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A Symmetry-Based Approach to the Heterobicyclic Core of the Zaragozic Acids – Model Studies in the Pseudo C_2-Symmetric Series

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Dedicated to Professor Roland Mayer on the occasion of his 80th birthday.

Abstract: Using a two-directional strategy, a concise synthesis of a pseudo C_2-symmetric tetrabenzyl ether of a hexaol diketone was accomplished. Hydrogenolysis of this compound in the presence of acetic acid and subsequent peracetylation triggered a group-selective intramolecular acetalization to give the desired 2,8-dioxabicyclo[3.2.1]octane derivative with correct relative and absolute configurations at all stereogenic centers of the heterobicyclic core.

Keywords: asymmetric catalysis; chemoselectivity; cyclization; dihydroxylation; heterocycles; zaragozic acids

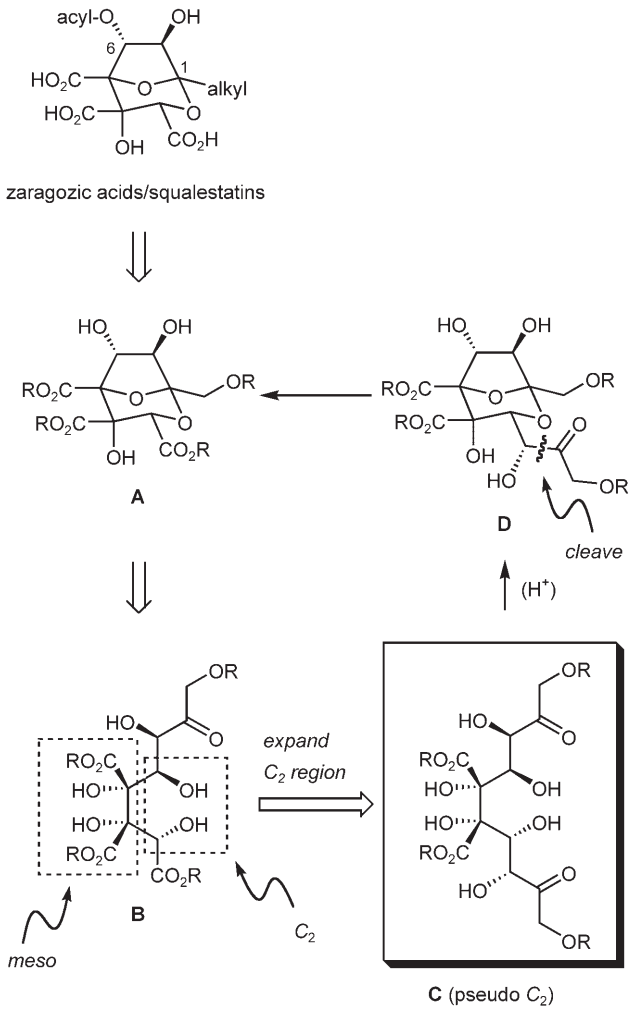
The zaragozic acids/squalestatins are a family of naturally occurring fungal metabolites isolated independently by three groups in 1991/1992.[1] These natural products are potent inhibitors of squalene synthase and *ras*-farnesyl protein transferase and additionally display significant activities toward a wide spectrum of yeast and fungal pathogens. Moreover, zaragozic acid A (squalestatin S1) protects against neuronal damage at low concentrations.[2] All zaragozic acids have a densely oxygenated hydrophilic 2,8-dioxabicyclo[3.2.1]octane core differing only in the C-1 alkyl and C-6 acyl side chains (Scheme 1). Due to their structural complexity and their biological activities, they have stimulated enormous synthetic efforts. Thus, the total syntheses of several zaragozic acids have been accomplished, and many synthetic studies toward the heterobicyclic core as well as detailed investigations on structure-activity relationships have been carried out.[1,3]

We reasoned that compound **A** would represent a suitably functionalized general building block for the synthesis of naturally occurring zaragozic acids as well as unnatural analogues. A conceptually novel symmetry-based approach[4,5] to this heterobicyclic system is depicted in Scheme 1. A retrosynthetic disconnection of the acetal moiety of **A** leads to polyhydroxy ketone **B** featuring regions with local *meso* and C_2 symmetry. Expansion of the C_2 region within **B** by addition of a two-carbon unit to the ester terminus enhances molecular complexity, however, a pseudo C_2-symmetric diketone **C** is attained,[6] which should be accessible by two-directional synthesis.[7] Diketone **C** might serve as a substitute for **B**, provided its intramolecular acetalization occurs chemoselectively and with simultaneous differentiation[8] of the two diastereotopic γ,ε-dihydroxy ketone moieties to give **D**. Finally, the superfluous appendage in **D** can be removed *via* a chemoselective oxidative cleavage to generate building block **A**.

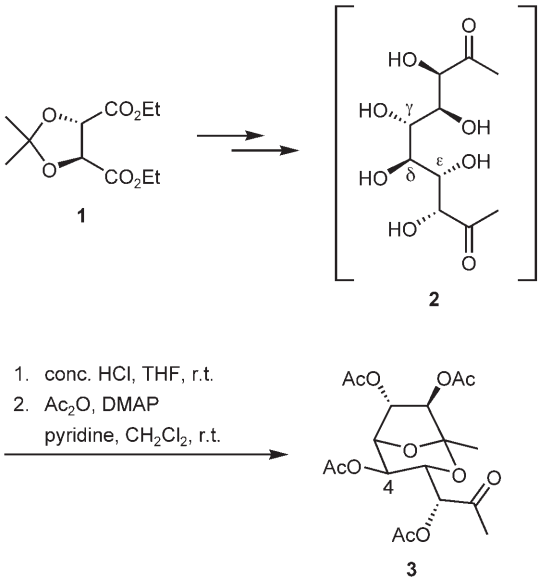
We have recently communicated a concise synthesis of the C_2-symmetric linear model compound **2** from the diethyl tartrate derivative **1**.[4] Under suitable conditions, the hexahydroxy diketone **2** cyclized with completely chemoselective participation of the γ,ε-hydroxy groups to afford the 2,8-dioxabicyclo-[3.2.1]octane derivative **3** which is epimeric at C-4 to the heterobicyclic core of the zaragozic acids in high yield after peracetylation (Scheme 2).

Here we report more advanced model studies in the pseudo C_2-symmetric series, which eventually gave rise to the C-4 epimer of **3** by chemoselective intramolecular acetalization of a linear hexahydroxy diketone prepared by a highly stereoselective two-directional route.

As one of the first efforts toward this goal, we tried to utilize a tartrate-based approach similar to the suc-



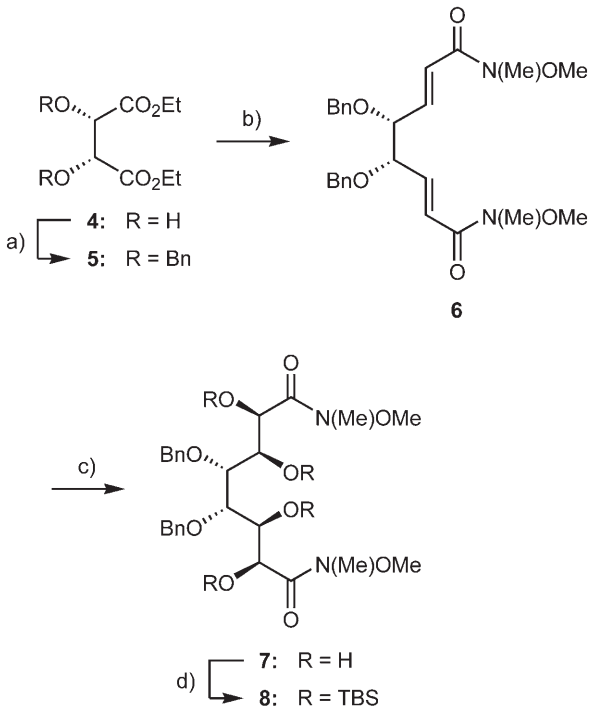
Scheme 1. Symmetry-based concept for the preparation of a general building block (**A**) for zaragozic acids/squalestatins.



Scheme 2. Model study in the C_2-symmetric series.

cessful conversion of **1** to **2** but now commencing with *meso* diethyl tartrate **4**,[9,10] which was transformed into the bis-Weinreb amide **6** by benzylation[11] followed by a sequential DIBAL-H reduction/HWE olefination[4,12] (Scheme 3). From a range of *meso* substrates similar to **6**, only this compound allowed a double asymmetric dihydroxylation (AD),[13] whereas the other substrates investigated either underwent an intramolecular cyclization after the first AD or else did not react at all.[14] While no conversion of **6** was noted using the commercially available AD-mix-α in the presence of methanesulfonamide, application of the $(DHQ)_2PYR$ ligand[15] permitted a two-fold AD reaction, however, with generation of the *meso* product **7**. The configuration of **7** was unambiguously established by an X-ray diffraction analysis of the tetrasilyl ether **8** (Figure 1).[16]

Since substrate control was clearly dominant in the formation of **7**, chances for success following a two-directional strategy starting from a *meso* compound[18] with a central 1,2-diol unit appeared rather low with the AD methodology currently available. Thus, we turned to the construction of a C_2-symmetric tetraol incorporating a central alkyne unit, from which generation of the desired pseudo C_2-symmetry was envis-



Scheme 3. *Reagents and conditions*: a) BnBr, TlOEt, MeCN, 55 °C, 74 %; b) (i) DIBAL-H, toluene, −78 °C, (ii) $(EtO)_2PO$-CH(Na)-CON(Me)OMe, DME, −78 °C to room temperature, 41 %; c) 4 mol % $K_2OsO_2(OH)_4$, $K_3[Fe(CN)_6]$, K_2CO_3, $NaHCO_3$, $MeSO_2NH_2$, 10 mol % $(DHQ)_2PYR$, *t*-BuOH, H_2O, 0 °C to room temperature; d) TBSOTf, 2,6-lutidine, CH_2Cl_2, room temperature, 56 % **8** from **6**.

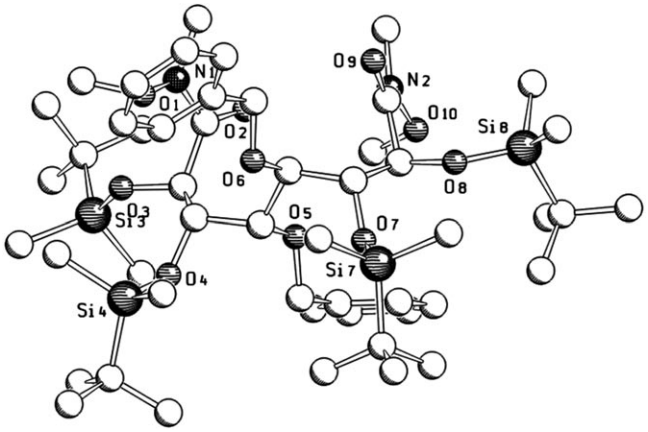
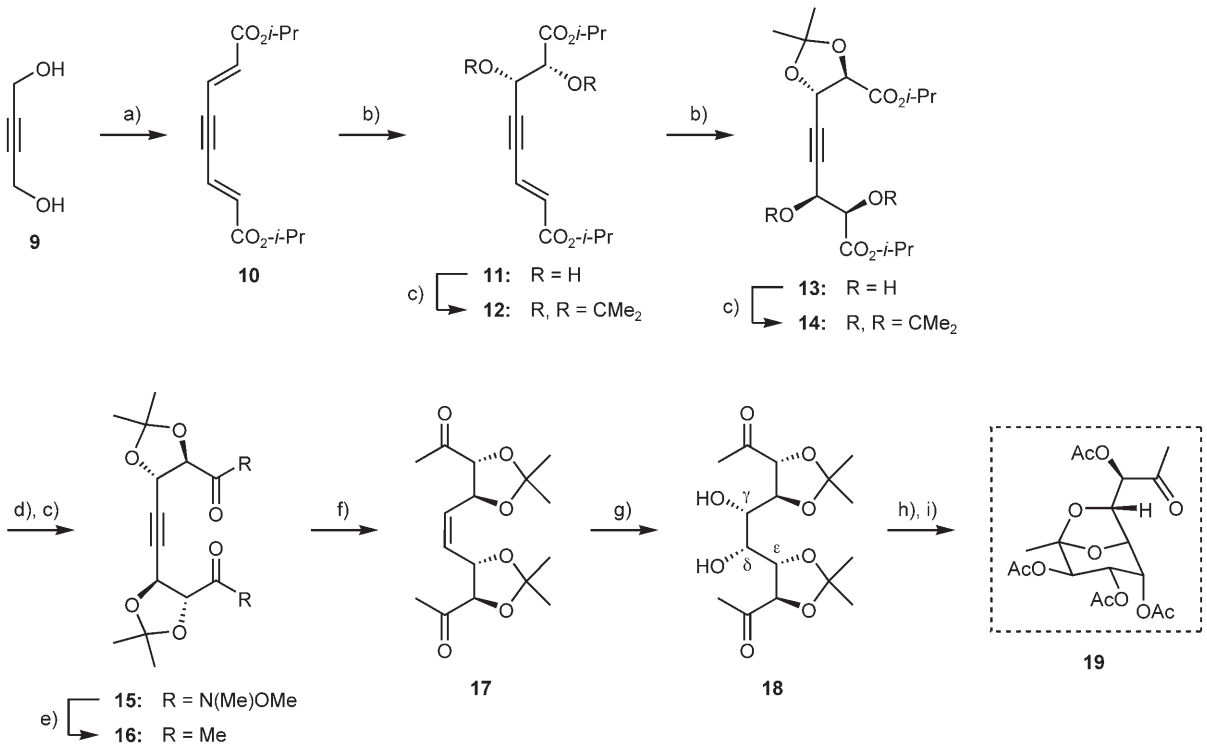


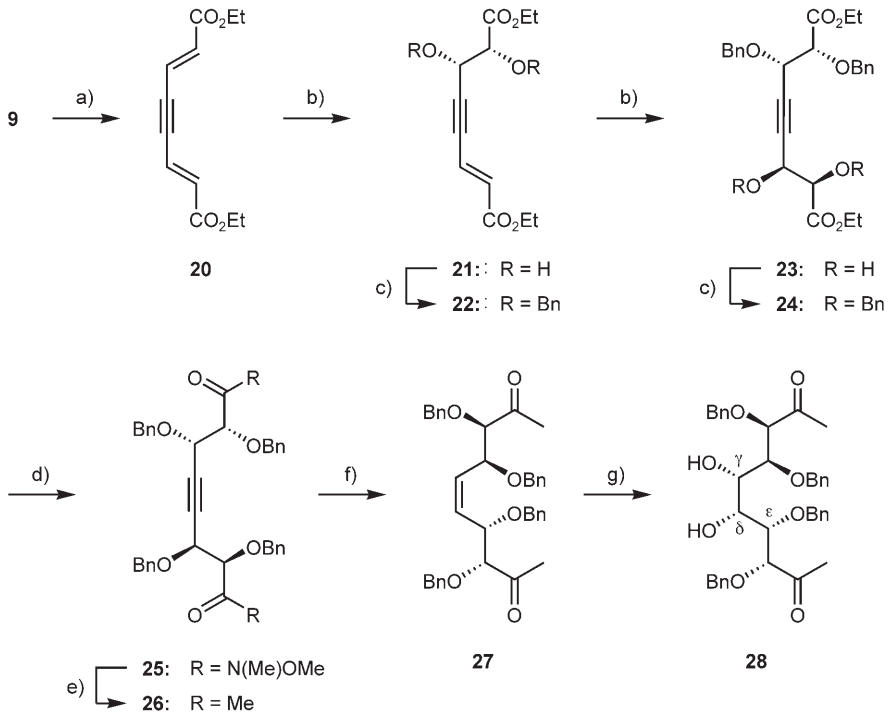
Figure 1. Crystal structure of *meso* compound **8**.[16,17]

aged by semihydrogenation and subsequent *syn* dihydroxylation. The crucial idea was to use a dienyne as the achiral AD substrate, where the central alkyne would serve as a spacer that prevents both an intramolecular Michael addition of dihydroxylated synthetic intermediates as well as an overriding substrate control during the second AD reaction. A two-directional route to the pseudo C_2-symmetric precursor **18** of a hexaol diketone according to this modified strategy is depicted in Scheme 4.

2-Butyne-1,4-diol (**9**) was converted to the (*E*,*E*) bis-enoate **10** in a one-pot Dess–Martin oxidation/Wittig olefination process (Scheme 4).[19] A one-pot double AD of **10** was not practical, since dihydroxylation of the intermediate diol **11** proved to be rather slow, and isolation of the resultant tetraol was not facile due to its high polarity. Thus, the dioxolane moieties of the C_2-symmetric diester **14** were established by an iterative protocol consisting of a single AD under modified Sharpless conditions[20] and subsequent isopropylidene protection. The diastereomerically pure C_2-symmetric bis-acetal **14** was isolated in high overall yield from **10** implying a very high enantiomeric purity after the two AD transformations.[21] Conversion of the ester termini of **14** to Weinreb amides[22] using trimethylaluminum caused a competing acetal cleavage, which required a reprotection to provide **15**. Double alkylation of **15** to give diketone **16**, partial reduction of the triple bond using the Lindlar catalyst and catalytic dihydroxylation of the re-



Scheme 4. *Reagents and conditions*: a) $Ph_3P{=}CHCO_2$-*i*-Pr, $PhCO_2H$, Dess–Martin periodinane, CH_2Cl_2, DMSO, room temperature, 62%; b) 3 mol% $K_2OsO_2(OH)_4$, $K_3[Fe(CN)_6]$, K_2CO_3, $NaHCO_3$, $MeSO_2NH_2$, 6 mol% $(DHQ)_2PHAL$, *t*-BuOH, H_2O, 0°C, 88% **11** from **10**, 79% **13** from **12**; c) 2,2-dimethoxypropane, TsOH, CH_2Cl_2, room temperature, 80% **12** from **11**, 90% **14** from **13**, 60% **15** from **14**; d) MeONHMe·HCl, Me_3Al, CH_2Cl_2, 0°C to room temperature; e) MeLi, THF, −78°C, 74%; f) 1 bar H_2, 10 wt% Lindlar catalyst, EtOAc, room temperature; g) 5 mol% OsO_4, NMO, acetone, H_2O, room temperature, 79% **18** from **16**; h) TFA, CH_2Cl_2, H_2O (10:20:1), room temperature; i) Ac_2O, DMAP, pyridine, room temperature, 59% **19** from **18**.



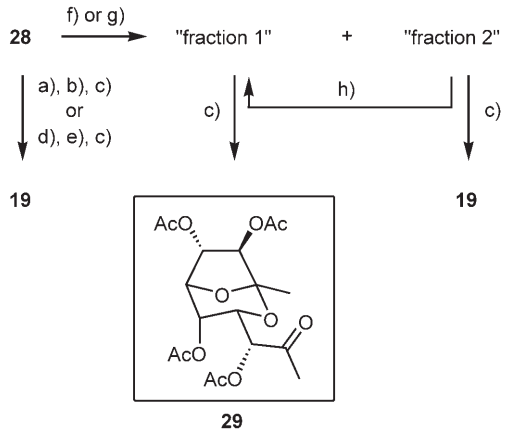
Scheme 5. *Reagents and conditions*: a) $Ph_3P{=}CHCO_2Et$, $PhCO_2H$, Dess–Martin periodinane, CH_2Cl_2, DMSO, room temperature, 73%; b) 5 mol% $K_2OsO_2(OH)_4$, $K_3[Fe(CN)_6]$, K_2CO_3, $NaHCO_3$, $MeSO_2NH_2$, 10 mol% $(DHQ)_2PHAL$, *t*-BuOH, H_2O, 0°C, 80% **21**, 76% **23**; c) BnBr, Ag_2O, Et_2O, reflux, 86% **22**, 92% **24**; d) MeONHMe·HCl, *i*-PrMgCl, THF, −20°C to room temperature, 97%; e) MeMgBr, THF, 0°C, 93%; f) 1 bar H_2, 20 wt% Lindlar catalyst, EtOAc, room temperature; g) (i) 1.1 equivs. OsO_4, pyridine, toluene, 0°C to room temperature, (ii) $NaHSO_3$, H_2O, 0°C to room temperature, 90% **28** from **26**.

sultant (*Z*) configured olefin **17** afforded the pseudo C_2-symmetric diol **18** as a hemi acetal mixture (Scheme 4). Treatment of **18** with trifluoroacetic acid under conditions that were favorable for intramolecular acetalizations of polyol monoketones to generate the heterobicyclic core of the zaragozic acids[23] only led to the undesired acetal isomer **19**[24] after peracetylation. This isomer is formed by acetalization of the "upper" ketone function of the polyol derived from **18** with its δ,ε-diol subunit; the desired cyclization involving this ketone and its γ,ε-diol moiety was not observed. While the requisite C-4 epimer of **3** was not yet obtained, this experiment nevertheless suggested that the presence of the diketone functionality in deblocked **18** did not cause any special difficulties, because similar problems with competing γ,ε- and δ,ε-cyclizations were also quite frequently observed during the acetalization of trihydroxy monoketones to give the 2,8-dioxabicyclo[3.2.1]octane of the zaragozic acids.[1,25]

A more facile formation of a six-membered hemi acetal involving the δ-hydroxy group was seen as a possible reason for the preferred generation of acetal **19**, since attack of the γ-hydroxy group prior to hydrolysis of the "upper" isopropylidene acetal would lead to two *trans*-fused five-membered rings.[3d,23b] Hence, we subsequently used acyclic (benzyl) protecting groups instead of a cyclic 1,2-diol protection for the four peripheral hydroxy groups in **18** (Scheme 5).

Tetrabenzyl ether **28** that exists as a hemiacetal mixture was synthesized from 2-butyne-1,4-diol (**9**) according to the strategy used for the preparation of **18** (Scheme 5). During the synthetic elaboration to bis-Weinreb amide **25**, the diethyl ester gave a significantly higher overall yield compared to the diisopropyl analogue. Again, an iterative AD[26]/protection protocol was followed, in the course of which a silver oxide-assisted[27] double benzylation proved to be highly efficient. For conversion of diethyl ester **24** to bis-Weinreb amide **25**, isopropylmagnesium chloride[28] was clearly superior to trimethylaluminum. Probably due to the steric shielding imparted by the two allylic benzyl ethers in **27**, a stoichiometric amount of osmium tetroxide had to be used for the final dihydroxylation step.

Hydrogenolytic debenzylation of **28** in ethyl acetate followed by treatment with trifluoroacetic acid in dichloromethane/water at room temperature and peracetylation again led only to the undesired acetal **19** in high yield (Scheme 6). Similarly, a slower debenzylation of **28** in tetrahydrofuran and subsequent treatment with concentrated hydrochloric acid in tetrahydrofuran[4] at room temperature followed by peracetylation solely gave rise to isomer **19**. Monitoring the



Scheme 6. *Reagents and conditions*: a) 10 bar H_2, 10% Pd/C, EtOAc, room temperature; b) TFA, CH_2Cl_2, H_2O (10:20:1), room temperature; c) Ac_2O, DMAP, pyridine, room temperature, 84% **19** *via* steps [a), b), c)] from **28**, 51% **19** *via* steps [d), e), c)] from **28**, 76% **29** from "fraction 1", 73% **19** from "fraction 2"; d) 10 bar H_2, 10% Pd/C, THF, room temperature; e) conc. HCl, THF, room temperature; f) 20 bar H_2, 10% Pd/C, THF, room temperature, 30% "fraction 1", 50% "fraction 2"; g) 30 bar H_2, 10% Pd/C, THF, 100 equivs. HOAc, room temperature, 75% "fraction 1", 21% "fraction 2"; h) 0.5 equivs. conc. HCl, THF, −10 °C, 60% "fraction 1", 33% "fraction 2".

debenzylation step by TLC revealed that in ethyl acetate only a very polar fraction was rapidly formed, whereas in addition to this fraction ("fraction 2") another less polar fraction ("fraction 1") was detected for the slower reaction in tetrahydrofuran.[29] Peracetylation of "fraction 1" delivered only the desired γ,ε-cyclization product **29**,[24] whereas peracetylation of "fraction 2" solely gave rise to the unwanted δ,ε-cyclization product **19**. Acid-catalyzed conversion of "fraction 2" into "fraction 1" proved to be possible at low temperature and high concentration of hydrochloric acid. Eventually, the optimum access to "fraction 1" was achieved by directly performing the hydrogenolysis of **28** in the presence of 100 equivalents of acetic acid. Using these conditions, the tetraacetate **29** was isolated in 57% overall yield from the tetrabenzyl ether **28**.

In conclusion, we have developed a short and highly stereoselective two-directional route to a model for the heterobicyclic core of the zaragozic acids featuring a group-selective intramolecular acetalization of a pseudo C_2-symmetric hexahydroxy diketone intermediate as the key step. Since a chemoselective oxidative removal of the superfluous two-carbon appendage present in **29** had already been achieved for the C-4 epimer **3**,[4] this approach also provides a good basis for a similar access to the fully substituted natural products as well as non-natural analogues. Investigations along these lines will be reported in due course.

Experimental Section

Asymmetric Dihydroxylation of 20

A solution of $K_2OsO_2(OH)_4$ (63 mg, 0.17 mmol), $K_3[Fe(CN)_6]$ (3.36 g, 10.20 mmol), K_2CO_3 (1.10 g, 10.2 mmol), $NaHCO_3$ (0.86 g, 10.2 mmol) and $(DHQ)_2PHAL$ (265 mg, 0.34 mmol) in a mixture of *t*-BuOH (30 mL) and water (30 mL) was stirred at room temperature for 2 h, $MeSO_2NH_2$ (646 mg, 6.80 mmol) was added, and stirring was continued for another 30 min. After cooling to 0 °C, a solution of bis-enoate **20** (750 mg, 3.40 mmol) in *t*-BuOH (5 mL) and water (5 mL) was added, and the resulting mixture was stirred for 2 h. The reaction was quenched by addition of sodium sulfite (5.10 g), stirring was continued for another 30 min at room temperature, and the layers were separated. After extraction of the aqueous layer with diethyl ether (3 × 30 mL), washing of the combined organic layers with brine, drying over magnesium sulfate and removal of the solvents under vacuum, the residue was subjected to flash chromatography on silica gel (diethyl ether/pentane, 3:1) to give diol **21** (yield: 688 mg, 80%, 86% *ee*) as a yellow oil and some starting material **20** (98 mg, 13%).

21: $R_f = 0.32$ (diethyl ether/pentane, 3:1); $[\alpha]_D^{27}$: +13.8 (*c* 1.0, $CHCl_3$); IR (neat): $\tilde{\nu} = 3444$ (br, OH), 2982 (w), 1713 (s, C=O), 1620 (s), 1368 (m), 1267 (s), 1151 (s), 1026 (s), 970 (m), 863 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 1.23$ (t, $^3J = 7.1$ Hz, 3H), 1.27 (t, $^3J = 7.0$ Hz, 3H), 2.73 (br s), 3.25 (br s), 4.12 (q, $^3J = 7.1$ Hz, 2H), 4.25 (d, $^3J = 4.5$ Hz, 1H), 4.28 (m_c, 2H), 4.75 (d, $^3J = 4.5$ Hz, 1H), 5.04 (d, $^3J = 15.9$ Hz, 1H), 6.73 (d, $^3J = 15.9$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 14.16$ (q, intense), 60.91 (t), 62.73 (t), 64.24 (d), 73.31 (d), 82.65 (s), 94.85 (s), 123.83 (d), 131.71 (d), 165.50 (s), 171.37 (s); MS (GC/MS, 70 eV): *m/z* (%) = 227 (1) [M^+−Et], 211 (4) [M^+−OEt], 183 (3) [M^+−CO_2Et], 153 (30) [M^+−CH(OH)CO_2Et], 104 (100) [M^+ −EtO_2C-CH=CH-C≡C-CHO], 76 (83), 63 (29), 51 (38); anal. calcd. for $C_{12}H_{16}O_6$: C 56.24, H 6.29; found: C 56.32, H, 6.35.

Hydrogenolytic Debenzylation of 28

A solution of tetrabenzyl ether **28** (100 mg, 0.16 mmol) in dry THF (4.0 mL) was treated with acetic acid (0.9 mL, 16 mmol) and 10% Pd/C (15 mg). The reaction mixture was stirred for 14 h under a hydrogen pressure of 30 bar at room temperature. After filtration through a glass filter funnel and thorough rinsing with ethyl acetate/methanol (1:1), the solution was washed with 0.5 M aqueous $NaHCO_3$ (20 mL). The solvent was removed under vacuum, and the residue was subjected to flash chromatography on silica gel (ethyl acetate/methanol, 8:1, + 1 vol% Et_3N) to give "fraction 1" (yield: 32 mg, 75%; $R_f = 0.35$) and "fraction 2" (yield: 9.1 mg, 21%; $R_f = 0.14$).

Typical Procedure for Peracetylation

A solution of "fraction 1" (36 mg, 0.14 mmol) in pyridine (3 mL) was treated with freshly dried acetic anhydride

(0.56 mL, 5.54 mmol) and 4-(*N,N*-dimethylamino)pyridine (17.5 mg, 0.14 mmol). After stirring the mixture at room temperature for 1 day, it was filtered through a plug of silica gel using diethyl ether/dichloromethane, 1:1, as eluent. Following removal of the solvent under vacuum, the crude product was purified by flash chromatography on silica gel (diethyl ether/dichloromethane, 1:9) to give the tetraacetate **29**; yield: 43 mg (76%).

19: $R_f = 0.10$ (dichloromethane/diethyl ether, 9:1); $[\alpha]_D^{24}$: +95.3 (*c* 0.77, $CHCl_3$); IR (neat): $\tilde{\nu} = 2932$ (w), 2849 (w), 1737 (s, C=O), 1215 (s), 1058 (s), 961 (m), 875 (w), 605 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 1.43$ (s, 3H), 1.96 (s, 3H), 2.07 (s, 3H), 2.13 (s, 3H), 2.18 (s, 3H), 2.21 (s, 3H), 4.42 (d, $^3J = 4.5$ Hz, 1H), 4.58 (d, $^3J = 2.2$ Hz, 1H), 5.09–5.12 (m, 2H), 5.15 (d, $^3J = 4.5$ Hz, 1H), 5.31–5.32 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz): $\delta = 19.40$ (q), 20.51 (q), 20.65 (q), 20.73 (q, intense), 27.73 (q), 68.08 (d), 68.69 (d), 73.02 (d), 76.10 (d), 77.18 (d), 77.25 (d), 108.26 (s), 169.86 (s), 169.99 (s), 170.06 (s, intense), 203.92 (s); MS (LC/MS, ESI): *m/z* (%) = 434 (100) $[M+NH_4^+]$; anal. calcd. for $C_{18}H_{24}O_{11}$: C 51.92, H 5.81; found: C 51.98, H 5.84.

29: $R_f = 0.30$ (dichloromethane/diethyl ether, 9:1); $[\alpha]_D^{24}$: +78.0 (*c* 0.60, $CHCl_3$); IR (neat): $\tilde{\nu} = 2925$ (w), 2853 (w), 1739 (s, C=O), 1213 (s), 1065 (s), 953 (m), 873 (w), 603 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 1.54$ (s, 3H), 2.03 (s, 3H), 2.11 (s, 3H), 2.168 (s, 3H), 2.171 (s, 3H), 2.28 (s, 3H), 4.34 (d, $^3J = 2.3$ Hz, 1H), 4.45 (dd, $^3J = 2.8$ Hz, $^3J = 5.0$ Hz, 1H), 4.86 (dd, $^3J = 2.3$ Hz, $^3J = 2.8$ Hz, 1H), 5.11 (d, $^3J = 2.3$ Hz, 1H), 5.16 (d, $^3J = 2.3$ Hz, 1H), 5.22 (d, $^3J = 5.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): $\delta = 20.42$ (q), 20.65 (q, intense), 20.71 (q), 22.47 (q), 27.94 (q), 65.52 (d), 70.77 (d), 76.13 (d), 77.26 (d), 80.46 (d, intense), 104.26 (s), 169.54 (s), 169.58 (s), 169.82 (s), 170.21 (s), 201.36 (s); MS (LC/MS, ESI): *m/z* (%) = 434 (100) $[M+NH_4^+]$; anal. calcd. for $C_{18}H_{24}O_{11}$: C 51.92, H 5.81; found: C 52.07, H 5.84.

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