^{1}H NMR (200 MHz, [D$_8$]THF, 298 K): $\delta = 7.78$ (4H), 7.12 (4H), 6.93 (2H), 2.20 (6H); ^{13}C NMR (50 MHz, [D$_8$]THF, 298 K): $\delta = 154.6$, 128.0, 127.6, 125.2, 94.3,[16] 39.7.

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[5] a) Crystal structure analysis of **10** ($C_{19}H_{24}LiNO_2$, $M_r = 305.33$): monoclinic, space group $P2_1/c$, $a = 1059.4(1)$, $b = 928.5(1)$, $c = 1775.4(1)$ pm, $\beta = 93.927(5)^\circ$, $V = 1742.3(2) \times 10^{-30}$ m^3, $Z = 4$, $\rho_{calcd} = 1.164$ Mg m^{-3}, $\mu(Cu_{K\alpha}) = 1.542$ mm^{-1}. Data collection on an Enraf-Nonius CAD4 diffractometer with graphite-monochromated $Cu_{K\alpha}$ radiation at $T = 213(2)$ K. Of 3063 reflections collected, 2954 were unique ($R_{int} = 0.0260$). The structure was solved with direct methods (SHELXS-97)[5b] and refined on F^2 with all reflections (SHELXL-97).[5c] Non-hydrogen atoms were anisotropic, and hydrogen atoms were placed at calculated positions with fixed isotropic temperature factors. Parameters for the weighting scheme calculated by the program: 0.0856, 0.8018; $R1 = 0.0547$ (2446 reflections with $I > 2\sigma(I)$), w$R2 = 0.1602$, GOF = 1.044; a total of 211 refined parameters. All calculations were performed on DEC Alpha Stations with VMS.[5d–f] b) G. M. Sheldrick, SHELXS-97, *Program for the Solution of Crystal Structures*, Göttingen, **1997**; c) G. M. Sheldrick, SHELXL-97, *Program for the Refinement of Crystal Structures*, Göttingen, **1997**; d) A. L. Spek, Platon 94, *Program for Geometrical Analysis of Crystal Structures*, Utrecht, **1994**; e) E. Keller, SCHAKAL-88B, *A FORTRAN Program for the Graphic Representation of Molecular and Crystallographic Models*, Freiburg, **1988**. f) Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-111982. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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[10] $[CH_3O^-Li^+ \cdot THF] + NH_3 \rightarrow [CH_3O^-Li^+ \cdot THF \cdot NH_3]$ leads to a stabilization of -20.0 kcal mol^{-1} (RHF/3-21G//PM3).

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[13] Therefore, without an anomeric effect in **10**, C1–N1 should be longer and C1–O1 shorter.

[14] After we started our investigations on α-aminolithium alkoxides,[15] the first solid-state structure of such a compound was published by J. E. Davies, P. R. Raithby, R. Snaith, and A. E. H. Wheatley (*Chem. Commun.* **1997**, 1721 – 1722). However, they discussed neither C–C, C–O, or C–N bond lengths nor the bond angles of these atoms. They were only interested in O–Li and N–Li interactions. This is also the case in a recent paper: D. R. Armstrong, J. E. Davies, R. P. Davies, P. R. Raithby, R. Snaith, A. E. H. Wheatley, *New J. Chem.* **1999**, 35 – 41.

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[16] The chemical shift of C1 in the ^{13}C spectrum ($\delta = 94.3$) corresponds to those of related tetrahedral carbon atoms: $\delta = 88.6$[14] and 105.9.[15]

Total Synthesis of (−)-Mucocin**

Stefan Bäurle, Sabine Hoppen, and Ulrich Koert*

The acetogenins of *Annonaceae* are characterized by their variety in structure and their potent biological features, for example, as antitumor agents or immunosuppressants.[1] Therefore, this class of compounds is subject to intensive synthetic efforts.[2] Within the acetogenins a group of compounds exists that also bear a tetrahydropyran (THP) ring additional to the usual tetrahydrofuran rings in the molecular scaffold. A representative member of that group is (−)-mucocin, which was isolated from *Rollinia Mucosa*.[3] The molecule shows a highly selective inhibitory effect against A-549 (lung cancer) and PACA-2 (pancreatic cancer) cell lines with a selectivity up to 10000 times that of the known antitumor agent adriamycin. A blockage of the mitochondrial complex I is discussed as the mode of action.[1]

Here we report on a total synthesis of (−)-mucocin that follows a highly convergent synthetic strategy.[4] According to our retrosynthetic analysis (disconnection at C16–C17) mucocin could be constructed by the addition of a THP organometallic compound **1** to a THF aldehyde **2** (Scheme 1).

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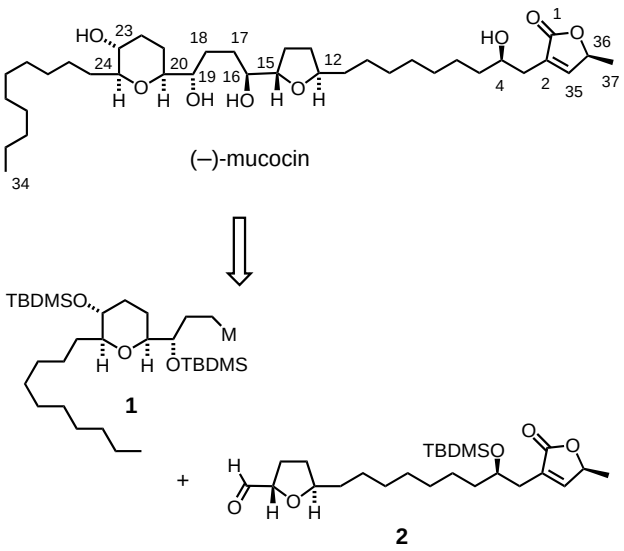
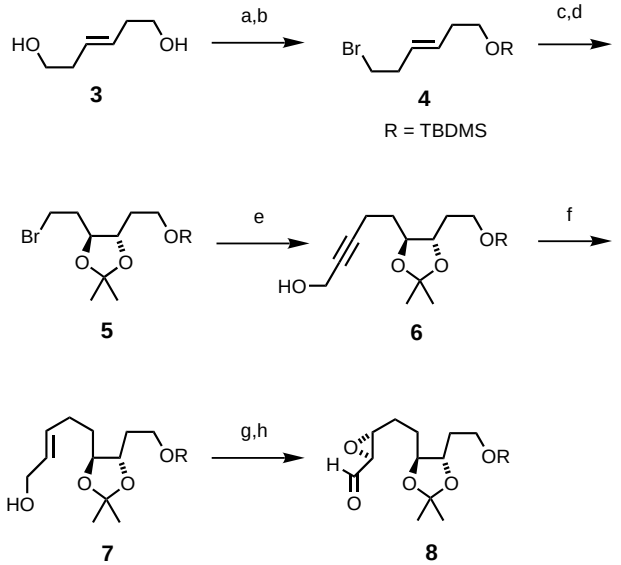
Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.



Scheme 1. Retrosynthetic analysis of (–)-mucocin. TBDS = *tert*-butyldimethylsilyl.

The compatibility of the butenolide with the reaction conditions in regard to a possible epimerization as well as the stereocontrol of the coupling reaction were considered as critical to the strategy.

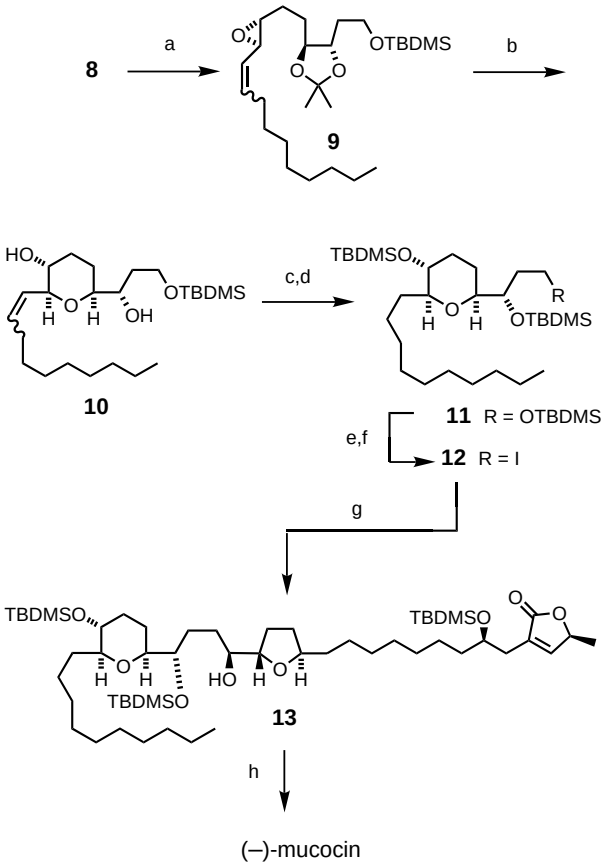
The synthesis of the left part of the molecule (Scheme 2) started with the diol **3**. After monosilylation[5] and subsequent bromination to **4**, the sequence of dihydroxylation/acetonide[6] protection gave the bromide **5**. The alkylation to **6**, followed by an *E*-selective reduction[7] of the resulting alkyne



Scheme 2. a) NaH (1.0 equiv), TBDMSCl (1.0 equiv), THF, 0 °C, 1 h, 54 %; b) 1. *p*-TsCl (2.0 equiv), Py (10 equiv), CH_2Cl_2, 0 °C, 12 h; 2. LiBr (4.0 equiv), acetone, 12 h, 85 %; c) AD-mix α, $MeSO_2NH_2$, H_2O/*t*BuOH (1/1), 0 °C → RT, 24 h; d) *p*-TsOH (5 mol %), 3,3-dimethoxypropane (4.0 equiv), CH_2Cl_2, 1 h, 92 % over two steps; e) propargylic alcohol (3.0 equiv), *n*BuLi (6.0 equiv), NH_3/THF/DMPU (5/5/2), –40 °C, 6 h, 91 %; f) Red-Al (2.0 equiv), THF, 0 °C, 4 h, 95 %; g) TBHP (2.0 equiv), (–)-DIPT (12 mol %), Ti(O*i*Pr)$_4$ (10 mol %), CH_2Cl_2, –20 °C, 3.5 h, 85 %; h) Dess–Martin periodinane (2.0 equiv), Py (10 equiv), CH_2Cl_2, 0 °C, 3 h, 89 %. *p*-Ts = *p*-toluenesulfonyl, Py = pyridine, DMPU = *N*,*N*′-dimethylpropylene urea, TBHP = *tert*-butylhydroperoxide, DIPT = diisopropyl tartrate.

to the alkene **7** opened the way for the elaboration of the THP ring. A 6-*endo* attack of the C20 oxygen atom on a C23–C24 epoxide by an activation of the C24 position by a C25–C26 double bond was envisaged for the construction of the THP ring.[8] Sharpless epoxidation[9] of the allylic alcohol **7** afforded an epoxy alcohol that was oxidized to the aldehyde **8** by using the Dess–Martin protocol.[10]

The precursor for the cyclization to the THP ring was obtained after Wittig reaction of **8** with the C25–C34 phosphonium ylide (Scheme 3). This reaction (**9** → **10**) deserves further comments: an acid-catalyzed intramolecular



Scheme 3. a) $H_{19}C_9PPh_3Br$ (1.4 equiv), NaHMDS (1.2 equiv), THF, –78 °C, 5 min, 85 %, *E*:*Z* = 1:1; b) CSA (8 mol %), CH_2Cl_2/*i*PrOH (30/1), –40 → 0 °C, 3.5 h, 89 %; c) 5 % Pt/C, H_2 (1 bar), EtOAc, 0 °C, 5 h, 95 %; d) TBDMSOTf (3.0 equiv), 2,6-lutidine (5.0 equiv), CH_2Cl_2, 0 °C, 1 h, 92 %; e) CSA (0.25 equiv), CH_2Cl_2/MeOH (2/1), 0 °C, 30 min, 73 %; f) I_2 (1.2 equiv), PPh_3 (1.1 equiv), imidazole (3.0 equiv), CH_2Cl_2, 0 °C, 3 h, 80 %; g) **12** (1.2 equiv), *t*BuLi (2.2 equiv), Et_2O, –105 °C, 5 min; then $MgBr_2 \cdot OEt_2$ (2.4 equiv), –100 → –35 °C, 1.5 h; → –78 °C, **2** (1.0 equiv), → –15 °C, 1.5 h, 56 %, 34 % of **2** was also recovered; h) HF (5 equiv), CH_3CN/CH_2Cl_2, 20 °C, 1 h, 91 %. NaHMDS = sodium hexamethyldisilazide, CSA = camphersulfonic acid.

6-*endo* attack on the alkenyl epoxide of the acetonide had to occur, while possible intermolecular side reactions at the epoxide[11] and cleavage of the silyl group had to be suppressed. Only when isopropyl alcohol was used as a weak nucleophilic protic cosolvent was a clean conversion accomplished.[12] The cleavage of the acetonide and the opening of the epoxide could possibly happen in a concerted manner without the free diol as an intermediate. After the selective

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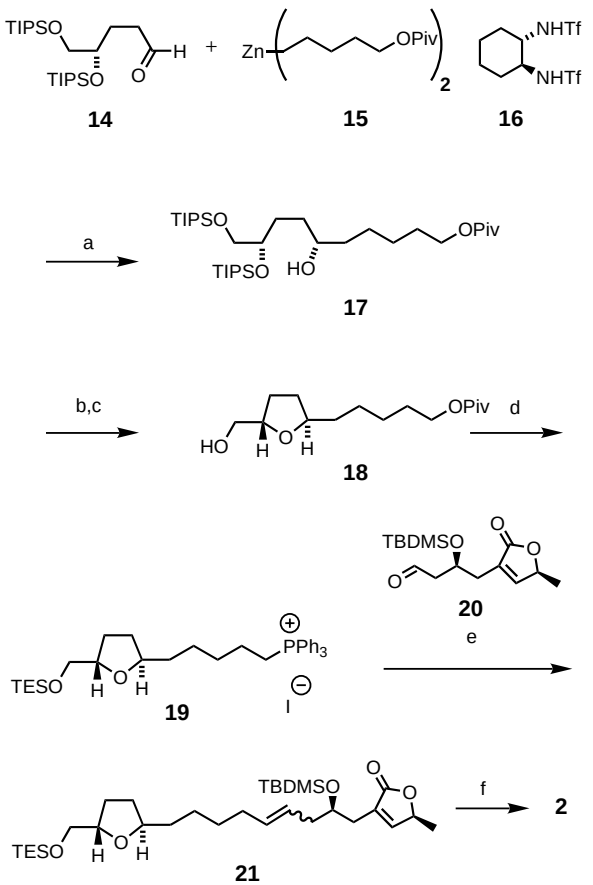
opening of the epoxide the double bond at C25–C26 was removed. A standard sequence (**10** → **11** → **12**) led to the iodide **12**, the precursor to the convergent final step of the synthesis. An iodine–lithium exchange in **12** was realized at −105 °C[13] followed by a transmetalation to magnesium. The precise choice of temperature and time was crucial for the success of the reaction. If the transmetalation did not take place within five minutes after the halogen–metal exchange and if the temperature rose above −100 °C a retro-Brook migration[14] from the silyl group at O–C19 to C17 was observed as a side reaction. Treatment of the aldehyde **2** with the organomagnesium compound and subsequent warming to −15 °C gave the desired product **13**. Noteworthy, only 1.2 equivalents of iodide **12** to 1 equivalent of aldehyde **2** were necessary. The stereoselectivity of the reaction was 4:1 in favor of the desired epimer **13**. The synthetically undesired, but pharmacologically interesting, C16 minor epimer could be separated by chromatography. Cleavage of the silyl protecting groups provided (−)-mucocin ($[\alpha]_D = -12.7$, $c = 0.27$ in CH_2Cl_2), which was found to be identical to the naturally occurring product in respect to the spectroscopical data (Table 1).

Table 1. Selected analytical and spectroscopic data of **13** and (−)-mucocin.

13: HPLC: $R_t = 10.3$ min (Rainin Si 60, *i*PrOH/*n*-hexane (1/99), 1.0 mL min^{-1}); $[\alpha]_D^{22} = -19.2°$ ($c = 0.60$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.09$ (d, $J = 1.1$ Hz, 1H), 4.98 (dq, $J = 6.8$, 1.1 Hz, 1H), 3.94 (m, 1H), 3.88–3.79 (m, 1H), 3.75 (dt, $J = 14.2$, 6.7 Hz, 1H), 3.62 (dt, $J =$ 10.5, 5.3 Hz, 1H), 3.38–3.27 (m, 1H), 3.27–3.14 (m, 2H), 2.98 (m, 1H), 2.43 (d, $J = 2.7$ Hz, 1H), 2.40 (d, $J = 5.3$ Hz, 2H), 2.04–1.88 (m, 3H), 1.76–1.15 (m, 47H), 1.39 (d, $J = 6.8$ Hz, 3H), 0.85 (brs, 30H), 0.02 (brs, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 174.0$ (C1), 151.6 (C35), 130.8 (C2), 82.4 (C24), 82.0 (C15), 79.9 (C20), 79.2 (C12), 77.4 (C36), 74.6 (C16), 74.1 (C19), 71.0 (C23), 70.1 (C4), 36.9, 35.7, 33.5, 32.7, 32.4, 31.9, 29.8, 29.7, 29.6, 29.5, 29.3, 28.8, 28.7, 28.4, 26.2, 25.5, 25.1, 22.7 (C3, C5–C11, C13, C14, C17, C18, C21, C22, C25–C33), 25.9, 25.9, 25.8, (3 SiC(CH_3)$_3$), 19.0 (C37), 18.2, 18.0, 18.0 (3 SiC(CH$_3$)$_3$), 14.1 (C34), −4.0, −4.4, −4.5, −4.6, −4.8, (6 SiCH_3); HR-MS (EI): calcd (found) for $C_{55}H_{109}O_8Si_3$ [$M^+ + H$]: 981.7430 (981.7441).

(−)-Mucocin: HPLC: $R_t = 8.9$ min (Rainin Si 60, *i*PrOH/*n*-hexane (30/70), 1.5 mL min^{-1}); $[\alpha]_D^{25} = -12.7°$ ($c = 0.27$, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.16$ (d, $J = 1.5$ Hz, 1H), 5.04 (dq, $J = 6.8$, 1.5 Hz, 1H), 3.95–3.67 (m, 3H), 3.52–3.34 (m, 2H), 3.32–3.18 (m, 1H), 3.18–3.08 (m, 1H), 3.02 (dt, $J = 8.8$, 2.2 Hz, 1H), 2.84 (brs, 1H), 2.71 (brs, 1H), 2.50 (d, $J =$ 15.1 Hz, 1H), 2.37 (dd, $J = 15.1$, 8.3 Hz, 1H), 2.30 (brs, 1H), 2.14–2.05 (m, 1H), 2.05–1.89 (m, 2H), 1.88–1.76 (m, 1H), 1.75–1.13 (m, 41H), 1.41 (d, $J = 6.8$ Hz, 3H), 0.85 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 174.6 (C1), 151.8 (C35), 131.2 (C2), 82.0 (C24), 81.9 (C15), 80.1 (C20), 79.3 (C12), 78.0 (C36), 73.8 (C16), 73.5 (C19), 70.5 (C23), 70.0 (C4), 37.4, 35.6, 33.3, 32.6, 32.4, 32.0, 31.9, 29.7, 29.6, 29.5, 29.4, 29.4, 29.3, 28.8, 28.7, 28.3, 26.9, 26.2, 25.5, 25.5, 22.7 (C3, C5–C11, C13, C14, C17, C18, C21, C22, C25–C33), 19.1 (C37), 14.1 (C34); HR-MS (EI): calcd (found) for $C_{37}H_{67}O_8$ [$M^+ + H$]: 639.4836 (639.4838).

The synthesis of aldehyde **2** began with a stereocontrolled addition of the functionalized diorganozinc compound **15** to the aldehyde **14** by using the chiral ligand **16** (Scheme 4) to give the alcohol **17** (diastereoselectivity 95:5).[15] A subsequent TBAF-induced intramolecular Williamson reaction afforded the 2,5-disubstituted THF-derivative **18**, which could be transformed into the phosphonium salt **19**. A Wittig reaction of **19** with the aldehyde **20** gave olefin **21**, and completed the construction of the right half of the molecule.



Scheme 4. a) **15** (1.8 equiv), **16** (0.1 equiv), Ti(O*i*Pr)$_4$ (2.0 equiv), xylene, −25 °C, 16 h, 65%; b) *p*-TsCl (4.0 equiv), Py/CH_2Cl_2 (1/1), RT, 12 h, 93%; c) TBAF (3.0 equiv), THF, RT, 45 min, 95%, *trans*:*cis* = 95:5 (HPLC); d) 1. TESCl (1.2 equiv), imidazole (2.0 equiv), CH_2Cl_2, RT, 2 h, 86%; 2. DIBAH (2.5 equiv), THF, −20 °C, 1 h, 93%; 3. I_2 (1.2 equiv), PPh_3 (1.1 equiv), imidazole (3.0 equiv), CH_2Cl_2, 0 °C → RT, 1.5 h, 84%; 4. PPh_3 (5.0 equiv), CH_3CN/toluene (1/1), 70 °C, 20 h; e) NaHMDS (1.0 equiv), THF, 0 °C, 30 min, then **20**, −70 → 0 °C, 20 min, 60%; f) 1. [(PPh_3)$_3$RhCl] (0.15 equiv), H_2 (1 atm), benzene, RT, 3 h, 95%; 2. CSA (0.08 equiv), CH_2Cl_2/MeOH (5/1), −20 °C, 10 min, 76%; 3. Dess–Martin periodinane (2.0 equiv), Py (10 equiv), CH_2Cl_2, 0 °C → RT, 4.5 h, 91%. TBAF = tetrabutylammonium fluoride, TES = triethylsilyl, DIBAH = diisobutylaluminum hydride.

Aldehyde **2** was obtained by hydrogenation of the isolated double bond of compound **21**,[16] selective cleavage of the primary silylether, and subsequent Dess–Martin oxidation.

The synthesis of the butenolide aldehyde **20**—which should be interesting for other acetogenin syntheses as well—is summarized in Scheme 5. The hydroxyl function was prepared from the β-ketoester **22** by dianion alkylation and subsequent Noyori reduction with BINAP[17] (**22** → **23**, *ee* = 97%). The β-hydroxyester **23** was transformed via the benzylether **24** to the carboxylic acid **25**. Treatment of **25** with (*S*)-propene oxide afforded the butyrolactone **26**. After introduction of the C2–C35 double bond (**26** → **27**) the desired butenolide aldehyde **20** was obtained by selective deprotection of the primary siloxy function and Dess–Martin oxidation.

The distinctive features of this synthesis of mucocin are the high convergence and the modular way of construction. New variations of mucocin with pharmacological importance

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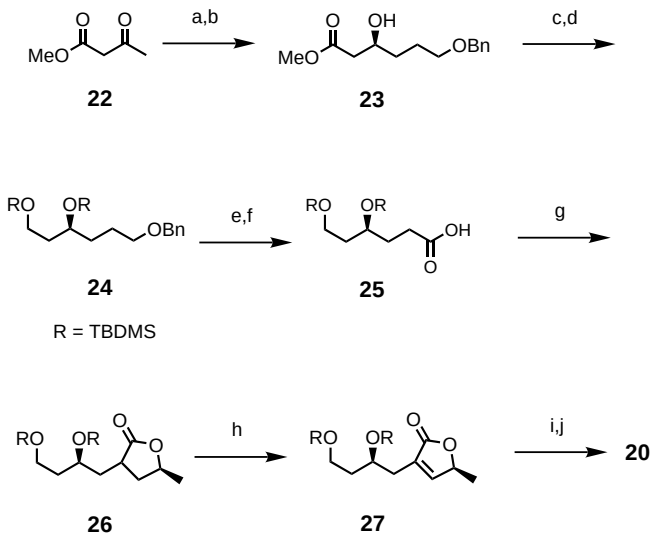

Scheme 5. a) NaH (1.5 equiv), *n*BuLi (1.5 equiv), THF, $-30 \rightarrow -15\,^{\circ}C$, 15 min, then $Br(CH_2)_2OBn$ (0.85 equiv), $-10\,^{\circ}C$, 2.5 h, 75%; b) H_2 (5 bar), Ru^{II}-(*S*)-(−)-BINAP (0.6 mol%), 95 °C, 18 h, 90%, *ee* = 97% (HPLC: Chiralcel OD-H, 10% *i*PrOH/hexane (1/9)); c) $BH_3 \cdot Me_2S$ (2.2 equiv), THF, 60 °C, 30 min, 83%; d) TBDMSCl (2.4 equiv), imidazole (3.0 equiv), DMAP (0.1 equiv), CH_2Cl_2, RT, 16 h, 88%; e) H_2 (1 atm), 10% Pd/C (5 mass%), EtOAc, 98%; f) 1. $(COCl)_2$ (2.0 equiv), DMSO (4.0 equiv), NEt_3 (5.0 equiv), CH_2Cl_2, $-78 \rightarrow -40\,^{\circ}C$, 1.5 h, 2. $NaClO_2$ (3.0 equiv), $NaH_2PO_4 \cdot 2H_2O$ (4.0 equiv), methyl-2-butene (20 equiv), *t*BuOH/H_2O (1/1), 3 h, 95%; g) 1. LDA (2.5 equiv), THF, 0 °C, 45 min, then (*S*)-(−)-propene oxide (3.0 equiv), RT, 3 h, 2. PivCl (1.1 equiv), NEt_3 (2.0 equiv), CH_2Cl_2, RT, 10 min, 73%; h) 1. KHMDS (3.0 equiv), THF, 0 °C, 30 min, then PhSeCl (3.0 equiv), 1 h, 2. MMPP (4.0 equiv), THF/MeOH (1/1), RT, 30 min, 88%; i) CSA (0.25 equiv), CH_2Cl_2/MeOH (1/1), 0 °C, 30 min, 79%; j) Dess–Martin periodinane (1.5 equiv), Py (10 equiv), CH_2Cl_2, $0\,^{\circ}C \rightarrow$RT, 4.5 h, 90%. BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphyl, DMAP = 4-dimethylaminopyridine, DMSO = dimethylsulfoxide, LDA = lithium diisopropylamide, Piv = pivaloyl ($(H_3C)_3CCO$), KHDMS = potassium hexamethyldisilazanide, MMPP = magnesium monoperoxophthalate.

should be easily available by a combination of different modules. The butenolide fragment proved to be compatible with the metalloorganic coupling reaction. This strategy should be applicable to the synthesis of other annonaceous acetogenins and presents a new, efficient, and flexible approach to this biologically important class of compounds.

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