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Stereoselective synthesis of versatile 2-chloromercurium-3,5-*syn*-dihydroxy esters via intramolecular oxymercuration

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ABSTRACT

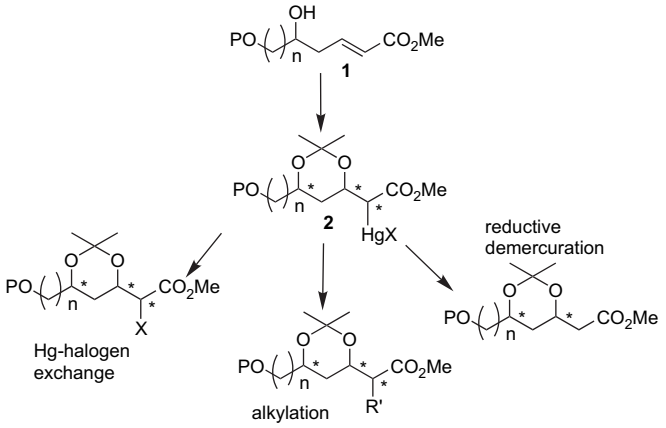
Regio- and stereocontrolled alkoxy mercuration of α,β-unsaturated esters allows direct access to 1,3-*syn* diols in good yields. Demercuration of adducts leads to 1,3 skipped dihydroxy esters, alcohols, and α-halo esters. The deprotection of acetonide with Amberlyst 15 on 1,3-*syn*-dihydroxy esters gives the corresponding δ-lactones.

1. Introduction

Many polyketide-derived natural products, containing *syn* or *anti*-1,3-diol units, display a range of potent and different biological properties, such as antibacterial and antifungal as well as cytotoxic and immunosuppressive activities.[1] Since no general approach exists for the flexible synthesis of polyols and other polyketide-derived structural units, a multitude of suitable and specific methods for the stereoselective synthesis of 1,3-diols has been developed.[2]

Our group has been engaged in the development of practical synthetic approaches toward chiral *syn*- and *anti*-1,3-diol,[3] and in their application to the syntheses of natural macrolides.[4]

Inspired by work on the diastereoselective oxymercurations of allylic and homoallylic alcohols[5] and by chirality transfer[6] we were interested in performing an intramolecular oxymercuration on δ-hydroxy α,β-unsaturated methyl esters of type **1** shown in Scheme 1. Herein we report the synthesis of a 1,3-diol array by introducing the first chiral center as a secondary alcohol. Particularly useful in this sense is its hemiketal derivative, which could direct the addition to neighboring carbon–carbon double bonds. In several cases this process results in a highly selective conversion of an unsaturated alcohol into a single diol product.



Scheme 1.

A substrate of type **1** could directly produce two new stereocenters, affording the 3,5 dihydroxy ketal **2**. So the 1,3-diol ester **2** could be seen as an important precursor for different transformations of functional groups.

Moreover, α-mercurio esters, derived from the regiospecific process of oxymercuration of α,β-unsaturated esters, have been studied for some time,[7] but have received very limited attention over more recent years. Normally, intramolecular oxymercurations are performed on terminal olefins, on electron-rich systems or cyclic compounds and there are no examples about nucleophilic hemiketal or hemiacetal additions on α,β-unsaturated systems. This electrophile-mediated addition affords vicinal functionalised

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products to be further easily transformed. In fact, the weak C–Hg bonds can readily enter into metal-exchange reactions with palladium reagents, or halogen replacement, and atom-transfer reactions.[8,9]

2. Results and discussion

Searching for a straightforward preparation of the starting δ-hydroxy enoate synthons **1**, we need to prepare the starting homoallylic alcohols **5a–f** (Scheme 2). These compounds were easily prepared by two different routes in racemic form;[10] (1) via epoxide ring opening with vinylmagnesium bromide[11] and (2) via addition of allylmagnesium bromide to the corresponding aldehydes.

The final cross-metathesis reaction[12] with methyl acrylate in the presence of Grubbs(II) catalyst in CH_2Cl_2 at reflux for 3 h, smoothly afforded the desired products **1a–f** (Table 1).

Compounds **1**, with variable chain lengths and different primary hydroxyl protecting groups, were obtained in good overall yields (84–96%) up to >99:1 *E*/*Z* ratio, except compound **1f**, which was obtained in 66% yield.

Initially the oxymercuration reaction of **1a–f** was performed with $Hg(OA)_2$ (1.1 equiv), followed by treatment with aq NaCl (method **A**) but, after purification of the crude reaction mixture, we did not obtain good results, as reported in Table 2. Low conversions and yields were obtained with all substrates using method **A**. Better yields were obtained using HgCl(OAc), method **B**,[5b] and in particular using HgCl(OAc) (2.5 equiv), $Yb(OTf)_3$ (0.05 equiv) in acetone at rt for 20–24 h (entries 10 and 11).[13] Under these conditions **1a**, **1c–e** were converted into acetonides **2a**, **2c–e** in high yields and isolated as pure products in about 50% yield by column chromatography on silica gel.[14] When compounds **1b** and **1f** were treated according to either method, the expected protected diols **2b**,**f** were not formed, but a large amount of by-products was detected (entries 2 and 6, Table 2).

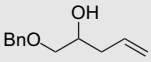
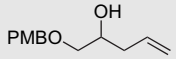
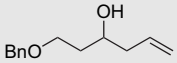
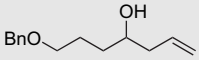
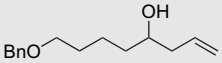
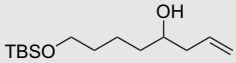
It is noteworthy that only the 1,3-*syn* diol was found, as showed by NMR spectroscopic analysis of the acetonides.[15]

As mentioned before, the obtained mercurial organic compounds could be easily transformed. The reduction of the mercurials **2a**,**e** (Scheme 3) using standard conditions ($NaBH_4$ in the presence of aq sodium hydroxide in THF)[16] afforded the desired reduction product along with small amounts of the corresponding carboxylic acids. Thus the demercurated esters **6a**,**e** were isolated in good yields (85–95%) when $NaCNBH_3$ in acetone was used.[17] The facile hydrolysis of acetonides with Amberlyst 15 in MeOH[18] directly afforded the corresponding δ-lactones **7a**,**e** in high yields (80% and 86%), previously prepared and used as analogs of mevinic acid[3] as well of naturally occurring lactones.[19]

After several attempts, $LiAlH_4$ in THF was found to be the reagent of choice for direct demercuration and reduction of the ester group, affording **8a**,**e** in 80–83% yield. Iodination of **2a**,**e** with I_2 in THF proceeded cleanly to afford a mixture of unstable epimers in a 1:1 ratio at C2 **9a**,**e** in quantitative yields. Direct iodo acetalization was first tested on compounds **1** without success, so this strategy could represent a methodology for the direct insertion of halogen atom α to an ester moiety, as a useful chiral synthon for Reformatsky type reaction.[20] Some attempts to perform the reaction in a stereoselective fashion, by using molecular bromine in pyridine, (reported with a total configuration retention)[21] only generated the two diastereomers in quantitative yield and in an 80:20 *syn*/*anti* ratio.

We have therefore showed that organomercurials could give access to structurally diverse compounds through different reductive conditions and halogenation reactions.

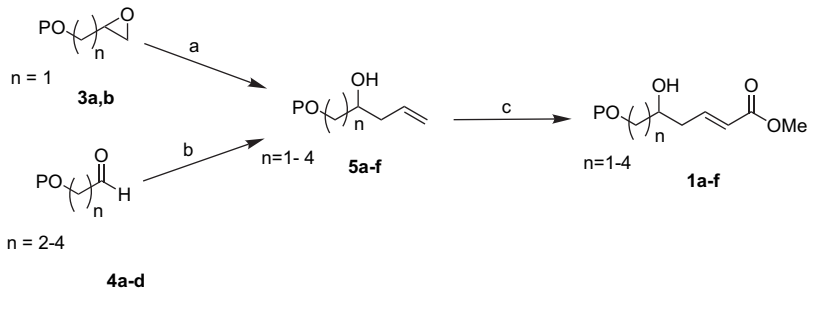
Table 1

Entry	P	*n*	Substrate[a]	Product **5** yield [%]	Product **1** yield [%]	*E*/*Z* ratio[b]
1	Bn	1	**3a**	 **5a** [100]	**1a** [94]	>99:1
2	PMB	1	**3b**	 **5b** [100]	**1b** [84]	99:1
3	Bn	2	**4a**	 **5c** [83]	**1c** [92]	>99:1
4	Bn	3	**4b**	 **5d** [78]	**1d** [89]	>99:1
5	Bn	4	**4c**	 **5e** [80]	**1e** [96]	>99:1
6	TBS	4	**4d**	 **5f** [80]	**1f** [66]	99:1

[a] The glycidol **3a** is commercially available, the aldehydes **4a–d** were prepared by oxidizing the corresponding commercial alcohols using PCC in CH_2Cl_2.
[b] The *E*/*Z* ratio was determined by GC–MS analysis.

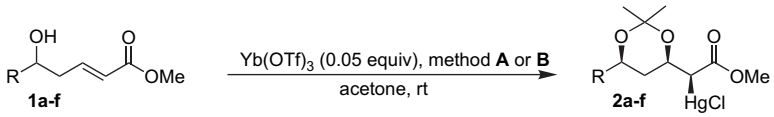
3. Stereochemistry of oxymercuration

We noticed that among the four possible diastereomers with the relative stereochemistry of the two newly generated chiral centers (1,2,4-*syn*/*syn*, *syn*/*anti*, *anti*/*syn* or *anti*/*anti*), only one compound was isolated for each reaction.

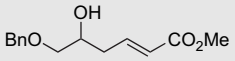
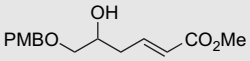
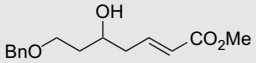
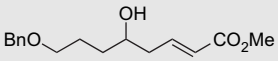
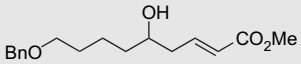
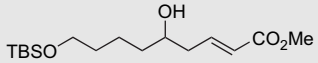


Scheme 2. (a) Vinylmagnesium bromide, CuI, THF, −20 °C, 20 min; (b) allylmagnesium bromide, THF, −20 °C, 30 min; (c) methyl acrylate, Grubbs(II) catalyst, CH_2Cl_2, reflux, 3 h.

Table 2
Preparation of compounds **2a**–**f** using $Hg(OAc)_2$ or HgCl(OAc)

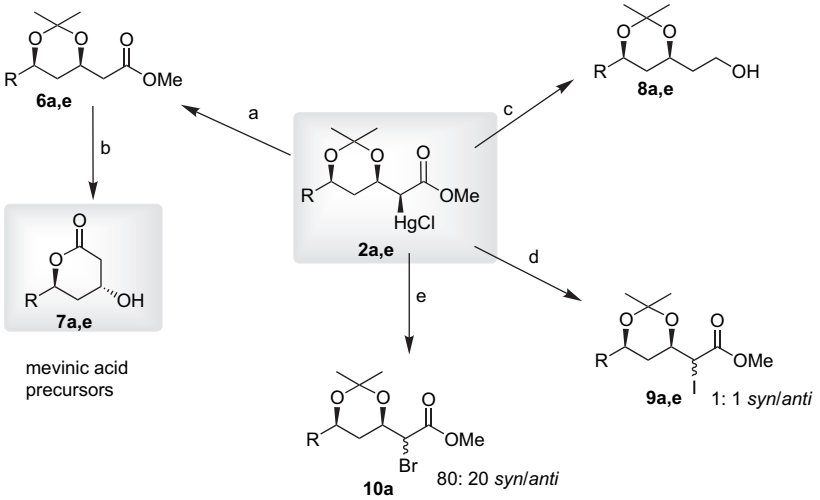


method **A**: $Hg(OAc)_2$, NaCl
method **B**: HgCl(OAc)

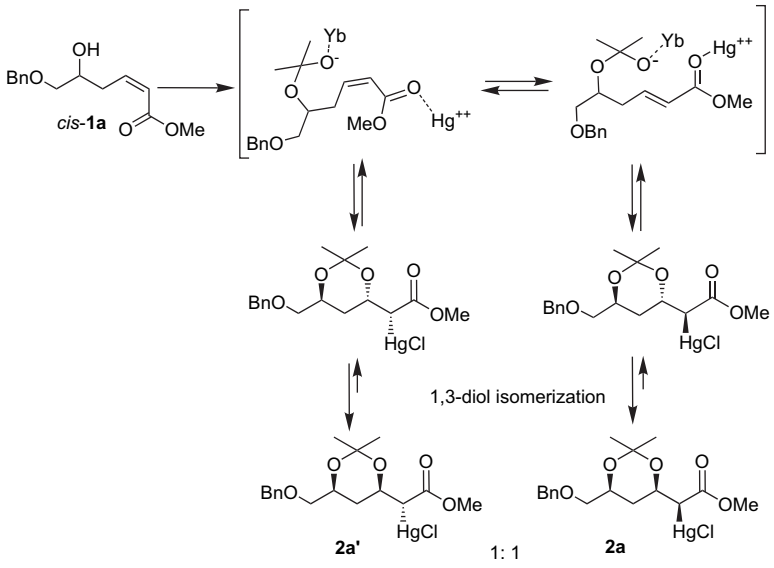
Entry	Substrate **1**	Time (h)	**A** or **B** [equiv]	Product **2** [crude][a][pure][b]
				2a
1	 **1a**	20	**A** [1.1]	[60] [22]
		24	**B** [1.1]	[80] [36]
		24	***B*** *[2.5]*	*[90] [49]*
				2b
2	 **1b**	43	**A** [1.1]	[—][c][—]
		24	**B** [1.1]	[—][c][—]
				2c
3	 **1c**	20	**A** [1.1]	[62] [22]
		24	**B** [1.1]	[70] [40]
		24	***B*** *[2.5]*	*[92] [51]*
				2d
4	 **1d**	24	**A** [1.1]	[65] [34]
		22	***B*** *[2.5]*	*[92] [53]*
				2e
5	 **1e**	24	**A** [1.1]	[65] [36]
		20	**B** [1.1]	[70] [43]
		22	***B*** *[2.5]*	*[91] [50]*
				2f
6	 **1f**	20	**A** [1.1]	[—][c][—]
		20	**B** [1.1]	[—][c][—]

[a] Yield of product **2** evaluated on the crude by ^1H NMR spectroscopic analysis.
[b] Yield of product **2** after column chromatography on silica gel.
[c] Complete disappearance and degradation of the substrate.

The intramolecular addition on the pure *trans*-**1** proceeded with excellent selectivity when reactions were left for more than 12 h and the 1,3-diol unit showed only the relative *syn*-configuration. In the first period of the reaction, two acetonides were detected showing both the *syn*- and *anti*-1,3-dihydroxy relationship.[15] In order to improve the conversion to a single diastereomer the reactions were left for 20 h, as reported in Table 2. Compounds **2** were thus subjected to the equilibrating oxymercuration condition with the thermodynamically more stable *syn* 1,3-diols to be the expected predominant.[5b]



Scheme 3. (a) $NaBH_3CN$, acetone, 2 h, rt (**6a**, 95%; **6e** 85%); (b) Amberlyst 15, MeOH, 18 h, reflux, (**7a**, 80%; **7e**, 86%); (c) $LiAlH_4$, THF, 3 h, rt (**8a**, 83%; **8e**, 80%); (d) I_2, THF, 2 h, rt (**9a**, 100%; **9e**, 100%); (e) Br_2, pyridine, −20 °C, 1 h, (**10a**, 100%, *syn*/*anti* 80:20).



Scheme 4.

By ^{1}H NMR spectroscopic analysis we noticed that the *syn* 1,3-diol **2a**[22] showed H-2 at 3.50 ppm as a doublet with $^{3}J_{2,3}$ 6.6 Hz and H-3 at 4.65 ppm as a multiplet, without any useful information on the C-2 relative configuration. Also the NOESY experiments on product **2a** did not allow the relative configuration of the C-2 carbon to be determined.[23]

Therefore in order to obtain more information, pure *cis* isomer ester **1a** (Scheme 4) was reacted under the usual conditions. Surprisingly, two diastereomers were isolated in all 50% yield with 1:1 ratio. Both products possess relative *syn*-configuration of the 1,3-dihydroxy moiety (as confirmed by ^{13}C NMR), but opposite configuration on the stereocenter bearing the mercury atom, with identical NMR spectroscopic data for **2a** obtained from *trans*-**1a**. The resonances for H-2 were at 3.50 ppm with $^{3}J_{2,3}$ of 6.6 Hz for the diastereomer **2a** (the same obtained from the *trans*-**1a**) and 3.23 ppm with $^{3}J_{2,3}$ of 7.5 Hz for the other diatereoisomer **2a**′. As reported for methoxymercuriated diastereomers[7b,7c] the larger value in $^{3}J_{2,3}$ can be confidently assigned to the isomer with the *erythro*-configuration, so now we tentatively assign to compound **2a** the 1,2,4-*syn*/*syn*-configuration and to compound **2a**′ the 1,2,4-*anti*/*syn*-configuration.

A possible mechanism for the formation of the two diastereomers is shown in Scheme 4. By the coordination of the mercury atom to the carbonyl oxygen[24] the α,β-unsaturated ester *cis*-**1a** isomerizes in the reaction medium to the *trans*-**1a**. Both compounds provide firstly the two 1,3-*anti* diols and subsequently, as already reported,[5b] the more stable 1,3-*syn* diols, respectively, compounds **2a** and **2a**′, the only detected and isolated.

4. Conclusions

The diastereoselective nucleophilic addition to α,β-unsaturated esters mediated by mercury(II) salts with concomitant chirality transfer provides a useful strategy for the stereoselective elaboration of acyclic structures bearing several contiguous stereocenters. Moreover, the different demercuriation procedures led to a variety of functionalities on the substrate making this sequence of reactions a versatile methodology in the preparation of 1,3-diol subunits.

Although the use of mercury salts limits the development of these reactions to academic research activities, the results presented in this communication should encourage the research for alternative electrophiles to perform these transformations.

5. Experimental section

5.1. General remarks

All chemicals were purchased from Aldrich or Fluka and were used without further purification. Solvents were dried and distilled by classical procedures. NMR spectra were recorded with Varian 400 and 500 and Bruker 300 spectrometers, operating at 300, 400, and 500 MHz (^{1}H) and 100 and 125 MHz (^{13}C), respectively. Chemical shifts (δ) are reported in parts per million (ppm) relative to $CHCl_3$ (δ=7.27 ppm) for ^{1}H NMR spectroscopy. For ^{13}C NMR, chemical shifts were reported in the scale relative to $CHCl_3$ (δ=77.0 ppm) as an internal reference. Multiplicities are abbreviated as: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The coupling constants are given in hertz (Hz). ESI-Tof mass spectra were recorded for organomercuriated compounds with a ToF micromass waters instrument using polyphosphoric acids as internal standard, for the other compounds mass spectra were obtained by GC/MS with electron impact ionization. Column chromatography was performed using silica gel 60 (0.040–0.063 mm). Thin-layer chromatography (TLC) was performed using precoated plates of silica gel 60 F254 and visualized under ultraviolet irradiation (254 nm) or by phosphomolybdic acid solution.

5.2. Cross-metathesis reaction

5.2.1. General procedure

Compounds **5a**–**f**[25] (1 equiv) were dissolved in CH_2Cl_2 (0.1 M). Methyl acrylates (3 equiv) and Grubbs(II) catalyst (0.01 equiv) were added and the mixture was heated at reflux until completion of the reaction (2–3 h, monitored by TLC). The mixture was concentrated and the crudes **1a**–**f**[20] were purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc 7:3).

*5.2.1.1. Methyl 9-(tert-butyl-dimethyl-silanyloxy)-5-hydroxy-non-2-enoate (**1f**).* Colorless liquid (130 mg, 66%). ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.04–7.00 (m, 1H), 5.92 (d, J=18.0 Hz, 1H), 3.82–3.78 (m, 1H), 3.78 (s, 3H), 3.63 (t, J=6.0 Hz, 2H), 2.52–2.38 (m, 2H), 1.75 (br s,

1H), 1.60–1.40 (m, 6H), 0.92 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=167.0, 145.8, 123.7, 70.7, 63.3, 51.8, 40.5, 36.9, 32.7, 26.2, 22.2, 18.6, -5.0. IR (cm^{-1}): 2927, 1724, 1657, 1471. GC–MS (EI): *m*/*z* (%)=301 [M−15$^+$], 115 (100). Anal. Calcd for $C_{16}H_{32}O_4Si$: C, 60.72; H, 10.19. Found: C, 60.69; H, 10.18.

5.3. Oxymercuration reaction

5.3.1. General procedure

All organomercury compounds should be regarded as potentially toxic and manipulated in a well-ventilated hood. Compounds **1a**–**f** (1 equiv) were dissolved in freshly distilled acetone (0.1 M), and in sequence HgCl(OAc) (1.1–2.5 equiv) and $Yb(OTf)_3$ (0.05 equiv) were added. The mixture was stirred at rt for 20–24 h. The reaction was quenched by adding Et_3N (1 equiv) and then the mixture was concentrated. The crude mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The reaction mixture was purified on silica gel chromatography affording pure products **2a**–**e** (eluent: petroleum ether/EtOAc 4:3) as colorless oil or white solid.

5.3.1.1. {(1S)-1-[(4R*,6S*)-6-((Benzyloxy)methyl)-2,2-dimethyl-1,3-dioxan-4-yl]-2-methoxy-2-oxoethyl} mercury(II) chloride (**2a**).* White solid (200 mg, 49%); mp: 100–102 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.40–7.25 (m, 5H), 4.63–4.56 (m, 1H), 4.60 (d, *J*=12 Hz, 1H), 4.55 (d, *J*=12 Hz, 1H), 4.18–4.12 (m, 1H), 3.70 (s, 3H), 3.52–3.49 (m, 1H), 3.52 (d, *J*=6.6 Hz, 1H), 3.40 (dd, *J*=10.0, 4.4 Hz, 1H), 2.08 (dt, *J*=14.0, 3 Hz, 1H), 1.47 (s, 3H), 1.39 (s, 3H), 1.28–1.13 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=171.5, 137.9, 128.4, 127.8, 127.7, 99.3, 73.5, 73.1, 68.1, 67.9, 58.1, 52.0, 37.3, 30.0, 20.0. IR (neat, KBr): 2998, 2951, 2940, 2886, 1719, 1700, 1263, 1204, 1198, 1129, 1102 cm^{-1}. ESI-Tof MS calcd for $C_{17}H_{23}ClHgO_5$ [M$^+$] 544.09, found [M−Cl$^+$] 509.36.

5.3.1.2. {(1R)-1-[(4R*,6S*)-6-((Benzyloxy)methyl)-2,2-dimethyl-1,3-dioxan-4-yl]-2-methoxy-2-oxoethyl} mercury(II) chloride (**2a′**).* Thick colorless oil (20 mg, 25%); ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.40–7.25 (m, 5H), 4.62–4.54 (m, 3H), 4.14–4.10 (m, 1H), 3.70 (s, 3H), 3.53–4.48 (m, 1H), 3.42–3.38 (m, 1H), 3.28–3.23 (m, 1H), 1.73 (br d, *J*=13.0 Hz, 1H), 1.51 (s, 3H), 1.41 (s, 3H), 1.23–1.15 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=171.9, 138.0, 128.5, 127.7, 127.7, 99.5, 73.4, 73.3, 73.0, 68.2, 57.9, 52.0, 34.8, 30.1, 20.0. IR (neat, KBr): 2998, 2951, 2940, 2886, 1719, 1700, 1263, 1204, 1198, 1129, 1102 cm^{-1}. ESI-Tof MS calcd for $C_{17}H_{23}ClHgO_5$ [M$^+$] 544.09, found [M−Cl$^+$] 509.36.

5.3.1.3. {(1S)-1-[(4R*,6R*)-6-(2-(Benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl]-2-methoxy-2-oxoethyl} mercury(II) chloride (**2c**).* Thick colorless oil (74 mg, 51%); ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.39–7.30 (m, 5H), 4.65–4.63 (m, 1H), 4.54 (d, *J*=12.0 Hz, 1H), 4.51 (d, *J*=12.0 Hz, 1H), 4.17–4.15 (m, 1H), 3.71 (s, 3H), 3.62–3.58 (m, 1H), 3.58–3.54 (m, 2H), 2.20 (br d, *J*=12.5 Hz, 1H), 1.80–1.76 (m, 2H), 1.46 (s, 3H), 1.37 (s, 3H), 1.18–1.14 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=171.5, 145.5, 138.4, 128.5, 127.8, 99.2, 73.0, 68.2, 65.9, 65.6, 58.2, 52.0, 40.9, 36.3, 30.1, 20.1. ESI-Tof MS calcd for $C_{18}H_{25}ClHgO_5$ [M$^+$] 558.11, found [M−Cl$^+$] 523.34.

5.3.1.4. {(1S)-1-[(4R*,6R*)-6-(3-(Benzyloxy)propyl)-2,2-dimethyl-1,3-dioxan-4-yl]-2-methoxy-2-oxoethyl} mercury(II) chloride (**2d**).* Thick colorless oil (92 mg, 53%); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.38–7.34 (m, 5H), 4.58–4.54 (m, 1H), 4.52 (s, 2H), 3.90–3.84 (m, 1H), 3.71 (s, 3H), 3.52–3.48 (m, H), 2.20 (br d, *J*=12.0 Hz, 1H), 1.64–1.58 (m, 4H), 1.44 (s, 3H), 1.38 (s, 3H), 1.08–0.82 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=171.5, 138.5, 128.4, 127.8, 127.5, 99.1, 72.8, 69.9, 68.2, 65.6, 58.2, 52.0, 40.8, 32.7, 30.1, 25.2, 20.1. ESI-Tof MS calcd for $C_{19}H_{27}ClHgO_5$ [M$^+$] 572.13, found [M−Cl$^+$] 537.34.

5.3.1.5. {(1S)-1-[(4R*,6R*)-6-(4-(Benzyloxy)butyl)-2,2-dimethyl-1,3-dioxan-4-yl]-2-methoxy-2-oxoethyl} mercury(II) chloride (**2e**).* White deliquescent solid (70 mg, 50%); ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.38–7.33 (m, 5H), 4.62–4.57 (m, 1H), 4.48 (s, 2H), 3.89–3.80 (m, 1H), 3.70 (s, 3H), 3.48–3.44 (m, 3H), 2.10–2.07 (m, 1H), 1.62–1.00 (m, 7H), 1.48 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.6, 138.5, 129.5, 128.3, 127.5, 99.1, 72.8, 70.1, 68.4, 68.3, 58.2, 52.0, 40.8, 35.9, 30.1, 29.5, 28.5, 21.6, 20.0. ESI-Tof MS calcd for $C_{20}H_{29}ClHgO_5$ [M$^+$] 586.14, found [M−Cl$^+$] 551.36.

5.4. Reduction with $NaCNBH_3$

5.4.1. General procedure

To a solution of **2a**,**e** (1 equiv) in freshly distilled acetone (0.05 M) $NaCNBH_3$ (1 equiv) was added. Immediately the precipitated mercury was filtered off through Celite washing with acetone. The crude mixture was concentrated and purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc 7:3) to afford pure products **6a**,**e** as oils.

5.4.1.1. Methyl {(4R,6S*)-6-[(benzyloxy)methyl]-2,2-dimethyl-1,3-dioxan-4-yl}-acetate (**6a**).* Brown oil (459 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.28–7.19 (m, 5H), 4.52 (d, *J*=12.0 Hz, 1H), 4.46 (d, *J*=12.0 Hz, 1H), 4.28–4.25 (m, 1H), 4.07–4.03 (m, 1H), 3.61 (s, 3H), 3.43 (dd, *J*=10.0, 5.6 Hz, 1H), 3.31(dd, *J*=10.0, 4.8 Hz, 1H), 2.49 (dd, *J*=15.2, 6.8 Hz, 1H), 2.32 (dd, *J*=15.2, 6.0 Hz, 1H), 1.56–1.53 (m, 1H), 1.41 (s, 3H), 1.33 (s, 3H), 1.23–1.14 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.3, 138.1, 128.4, 127.7, 127.6, 98.9, 73.4, 73.4, 68.3, 65.6, 51.7, 41.2, 33.2, 30.0, 29.9, 19.6. IR (neat, KBr): 2997, 2957, 2897, 2364, 1735, 1654, 1278, 1120 cm^{-1}. GC–MS (EI): *m*/*z* (%)=293 [M−15$^+$], 91 (100). Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.29; H, 7.89.

5.4.1.2. Methyl {(4R,6R*)-6-(4-(benzyloxy)butyl)-2,2-dimethyl-1,3-dioxan-4-yl}-acetate (**6e**).* Brown oil (45 mg, 85%). ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.36–7.32 (m, 5H), 4.51 (s, 2H), 4.32–4.28 (m, 1H), 3.87–3.83 (m, 1H), 3.70 (s, 3H), 3.48 (t, *J*=5.8 Hz, 2H), 2.56 (dd, *J*=15.5, 6.8, 2H), 2.38 (dd, *J*=15.5, 6.2 Hz, 2H), 1.61–1.10 (m, 8H), 1.45 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.5, 138.5, 128.3, 127.6, 127.5, 98.7, 72.8, 70.2, 68.6, 65.9, 51.6, 41.2, 36.4, 36.0, 30.0, 29.6, 21.5, 19.7. IR (neat, KBr): 2996, 2953, 2897, 2364, 1735, 1654, 1278, 1120, 1097 cm^{-1}. GC–MS (EI): *m*/*z* (%)=335 [M−15$^+$], 91 (100). Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.59; H, 8.68.

5.5. Lactonization

5.5.1. General procedure

To a solution of **6a**,**e** (1 equiv) in dry MeOH (0.1 M), Amberlyst 15 (200 mg/mmol) was added. The mixture was stirred at reflux temperature overnight. The reaction was quenched by filtering with ethyl acetate and concentrated. The residue was purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc 95:5) to afford pure products **7a**,**e** as white solids.

5.5.1.1. (4R,6S*)-6-[(Benzyloxy)methyl]-tetrahydro-4-hydroxypyran-2-one (**7a**).* Same spectroscopic data reported in the literature.[19a]

5.5.1.2. (4S,6S*)-6-[4-(Benzyloxy)butyl]-tetrahydro-4-hydroxypyran-2-one (**7e**).* White solid (56 mg, 86%), dec: 120 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.35–7.27 (m, 5H), 4.78–4.64 (m, 1H), 4.51 (s, 2H), 4.34–4.32 (m, 1H), 3.49 (t, *J*=6.0 Hz, 2H), 2.69 (dd, *J*=17.5, 5.0 Hz, 1H), 2.62 (dd, *J*=17.5, 3.5 Hz, 1H), 1.94 (d, *J*=12.5 Hz, 1H), 1.78–1.50 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=170.2, 138.5, 129.5, 128.5, 127.6, 75.7, 73.0, 70.0, 62.8, 38.6, 36.0, 35.2, 29.5, 21.6. IR (neat, KBr): 2948, 2908, 2365, 2352, 1735, 1235, 1097 cm^{-1}. GC–

MS (EI): m/z (%)=259 [M−18$^+$], 91 (100). Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.09; H, 7.95.

5.6. Reduction with $LiAlH_4$

5.6.1. General procedure

To a solution of **2a**,**e** (1 equiv) in dry THF (0.1 M) $LiAlH_4$ (4 equiv) was added. The mixture was stirred at rt for 18–24 h until disappearance of the substrate. The reaction was quenched adding ethyl acetate and a saturated solution of aq NH_4Cl. The mixture was stirred for several hours. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc 1:1) to afford pure products **8a**,**e** as colorless oils.

5.6.1.1. 2-{(4S,6S*)-6-[(Benzyloxy)methyl]-2,2-dimethyl-1,3-dioxan-4-yl}-ethanol (**8a**).* Colorless oil (256 mg, 83%); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.38–7.34 (m, 5H), 4.52 (d, J=12.5 Hz, 1H), 4.48 (d, J=12.5 Hz, 1H), 4.10–4.02 (m, 2H), 3.72–3.68 (m, 2H), 3.46–3.42 (m, 1H), 3.33–3.29 (m, 1H), 2.40 (br s, 1H), 1.69–1.65 (m, 2H), 1.41 (s, 3H), 1.34 (s, 3H) 1.47–1.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=138.1, 128.4, 127.7, 127.6, 98.7, 73.4, 69.1, 68.4, 60.9, 38.1, 33.5, 30.1, 19.8. IR (neat, KBr): 3414, 2964, 2920, 2856, 1453, 1377, 1255, 1165, 1090, 1044 cm^{-1}. GC–MS (EI): m/z (%)=281 [M+1$^+$], 91 (100). Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.56; H, 8.60.

5.6.1.2. 2-{(4S,6R*)-6-[4-(Benzyloxy)butyl]-2,2-dimethyl-1,3-dioxan-4-yl}-ethanol (**8e**).* Colorless oil (63 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.36–7.27 (m, 5H), 4.51 (s, 2H), 4.13–4.09 (m, 1H), 3.84–3.76 (m, 3H), 3.49 (t, J=6.4 Hz, 2H), 1.78–1.21 (m, 10H), 1.46 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=138.6, 128.7, 127.8, 127.6, 98.6, 72.9, 70.2, 69.6, 68.9, 61.1, 38.0, 36.5, 30.2, 29.7, 21.7, 19.9. IR (neat, KBr): 3410, 2969, 2928, 2852, 1453, 1377, 1255, 1165, 1090, 1044 cm^{-1}. GC–MS (EI): m/z (%)=307 [M−15$^+$], 91 (100). Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.74; H, 9.35.

5.7. Iodination

5.7.1. General procedure

To a solution of **2a**,**e** (1 equiv) in dry THF (0.1 M) was added I_2 (1 equiv). The reaction mixture was stirred at rt for 4 h. At complete disappearance of the substrate, the reaction was quenched by adding a saturated aq solution of $Na_2S_2O_3$. This mixture was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated under vacuum to afford pure products **9a**,**e** as red oils.

5.7.1.1. Methyl 2-{(4R,6S*)-6-[(benzyloxy)methyl]-2,2-dimethyl-1,3-dioxan-4-yl}-2-iodoacetate (**9a**).* Red oil (57 mg, 100%); mixture 1:1 of diastereomers: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.35–7.32 (m, 10H), 4.64–4.53 (m, 4H), 4.21–4.06 (m, 6H), 3.77 (s, 6H), 3.56–3.49 (m, 2H), 3.45–3.38 (m, 2H), 2.10 (dt, J=12.8, 2.4 Hz, 1H), 1.76 (dt, J=12.4, 2.4 Hz, 1H), 1.48 (s, 3H), 1.45 (s, 3H), 1.44 (s, 3H) 1.39 (s, 3H), 1.30–110 (m, 2H). GC–MS (EI): m/z (%)=419 [M−15$^+$], 91 (100). Anal. Calcd for $C_{17}H_{23}IO_5$: C, 47.02; H, 5.34. Found: C, 47.09; H, 5.38.

5.7.1.2. Methyl 2-{(4R,6R*)-6-[4-(benzyloxy)butyl]-2,2-dimethyl-1,3-dioxan-4-yl}-2-iodoacetate (**9e**).* Red oil (45 mg, 100%); mixture 1:1 of diastereomers: ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.35–7.32 (m, 10H), 4.64–4.53 (m, 4H), 4.28–4.24 (m, 6H), 3.72 (s, 6H), 3.50 (t, J=6.5 Hz, 4H), 1.30–110 (m, 2H) 2.11–2.09 (m, 1H), 1.80–0.84 (m, 15H), 1.40 (s, 3H), 1.38 (s, 3H), 1.32 (s, 3H), 1.24 (s, 3H). GC–MS (EI): m/z (%)=461 [M−15$^+$], 91 (100). Anal. Calcd for $C_{20}H_{29}IO_5$: C, 50.43; H, 6.14. Found: C, 50.49; H, 6.18.

5.8. Bromination

5.8.1. Methyl 2-{(4R,6S*)-6-[(benzyloxy)methyl]-2,2-dimethyl-1,3-dioxan-4-yl}-2-bromoacetate (**10a**)*

To a solution of **2a** (1 equiv) in dry pyridine (0.1 M) was added Br_2 (1 equiv). The reaction mixture was stirred at −20 °C for 1 h. At complete disappearance of the substrate, the reaction mixture was filtered and concentrated under vacuum to afford product **9a** as red oil in quantitative yield (80 mg) and in 80:20 diastereomeric ratio *syn*/*anti*. ^{1}H NMR (500 MHz, $CDCl_3$) of the major diastereomer: δ=7.38–7.32 (m, 5H), 4.62–4.55 (m, 2H), 4.30–4.26 (m, 1H), 4.13–4.11 (m, 1H), 3.98 (d, J=9.0 Hz, 1H), 3.79 (s, 3H), 3.54–3.51 (m, 1H), 3.44–3.41 (m, 1H), 2.00 (br d, J=12.5 Hz, 1H), 1.48 (s, 3H), 1.44 (s, 3H), 1.25–1.21 (m, 1H). GC–MS (EI): m/z (%)=294 (100). Anal. Calcd for $C_{17}H_{23}BrO_5$: C, 52.72; H, 5.99. Found: C, 52.69; H, 5.88.

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