (0.1 M in THF, 15.2 mL, 1.52 mmol, 8 equiv) after column chromatography on silica gel, eluting with 10% ethyl acetate in hexane gave 2-hydroxy-1-isobutyl-3-methylcyclopentanecarboxylic acid (31 mg, 0.189 mmol, 82%) as a colorless oil. The product was obtained as a mixture of four diastereoisomers which **37** was the major diastereoisomer (3:1 (others)). Characterization was undertaken on the product of subsequent esterification and oxidation **44**.

General Procedure C: Esterification-oxidation sequence to form keto-esters

***rac*-(1*R*,3*S*)-3-Benzyl-1-cyclohexylmethyl-2-oxocyclopentanecarboxylic acid methyl ester (23)**: To a stirred solution of the four diastereoisomers of 3-benzyl-1-cyclohexylmethyl-2-hydroxycyclopentanecarboxylic acid (33 mg, 0.104 mmol, 1 equiv) in methanol (4.0 mL) and toluene (1.0 mL), was added dropwise trimethylsilyl diazomethane (2 M in hexane, 0.115 mL, 0.229 mmol, 2.2 equiv) and the reaction stirred for 1 h. The solvent was removed in vacuo and the crude product redissolved in CH_2Cl_2 (5.0 mL). Dess–Martin periodinane (65 mg, 0.155 mmol, 1.6 equiv) was subsequently added, and the reaction stirred for 1.5 h prior to quenching with water (15 mL). The aqueous phase was extracted with CH_2Cl_2 (3× 10 mL), the combined organic phases dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography on silica gel, eluting with 5% ethyl acetate in hexane gave 3-benzyl-1-cyclohexylmethyl-2-oxo-cyclopentanecarboxylic acid methyl ester (30 mg, 0.092 mmol, 88%) as a colorless oil and as an 12:1 mixture of diastereoisomers of which **23** was the major. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97–1.10 (m, 2H, CH_2 from Cy), 1.14–1.36 (m, 2H, CH_2 from Cy), 1.35–1.49 (m, 1H, CH from Cy), 1.56 (dd, 1H, J = 14.1, 6.6 Hz, 1H from CH_2Cy), 1.61–1.88 (m, 8H, 6H from Cy, 1H from CHCH_2CH$_2$, 1H from CHCH$_2$CH_2), 2.09–2.17 (m, 1H, 1H from CHCH_2CH$_2$), 2.20 (dd, 1H, J = 14.1, 6.6 Hz, 1H from CH_2Cy), 2.51–2.66 (m, 1H, CHCH$_2$Ph), 2.67–2.75 (m, 2H, 1H from CH_2Ph, 1H from CHCH$_2$CH_2), 3.27 (dd, 1H, J = 13.5, 3.9 Hz, 1H from CH_2Ph), 3.74 (s, 3H, OCH_3), 7.27 ppm (m, 5H, 5 × Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.1 (CH_2 from Cy), 26.2 (2 × CH_2 from Cy), 26.4 (CH_2 from Cy), 30.9 (CHCH$_2$CH_2), 33.5 (CH_2 from Cy), 34.1 (CH_2 from Cy), 34.8 (CH from Cy), 36.3 (CH_2Ar), 42.5 (CCH_2), 50.9 (CHCH$_2$Ar), 52.5 (OCH_3), 61.2 (C^q), 126.2 (ArCH), 128.3 (2 × ArCH), 129.0 (2 × ArCH), 139.4 (ArC^q), 170.9 (C$OOCH_3$), 214.9 ppm (C=O); IR (evap. film): ν_{max} = 2923, 2850, 2362, 1747 (C=O), 1721 (C=O), 1450, 1210, 912, 699 cm^{-1}; MS (ES+): *m/z*: calcd for $C_{21}H_{28}O_3Na$: 351.1917; found: 351.1931 $[M+Na]^+$.

***rac*-(1*R*,3*S*)-3-(4-Bromobenzyl)-1-cyclohexylmethyl-2-oxo-cyclopentane carboxylic acid methyl ester (38)**: As for general procedure C, the four diastereoisomers of 3-(4-bromobenzyl)-1-cyclohexylmethyl-2-hydroxycyclopentanecarboxylic acid (58 mg, 0.109 mmol, 1 equiv) in methanol (1.0 mL) and toluene (0.25 mL), were treated with trimethylsilyl diazomethane (2 M in hexane, 0.436 mL, 0.872 mmol, 8 equiv) added dropwise over 4 h. When the reaction was complete, the solvent was removed in vacuo and the crude product redissolved in CH_2Cl_2 (2.0 mL). Treatment with the Dess–Martin periodinane (96 mg, 0.230 mmol, 2.1 equiv) and purification by column chromatography on silica gel, eluting with 3% ethyl acetate in hexane, gave 3-(4-bromobenzyl)-1-cyclohexylmethyl-2-oxo-cyclopentane carboxylic acid methyl ester (37 mg, 0.089 mmol, 82%) as a colorless oil and as a 33:1 mixture of diastereoisomers of which **38** was

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the major. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83–0.98 (m, 2H, CH_2 from Cy), 1.06–1.21 (m, 2H, CH_2 from Cy), 1.21–1.34 (m, 1H, CH), 1.43 (dd, 1H, J=14.2, 6.4 Hz, 1H from CH_2Cy), 1.51–1.71 (m, 8H, 6H from Cy, 1H from $CHCH_2CH_2$, 1H from $CHCH_2CH_2$), 1.95–2.04 (m, 1H, 1H from $CHCH_2CH_2$), 2.08 (dd, 1H, J=14.2, 6.4 Hz, CH_2 from Cy), 2.42–2.51 (m, 1H, $CHCH_2$Ar), 2.53–2.63 (m, 2H, 1H from CH_2Ar, 1H from $CHCH_2CH_2$), 3.07 (dd, 1H, J=13.7, 4.2 Hz, 1H from CH_2Ar), 3.62 (s, 3H, OCH_3), 7.03 (d, 2H, J=8.3 Hz, 2 × ArCH), 7.38 ppm (d, 2H, J=8.3 Hz, 2 × ArCH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.1 (CH_2), 26.3 (brs, 3 × CH_2), 31.0 ($CHCH_2CH_2$), 33.5 (CH_2 from Cy), 34.2 (CH_2 from Cy), 34.9 (CH from Cy), 35.7 (CH_2Ar), 42.6 (CH_2Cy), 50.6 ($CHCH_2$Ar), 52.5 (OCH_3), 61.2 (C^q), 120.1 (ArC^q), 130.9 (2 × ArCH), 131.4 (2 × ArCH), 138.3 (ArC^q), 170.9 (COOH), 214.7 ppm (C=O); IR (neat): ν_{max} = 2921, 2850, 1748 (C=O), 1720 (C=O), 1487, 1447, 1207, 1157, 1071, 1010, 732 cm^{-1}; MS (ES+): m/z: calcd for $C_{21}H_{27}O_3BrNa$: 429.1036; found: 429.1034 $[M+Na]^+$.

***rac*-(1*R*,3*S*)-3-Benzyl-1-isobutyl-2-oxo-cyclopentanecarboxylic acid methyl ester (39)**: As for general procedure C, the four diastereoisomers of 3-benzyl-2-hydroxy-1-isobutylcyclopentanecarboxylic acid (43 mg, 0.158 mmol, 1 equiv) in methanol (1.0 mL) and toluene (0.25 mL), were treated with trimethylsilyl diazomethane (2 M in hexane, 0.630 mL, 1.26 mmol, 8 equiv) added dropwise over 4 h. When the reaction was complete, the solvent was removed in vacuo and the crude product redissolved in CH_2Cl_2 (2.0 mL). Treatment with the Dess–Martin periodinane (120 mg, 0.255 mmol, 1.8 equiv) and purification by column chromatography on silica gel, eluting with 3% ethyl acetate in hexane gave3-benzyl-1-isobutyl-2-oxo-cyclopentanecarboxylic acid methyl ester (35 mg, 0.137 mmol, 81%) as a colorless oil and as a 7:1 mixture of diastereoisomers of which **39** was the major. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (d, 3H, J=6.6 Hz, $CHCH_3$), 0.86 (d, 3H, J=6.6 Hz, $CHCH_3$), 1.40 (dd, 1H, J=14.0, 6.9 Hz, 1H from CH_2CHCH_3), 1.55–1.74 (m, 3H, $CHCH_3$, 1H from $CHCH_2CH_2$, 1H from $CHCH_2CH_2$)), 1.95–2.04 (m, 1H, 1H from $CHCH_2CH_2$), 2.12 (dd, 1H, J=14.0, 6.6 Hz, 1H from CH_2CHCH_3), 2.42–2.52 (m, 1H, $CHCH_2$Ar), 2.54–2.62 (m, 2H, 1H from $CHCH_2CH_2$, 1H from CH_2Ar), 3.12 (dd, 1H, J=13.6, 4.0 Hz, 1H from CH_2Ar), 3.60 (s, 3H, OCH_3), 7.09–7.14 (m, 2H, 2 × ArCH), 7.17–7.21 (m, 1H, ArCH), 7.22–7.28 ppm (m, 2H, 2 × ArCH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.1 ($CHCH_3$), 23.6 ($CHCH_3$), 25.6 ($CH(CH_3)_2$), 26.4 ($CHCH_2CH_2$), 31.0 ($CHCH_2CH_2$), 36.3 (CH_2Ar), 44.0 ($CH_2CH(CH_3)_2$), 50.9 ($CHCH_2$Ar), 52.5 (OCH_3), 61.6 (C^q), 126.3 (ArCH), 128.4 (2 × ArCH), 129.0 (2 × ArCH), 139.4 (ArC^q), 170.7 ($COOCH_3$), 214.8 ppm (C=O); IR (neat): ν_{max} = 2954, 2871, 2361, 2343, 1748 (C=O), 1721 (C=O), 1453,1216, 1161, 699 cm^{-1}; MS (ES+): m/z: calcd for $C_{18}H_{24}O_3Na$: 311.1618; found: 311.1629 $[M+Na]^+$.

***rac*-(1*R*,3*S*)-3-(4-Bromobenzyl)-1-isobutyl-2-oxo-cyclopentane carboxylic acid methyl ester (40)**: As for general procedure C, the four diastereoisomers of 3-(4-bromobenzyl)-2-hydroxy-1-isobutylcyclopentanecarboxylic acid (78 mg, 0.22 mmol, 1 equiv) in methanol (4.0 mL) and toluene (1.0 mL), were treated with trimethylsilyl diazomethane (2 M in hexane, 0.240 mL, 0.485 mmol, 2.2 equiv) dropwise over 1 h. When the reaction was complete, the solvent was removed in vacuo and the crude product redissolved in CH_2Cl_2 (5.0 mL). Treatment with the Dess–Martin periodinane (136 mg, 0.320 mmol, 1.55 equiv) and purification by column chromatography on silica gel, eluting with 5% ethyl acetate in hexane gave 3-(4-bromobenzyl)-1-isobutyl-2-oxo-cyclopentanecarboxylic acid methyl ester (31 mg, 0.084 mmol, 60%) as a yellow oil and as an 25:1 mixture of diastereoisomers of which **40** was the major. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (d, 3H, J=6.6 Hz, $CHCH_3$), 0.87 (d, 3H, J=6.6 Hz, $CHCH_3$), 1.41 (dd, 1H, J=14.1, 6.8 Hz, 1H from CH_2CHCH_3), 1.56–1.74 (m, 3H, $CHCH_3$, 1H from $CHCH_2CH_2$, 1H from $CHCH_2CH_2$), 1.94–2.06 (m, 1H, 1H from $CHCH_2CH_2$), 2.13 (dd, 1H, J=14.1, 6.6 Hz, CH_2CHCH_3), 2.39–2.52 (m, 1H, $CHCH_2CH_2$), 2.55–2.63 (m, 2H, 1H from $CHCH_2CH_2$, 1H from CH_2Ar), 3.06 (dd, 1H, J=13.7, 4.2 Hz, 1H from CH_2Ar), 3.61 (s, 3H, OCH_3), 7.01 (d, 2H, J=8.3 Hz, 2 × ArH), 7.39 ppm (d, 2H, J=8.3 Hz, 2 × ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.0 ($CHCH_3$), 23.6 ($CHCH_3$), 25.5 ($CH(CH_3)_2$), 26.2 ($CHCH_2CH_2$), 31.0 ($CHCH_2CH_2$), 35.6 ($CHCH_2$Ar), 43.9 ($CH_2CH(CH_3)_2$), 50.6 ($CHCH_2$Ar), 52.5 (OCH_3), 61.5 (C^q), 120.1 (ArC^q), 130.8 (2 × ArCH), 131.4 (2 × ArCH), 138.2 (ArC^q), 170.6 ($COOCH_3$), 214.5 ppm (C=O); IR (evap. film): ν_{max} = 2925, 2955, 1750, 1749 (C=O), 1723 (C=O), 1487, 1488, 1218, 1162, 1011, 903, 704 cm^{-1}; MS (ES+): m/z: calcd for $C_{18}H_{23}O_3BrNa$: 391.0692; found: 391.0702 $[M+Na]^+$.

***rac*-(1*R*,3*S*)-1-Isobutyl-3-naphthalen-1-ylmethyl-2-oxocyclopentanecarboxylic acid methyl ester (41)**: As for general procedure C, the four diastereoisomers of 2-hydroxy-1-isobutyl-3-naphthalen-1-ylmethyl-cyclopentanecarboxylic acid (33 mg, 0.101 mmol, 1 equiv) in methanol (4.0 mL) and toluene (1.0 mL), were treated with trimethylsilyl diazomethane (2 M in hexane, 0.110 mL, 0.223 mmol, 2.2 equiv) dropwise over 1 h. When the reaction was complete, the solvent was removed in vacuo and the crude product redissolved in CH_2Cl_2 (5.0 mL). Treatment with the Dess–Martin periodinane (61.2 mg, 0.146 mmol, 1.55 equiv) and purification by column chromatography on silica gel, eluting with 5% ethyl acetate in hexane gave 1-isobutyl-3-naphthalen-1-ylmethyl-2-oxo-cyclopentanecarboxylic acid methyl ester (25 mg, 0.073 mmol, 81%) as a yellow oil and as a 7:1 mixture of diastereoisomers of which **41** was the major. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (d, 3H, J=4.8 Hz, $CHCH_3$), 0.88 (d, 3H, J=4.8 Hz, $CHCH_3$), 1.45 (dd, 1H, J=14.1, 6.8 Hz, CH_2CHCH_3), 1.60–1.79 (m, 3H, $CHCH_3$, 1H from $CHCH_2CH_2$, 1H from $CHCH_2CH_2$), 1.88–2.02 (m, 1H, $CHCH_2CH_2$), 2.17 (dd, 1H, J=14.1, 6.8 Hz, CH_2CHCH_3), 2.58–2.71 (m, 2H, 1H from $CHCH_2CH_2$, 1H from $CHCH_2CH_2$), 2.78–2.85 (m, 1H, CH_2Ar), 3.71 (s, 3H, OCH_3), 3.84 (dd, 1H, J=14.1, 3.7 Hz, CH_2Ar), 7.29–7.33 (m, 1H, ArH), 7.37–7.42 (m, 1H, ArH), 7.47–7.56 (m, 2H, ArH), 7.75 (d, 1H, J=8.1 Hz, ArH), 7.87 (d, 1H, J=7.6 Hz, ArH), 8.06 ppm (d, 1H, J=8.3 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.0 ($CHCH_3$), 23.6 ($CHCH_3$), 25.5 ($CH(CH_3)_2$), 27.3 ($CHCH_2CH_2$), 31.0 ($CHCH_2CH_2$), 33.8 (CH_2Ar), 43.9 ($CH_2CH(CH_3)_2$), 50.2 ($CHCH_2$Ar), 52.5 (OCH_3), 61.4 (C^q), 123.5 (ArCH), 125.4 (ArCH), 125.6 (ArCH), 126.0 (ArCH), 126.8 (ArCH), 127.1 (ArCH), 128.8 (ArCH), 131.6 (ArC^q), 133.9 (ArC^q), 135.7 (ArC^q), 171.0 ($COOCH_3$), 214.9 ppm (C=O); IR (evap. film): ν_{max} = 2954, 2862, 1747 (C=O), 1717 (C=O), 1446, 1217, 1161, 1013, 776 cm^{-1}; MS (ES+): m/z: calcd for $C_{22}H_{26}O_3Na$: 361.1774; found: 361.1769 $[M+Na]^+$.

***rac*-(1*R*,3*S*)-3-(5-Bromo-2-methoxybenzyl)-1-isobutyl-2-oxocyclopentanecarboxylic acid methyl ester (42)**: As for general procedure C, the four diastereoisomers of 3-(5-bromo-2-methoxybenzyl)-2-hydroxy-1-isobutylcyclopentanecarboxylic acid (43 mg, 0.112 mmol, 1 equiv) in methanol (4.0 mL) and toluene (1.0 mL), were treated with trimethylsilyl diazomethane (2 M in hexane, 0.120 mL, 0.246 mmol, 2.2 equiv) dropwise over 1 h. When the reaction was complete, the solvent was removed in vacuo and the crude product redissolved in CH_2Cl_2 (5.0 mL). Treatment with the Dess–Martin periodinane (72 mg, 0.171 mmol, 1.55 equiv) and purification by column chromatography on silica gel, eluting with 5% ethyl acetate in hexane gave 3-(5-bromo-2-methoxybenzyl)-1-isobutyl-2-oxocyclopentanecarboxylic acid methyl ester (30 mg, 0.075 mmol, 70%) as a colorless oil and as a 5:1 mixture of diastereoisomers of which **42** was the major. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78 (d, 3H, J=6.8 Hz, $CHCH_3$), 0.80 (d, 3H, J=6.8 Hz, $CHCH_3$), 1.41 (dd, 1H, J=14.1, 6.8 Hz, CH_2CHCH_3), 1.47–1.71 (m, 3H, $CHCH_3$, 1H from $CHCH_2CH_2$, 1H from $CHCH_2CH_2$), 1.89–2.03 (m, 1H, $CHCH_2CH_2$), 2.13 (dd, 1H, J=14.1, 6.8 Hz, CH_2CHCH_3), 2.39–2.51 (m, 2H, 1H from $CHCH_2CH_2$, 1H from CH_2Ar), 2.51–2.72 (m, 1H, $CHCH_2CH_2$), 3.15–3.23 (m, 1H, CH_2Ar), 3.68 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 6.68–6.73 (m, 1H, ArH), 7.18–7.22 (m, 1H, ArH), 7.25–7.32 ppm (m, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.0 ($CHCH_3$), 23.6 ($CHCH_3$), 25.5 ($CH(CH_3)_2$), 26.6 ($CH_2CH_2CH_2$), 30.6 ($CHCH_2CH_2$), 31.0 ($CH_2CH_2CH_2$), 44.0 ($CH_2CH(CH_3)_2$), 49.1 ($CHCH_2$Ar), 52.5 (OCH_3), 55.4 (OCH_3Ar), 61.3 (C^q), 111.8 (ArCH), 112.4 (ArC^q), 130.1 (ArC^q), 130.2 (ArCH), 133.1 (ArCH), 156.6 (ArC^q), 170.9 ($COOCH_3$), 214.8 ppm (C=O); IR (evap. film): ν_{max} = 2954, 1747 (C=O), 1723 (C=O), 1489, 1247, 1029, 803, 623 cm^{-1}; MS (ES+): m/z: calcd for $C_{19}H_{25}O_4BrNa$: 419.0828; found: 419.0830 $[M+Na]^+$.

***rac*-(1*R*,3*R*)-1-Cyclohexylmethyl-3-methyl-2-oxocyclopentane carboxylic acid methyl ester (43)**: As for general procedure C, the four diastereoisomers of 1-cyclohexylmethyl-2-hydroxy-3-methyl-cyclopentanecarboxylic acid (40 mg, 0.170 mmol, 1 equiv) in methanol (1.0 mL) and toluene

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(0.25 mL), were treated with trimethylsilyl diazomethane (2 M in hexane, 0.680 mL, 1.36 mmol, 8 equiv) added dropwise over 4 h. When the reaction was complete, the solvent was removed in vacuo and the crude product redissolved in CH_2Cl_2 (2.0 mL). Treatment with the Dess–Martin periodinane (107 mg, 0.255 mmol, 1.5 equiv) and purification by column chromatography on silica gel, eluting with 3% ethyl acetate in hexane gave 1-cyclohexylmethyl-3-methyl-2-oxo-cyclopentanecarboxylic acid methyl ester (35 mg, 0.137 mmol, 81%) as a colorless oil and as a 3:1 mixture of diastereoisomers of which **43** was the major. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82–0.98 (m, 2H, CH_2 from Cy), 1.04–1.22 (m, 5H, CH_2 from Cy, $CHCH_3$), 1.27–1.35 (m, 1H, CH from Cy), 1.42 (dd, 1H, J=14.1, 6.6 Hz, 1H from CH_2Cy), 1.52–1.69 (m, 7H, 6H from Cy, 1H from $CHCH_2CH_2$), 1.75 (ddd, 1H, J=13.0, 11.6, 6.2 Hz, 1H from $CHCH_2CH_2$), 2.06 (dd, 1H, J=14.1, 6.6 Hz, 1H from CH_2Cy), 2.13–2.28 (m, 2H, $CHCH_3$, 1H from $CHCH_2CH_2$), 2.60 (ddd, 1H, J=13.0, 6.4, 2.0 Hz, 1H from $CHCH_2CH_2$), 3.69 ppm (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.1 ($CHCH_3$), 26.1 (CH_2 from Cy), 26.2–26.3 (brs, 2 × CH_2 from Cy), 29.1 ($CHCH_2CH_2$), 31.1 ($CHCH_2CH_2$), 33.5 (CH_2 from Cy), 34.1 (CH_2 from Cy), 34.8 (CH from Cy), 42.5 (CH_2Cy), 43.7 ($CHCH_3$), 52.4 (OCH_3), 60.5 (C^q), 171.5 ($COOCH_3$), 216.6 ppm (C=O); IR (neat): ν_{max} = 2923, 2851, 2358, 1748 (C=O), 1722 (C=O), 1488, 1247, 1207, 1130 1011, 925, 767 cm^{-1}; MS (ES+): m/z: calcd for $C_{15}H_{24}O_3Na$: 275.1611; found: 275.1618 $[M+Na]^+$.

***rac*-(1*R*,3*S*)-1-Isobutyl-3-methyl-2-oxocyclopentanecarboxylic acid methyl ester (44)**: As for general procedure C, the four diastereoisomers of 1-cyclohexylmethyl-2-hydroxy-3-methylcyclopentanecarboxylic acid (40 mg, 0.170 mmol, 1 equiv) in methanol (1.0 mL) and toluene (0.25 mL), were treated with trimethylsilyl diazomethane (2 M in hexane, 0.680 mL, 1.36 mmol, 8 equiv) added dropwise over 4 h. When the reaction was complete, the solvent was removed in vacuo and the crude product redissolved in CH_2Cl_2 (2.0 mL). Treatment with the Dess–Martin periodinane (107 mg, 0.255 mmol, 1.5 equiv) and purification by column chromatography on silica gel, eluting with 3% ethyl acetate in hexane gave 1-cyclohexylmethyl-3-methyl-2-oxocyclopentanecarboxylic acid methyl ester (35 mg, 0.137 mmol, 81%) as a colorless oil and as a 3:1 mixture of diastereoisomers of which **44** was the major. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (d, 3H, J=6.8 Hz, $CHCH_3$), 0.89 (d, 3H, J=6.8 Hz, $CHCH_3$), 1.12 (d, 3H, J=7.1 Hz, CH_3), 1.42 (dd, 1H, J=14.1, 6.6 Hz, 1H from CH_2CHCH_3), 1.46–1.51 (m, 1H, 1H from CH_2), 1.60–1.74 (m, 1H, $CHCH_3$), 1.95 (dd, 1H, J=14.1, 6.8 Hz, 1H from CH_2CHCH_3), 1.96–2.02 (m, 1H, 1H from CH_2), 2.16–2.25 (m, 1H, 1H from CH_2), 2.30–2.40 (m, 1H, CHCO), 2.53 (ddd, 1H, J=13.4, 9.3, 7.1 Hz, CH_2), 3.69 ppm (s, 3H, OCH_3); ^{13}C (100 MHz, $CDCl_3$): δ = 15.2 (CH_3), 22.8 ($CHCH_3$), 23.8 ($CHCH_3$), 25.2 ($CH(CH_3)_2$), 27.6 (CH_2), 29.6 (CH_2), 41.8 (CH_2), 43.2 ($CHCH_3$), 52.4 (OCH_3), 60.2 (C^q), 171.8 ($COOCH_3$), 215.7 ppm (C=O); IR (neat): ν_{max} = 2956, 2851, 2854, 1750 (C=O), 1728 (C=O), 1460, 1214, 1161, 1011, 967, 723 cm^{-1}; MS (ES+): m/z: calcd for $C_{12}H_{20}O_3Na$: 235.1305; found: 235.1305 $[M+Na]^+$.

***rac*-(1*S*,8*S*)-8-Hydroxy-bicyclo[3.2.1]octane-1-carboxylic acid (50)**: To a stirred solution of **49** (25 mg, 0.112 mmol, 1 equiv) in THF (2.0 mL) and H_2O (2.2 mL, 134 mmol, 1200 equiv) was added SmI_2 (0.1 M in THF, 8.93 mL, 0.893 mmol, 8 equiv) dropwise using a syringe pump over 1 hour. After decolorization of the reaction mixture, the flask was opened to air and saturated aqueous sodium chloride (10 mL) and tartaric acid (50 mg) was added. The aqueous phase was extracted with ethyl acetate (3×15 mL) and the combined organic phases dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography on silica gel, eluting with a gradient of 40% ethyl acetate in hexane gave **50** (10 mg, 0.060 mmol, 54%) as a white solid. M.p. 109–111 °C (ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20–1.29 (m, 1H, 1H from CH_2), 1.47–1.69 (m, 4H, 2 × CH_2), 1.73–1.89 (m, 2H, CH_2), 1.90–2.01 (m, 2H, CH_2), 2.06–2.16 (m, 1H, 1H from CH_2), 2.19–2.26 (m, 1H, $CHCHOH$), 4.17 ppm (d, 1H, J=5.3 Hz, $CHOH$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.6 (CH_2), 23.4 (CH_2), 23.6 (CH_2), 27.3 (CH_2), 28.7 (CH_2), 37.6 ($CHCHOH$), 50.4 (C^q), 74.5 ($CHOH$), 182.4 ppm (C=O); IR (evap. film): ν_{max}= 3422 (br. OH), 2925, 2871, 1703 (C=O), 1694 (C=O), 1454, 1291, 1187, 1143, 1096, 1064 cm^{-1}; MS (ES+): m/z: calcd for $C_9H_{13}O_3$: 169.0865; found: 169.0863 $[M-H]^+$.

General Procedure D: **SmI_2-mediated cyclization cascades in THF/H_2O**

rac-(1*R*,3a*S*,6*R*,6a*S*)-1,6-Dibenzyl-6a-hydroxyoctahydropentalene-3a-carboxylic acid (54): To a stirred solution of **51** (100 mg, 0.250 mmol, 1 equiv) in THF (1.0 mL) and H_2O (5.4 mL, 297 mmol, 1200 equiv) was added SmI_2 (0.1 M in THF, 19.8 mL, 1.98 mmol, 8 equiv) dropwise using a syringe pump over 30 min. After decolorization of the reaction mixture, the flask was opened to air and saturated aqueous sodium chloride (15 mL) was added. The aqueous phase was extracted with ethyl acetate (3×15 mL) and the combined organic phases dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography on silica gel, eluting with a gradient of 20% ethyl acetate in petroleum ether (40–60 °C) gave **54** (60 mg, 0.173 mmol, 69%) as a white solid. M.p. 132–134 °C (ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15–1.40 (m, 2H, 2H from CH_2), 1.54 (dd, 1H, J=13.1, 6.3 Hz, 1H from CH_2), 1.58–1.72 (m, 2H, 2H from CH_2), 1.72–1.81 (m, 1H, 1H from CH_2), 2.04–2.23 (m, 3H, 1H from CH_2, 2 × CH), 2.48 (ddd, 1H, J=13.1, 6.1, 1.5 Hz, 1H from CH_2), 2.54–2.64 (m, 2H, 2H from $PhCH_2$), 3.14 (dd, 1H, J=13.6, 2.5 Hz, 1H from $PhCH_2$), 3.34 (dd, 1H, J=12.7, 3.2 Hz, 1H from $PhCH_2$), 7.20–7.26 (m, 6H, 6 × ArH), 7.28–7.36 ppm (m, 4H, 4 × ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.6 (CH_2), 32.0 (CH_2), 34.8 (CH_2), 35.7 ($PhCH_2$), 35.9 (CH_2), 36.5 ($PhCH_2$), 48.2 (CH), 55.4 (CH), 64.4 (C^q), 92.7 (C^q), 125.9 (ArCH), 126.0 (ArCH), 128.4 (2 × ArCH), 128.4 (2 × ArCH), 128.8 (2 × ArCH), 128.9 (2 × ArCH), 141.3 (ArC^q), 142.1 (ArC^q), 181.9 ppm (C=O); IR (evap. film): ν_{max} = 2950, 1703, 1682, 1494, 1454, 1276, 698 cm^{-1}; MS (ES+): m/z: calcd for $C_{23}H_{25}O_3$: 349.1804; found: 349.1797 $[M-H]^+$.

***rac*-(1*R*,3a*S*,6*R*,6a*S*)-1,6-di-(4-Bromobenzyl)-6a-hydroxyhexahydropentalene-3a-carboxylic acid (55)**: As for a general procedure D, reaction of **52** (50 mg, 0.089 mmol, 1 equiv) in THF (2.0 mL) and H_2O (1.92 mL, 107 mmol, 1200 equiv) with (0.1 M in THF, 7.1 mL, 0.710 mmol, 8 equiv) after column chromatography on silica gel, eluting with a gradient of 20% ethyl acetate in petroleum ether (40–60 °C) gave **55** (23 mg, 0.045 mmol, 54%) as a white solid. M.p. 108–110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15–1.35 (m, 2H, 2H from CH_2), 1.56 (m, 3H, 3H from CH_2), 1.65–1.75 (m, 1H, 1H from CH_2), 1.93–2.03 (m, 1H, CH), 2.04–2.17 (m, 2H, 1H from CH_2, CH), 2.41–2.51 (m, 2H, 1H from CH_2, 1H from $ArCH_2$), 2.56 (dd, 1H, J=13.9, 11.3 Hz, 1H from $ArCH_2$), 3.02 (dd, 1H, J=13.9, 2.5 Hz, 1H from $ArCH_2$), 3.24 (dd, 1H, J=12.9, 3.0 Hz, 1H from $ArCH_2$), 7.09 (dd, 4H, J=8.3, 3.0 Hz, 4 × ArH), 7.42 (dd, 4H, J=8.3, 2.0 Hz, 4 × ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.4 (CH_2), 31.8 (CH_2), 34.8 (CH_2), 35.2 (2 × ArCH), 35.9 (2 × ArCH), 36.0 (CH_2), 47.9 (CH), 55.2 (CH), 64.0 (C^q), 92.1 (C^q), 119.7 (ArC^q), 119.8 (ArC^q), 130.5 (2 × ArCH), 130.6 (2 × ArCH), 131.4 (2 × ArCH), 131.5 (2 × ArCH), 140.2 (ArC^q), 140.9 (ArC^q), 180.6 (C=O); IR (neat): ν_{max} = 3040 (br. OH), 2928, 2859, 1896, 1693 (C=O), 1486, 1453, 1403, 1262, 1095, 1070, 1010, 841, 792, 741, 668 cm^{-1}; MS (ES−): m/z (%): calcd for $C_{23}H_{25}O_3$: 06.9989; found: 506.9998 $[M-H]^+$.

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