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The Total Synthesis of the Annonaceous Acetogenin, Muricatetrocin C**

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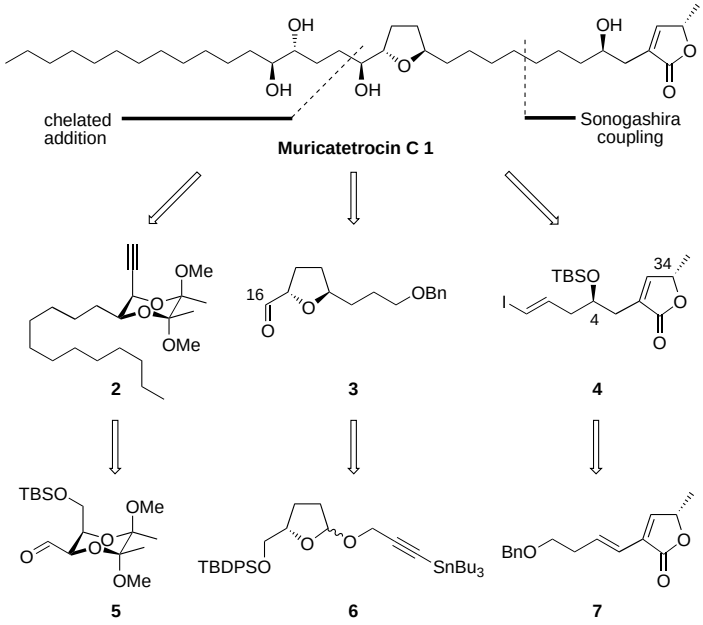
The annonaceous acetogenins comprise a rapidly growing class of natural products exhibiting a broad spectrum of biological properties. These include antibacterial, antimalarial, in vivo antitumor, parasiticidal, and pesticidal effects.[1] Perhaps most exciting is their novel and selective mode of action as inhibitors of oxidative phosphorylation, which offers a unique potential for these compounds as anticancer agents. The acetogenins are known to be powerful inhibitors of complex I (NADH:ubiquinone oxidoreductase) in mammalian and insect mitochondrial electron transport systems and of NADH oxidase found in the plasma membranes of cancer cells.[2, 3] These actions lead to ATP deprivation and subsequent apoptosis.[4] More recently the annonaceous acetogenins have also been shown to overcome resistance in multidrug resistant (MDR) tumors.[5] Thus, for the above reasons and by virtue of their limited availability from natural sources, these compounds have been targeted for total synthesis by a number of research groups.[6]

In 1996 McLaughlin and co-workers reported the isolation of muricatetrocin C (**1**; see Scheme 1) from the leaves of *Rollina mucosa*.[7] The molecule exhibits potent inhibitory action against PC-3 prostatic adenocarcinoma, PACA-2 pancreatic carcinoma, and A-549 lung carcinoma. Herein we report the first total synthesis of **1**, which was achieved by using a highly convergent synthetic strategy.[8]

The synthetic plan to **1** hinged on the enantioselective preparation of fragments **2**, **3**, and **4** and their subsequent coupling reactions (Scheme 1). It was believed that in addition to allowing an efficient synthesis of **1**, these three components would provide an excellent platform for both the evolution of existing group methodology and the potential development of new synthetic tools. The key features of our approach are: the application of the recently reported (*R*′,*R*′,*R*,*S*)-2,3-butanediacetal-protected butane tetrol **8** (see Scheme 2) as a building block for the *anti*-1,2-diol component **2** through selective chemical differentiation of the incongruous hydroxy termini;[9] the use of the recently developed anomeric O – C rearrangement protocol for the stereoselective construction of the 2,5-*trans*-disubstituted THF ring component **3**;[10] and finally the implementation of a new approach to the (*S*)-hydroxy-butenolide terminus **4**, using a hetero-Diels – Alder (HDA) reaction to simultaneously install the 1,5-stereochemical relationship and mask the butenolide double bond.



Scheme 1. Synthetic plan for **1**. Bn = benzyl, TBS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl.

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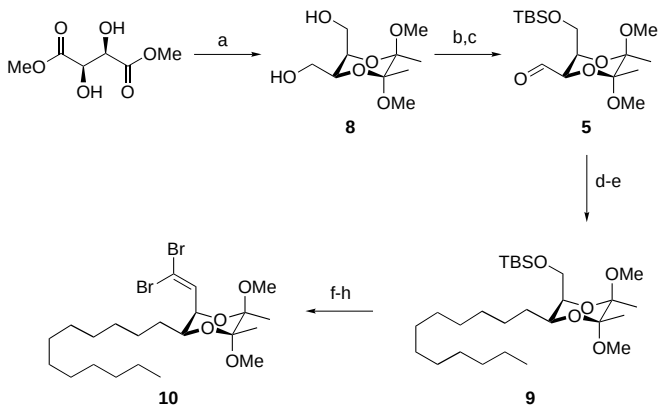


Scheme 2. Synthesis of fragment **10**, a fragment for **2**. a) Reference [9]; b) NaH, THF, 30 min, 20 °C then TBSCl, 1 h, 20 °C (72 %); c) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C; NEt_3, −78 °C→0 °C; d) $CH_3(CH_2)_{10}PPh_3I$, *n*BuLi, THF, 30 min, −78 °C (75 %; two steps); e) RaNi, H_2, EtOH, 30 min, 20 °C; f) TBAF, THF, 2 h, 20 °C (93 %, two steps); g) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C; NEt_3, −78 °C→0 °C; h) PPh_3, CBr_4, CH_2Cl_2, 30 min, 0 °C (91 %; two steps). TBSCl = *tert*-butyldimethylsilyl chloride, DMSO = dimethyl sulfoxide, RaNi = Raney nickel, TBAF = tetrabutylammonium fluoride.

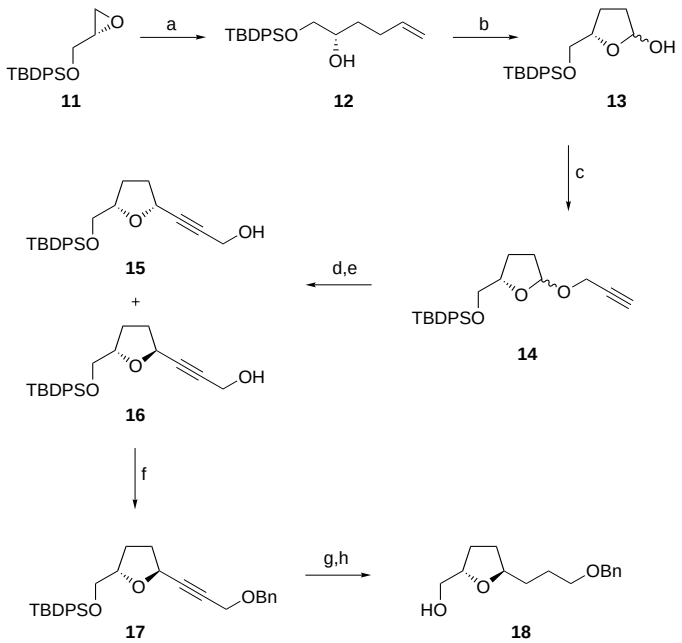
With regard to the final steps of the synthesis, addition of the alkynyllithium reagent derived from **2** to the anomerically disposed aldehyde **3** was envisaged to introduce the remaining stereogenic center at C-16. Subsequent manipulation to unmask a terminal alkyne, would then allow a Sonogashira coupling with **4** to complete the carbon skeleton; upon selective hydrogenation and global deprotection this would afford the natural product **1**.

The synthesis of fragment **2** began with the easily accessible diol **8**, which was readily converted to the equatorial aldehyde **5** in two steps according to the previously established procedure (Scheme 2).[9b] Subsequent Wittig reaction allowed introduction of an eleven-carbon side chain with moderate (1:4, *E/Z*) selectivity—for ease of characterization the unsaturation was removed at this stage by hydrogenation over Raney nickel to afford **9** in good yield (50 %, four steps). Conversion to the vinyl dibromide required a further three steps; thus desilylation, Swern oxidation, then olefination according to the Corey–Fuchs procedure furnished **10** in 46 % yield starting from **8**.[11]

The 2,5-*trans*-disubstituted tetrahydrofuran unit **3** was then constructed by addition of allylmagnesium bromide to the least hindered end of *O*-silylated-(*R*)-glycidol **11**, which proceeded—in the presence of catalytic Li_2CuCl_4—in excellent yield (93 %) (Scheme 3).[12] Ozonolysis of the alkenol **12** to give the lactol **13**, followed by treatment of this crude material with an excess of propargyl alcohol and a catalytic amount of Amberlyst A15 in refluxing benzene afforded the rearrangement precursor **14** in 93 % yield as a 1:1 mixture of anomers. With multigram quantities of the propargylic ether available, the anomeric O–C rearrangement was attempted following our original protocol.[10a] Thus standard stannylation, followed by treatment of the resulting crude material with boron trifluoride diethyl etherate produced the rearranged species **16** and **15** in a combined yield of 85 %, and in a 5.5:1 ratio favoring the *trans* product **16**. Subsequent benzylation of the mixture allowed chromatographic separation to give diastereomerically pure material, **17** (80 % yield) at this stage. Treatment of **17** with TBAF followed by selective hydrogenation of the alkyne over Raney nickel, gave **18**, a direct precursor to the desired coupling fragment **3**, in 89 % yield.

With the two units **10** and **18** completed, the remaining butenolide fragment **4** was then investigated. It was envisaged that the 1,5-stereochemical relationship could be installed by a HDA reaction between diene **7** and nitrosobenzene. The required regioselectivity was predicted by frontier orbital calculations,[13] whilst it was believed that unfavorable steric interaction between the aryl ring of the dienophile and the methyl substituent of **7** would deliver the necessary diastereoselectivity. Subsequent N–O bond cleavage followed by elimination of the aryl amine portion to reintroduce the butenolide unsaturation would permit elaboration to **4**.

Thus, starting with 1,4-butanediol **19**, monobenzylation by trapping of the sodium anion precipitate of **19** with benzyl bromide, followed by tandem Swern–Wittig reaction afforded the α,β-unsaturated ester **20** in excellent yield (79 %) over three steps (Scheme 4). Homo-enolate formation by deprotonation with LDA in the presence of HMPA,[14] followed by quenching with (*S*)-(2)-(*tert*-butyldimethylsilyloxy)propanal,[15] then subjection of the resulting crude oil to acidic methanol allowed cyclization to form a β-hydroxy-γ-lactone. Subsequent treatment with methanesulfonyl chloride and triethylamine afforded diene **21** in 60 % yield, with a 6:1 (*Z/E*) selectivity at the external double bond. The desired *E* isomer



Scheme 3. Synthesis of fragment **18**, a precursor for **3**. a) allylMgBr, $CuLi_2Cl_4$, (10 mol %), THF, 2 h, −30 °C (93 %); b) O_3, CH_2Cl_2, 15 min, −78 °C; PPh_3, 14 h, −78 °C→20 °C (93 %); c) propargyl alcohol, A15, benzene, 15 min, reflux (quant); d) *n*BuLi, THF, 30 min, −78 °C; Bu_3SnCl, 30 min, −78 °C→20 °C; e) $BF_3 \cdot OEt_2$, CH_2Cl_2, 5 min, −10 °C (85 %; two steps (5.5:1, **16**:**15**)); f) KHMDS, 30 min, −78 °C, BnBr, THF, −78 °C→20 °C (80 %); g) TBAF, THF, 2 h, 20 °C; h) RaNi, H_2, EtOH, 30 min, 20 °C (89 %; two steps). A15 = Amberlyst 15, KHMDS = potassium hexamethyldisilazide.

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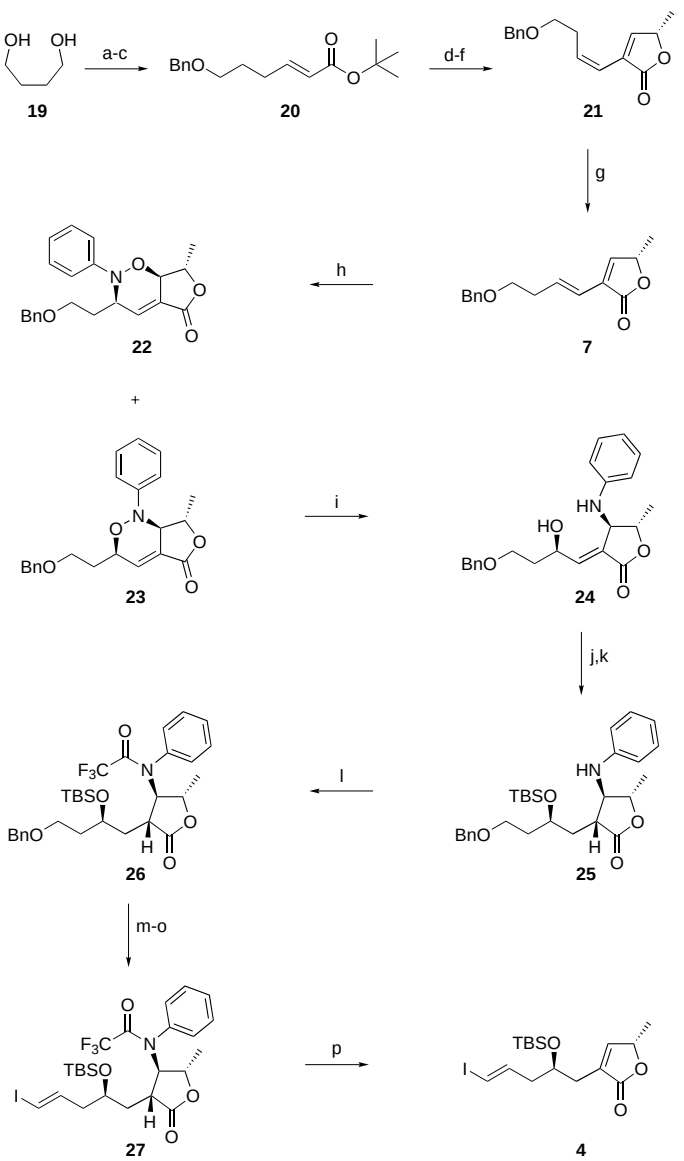

Scheme 4. Synthesis of fragment **4**. a) NaH, BnBr, DMF, 20 °C (82 %); b) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C; NEt_3, −78 °C → 0 °C; c) (*tert*-butoxycarbonylmethylene)triphenylphosphorane, CH_2Cl_2, 14h, 0 °C → 20 °C (96 %; two steps); d) LDA/HMPA/THF, 30 min, −78 °C, then (*S*)-2-(*tert*-butyldimethylsilyloxy)propanal, −78 °C → 0 °C; e) MeOH/HCl (sat.), 5 min, (repeat), 20 °C; f) MsCl, NEt_3, CH_2Cl_2, 30 min, 0 °C; g) I_2 (5 mol %), 4 h, irradiation (60 %; four steps); h) PhNO, $MeOH/CH_2Cl_2$ (1/1), 14 h, 0 °C (89 % (7:3, **23**:**22**)); i) $[Mo(CO)_6]$, MeCN, reflux 4 h; then **23**, H_2O, 15 min, 20 °C (70 %); j) TBSCl, imidazole, DMF, 14 h, 20 °C (80 %); k) PtO_2 (20 mol %), H_2, EtOH, 30 min, 20 °C (92 %); l) TFAA, Hünig's base, CH_2Cl_2, 30 min, 0 °C; m) $Pd(OH)_2$ (20 mol %), H_2, MeOH, 2 h, 20 °C (80 %; two steps); n) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C; NEt_3, −78 °C → 0 °C; o) $CrCl_2$, CHI_3, 14 h, THF 0 °C → 20 °C (80 %; two steps); p) DBU, CH_2Cl_2, 30 min, 0 °C (95 %). DMF = *N*,*N*-dimethylformamide, LDA = lithium diisopropylamide, HMPA = hexamethyl phosphoramide, MsCl = methanesulfonyl chloride, TFAA = trifluoroacetic anhydride, DBU = 1,8-diazobicyclo[5.4.0]undec-7-ene.

7 was then accessed with a ratio of greater than 20:1 by sunlamp irradiation of **21** in the presence of a catalytic quantity of iodine.[16]

With **7** in hand, the key HDA reaction was then investigated. It was found that overnight stirring of a methanol/dichloromethane (1/1) solution of **7** with nitrosobenzene at 0 °C afforded a mixture of regioisomers (7:3, **23**:**22**), favoring the desired adduct **23** in overall 89 % yield. Pleasingly, inspection of the crude ^1H NMR spectrum showed that the major regioisomer **23** had been formed with a diastereomeric ratio of over 20:1—thus the observed diastereoselection appeared to be limited only by the original geometry of the external olefin in the diene precursor. The required diastereomerically pure regioisomer **23** was obtained in 55 % yield following separation by HPLC; the slightly diminished yield reflecting the propensity for retro-Diels–Alder reaction on silica that has been previously documented for these types of compounds.[17]

The next synthetic challenge required selective cleavage of the N–O bond in the presence of the α,β-unsaturation. This was crucial in order to avoid translactonization to the other possible γ-lactone species.[18] After screening a variety of reagents we found that freshly prepared $[Mo(CO)_3(MeCN)_3]$ in the presence of water could effect this transformation at ambient temperature, affording **24** in 70 % yield.[19] Subsequent silylation of the resultant secondary alcohol followed by hydrogenation of the α,β-unsaturation over platinum dioxide proceeded to give **25** as one diastereoisomer in 74 % yield over two steps. The aryl amine was activated as a suitable leaving group to unmask the butenolide double bond by treatment with trifluoroacetic anhydride and Hünig's base, leading to the formation the trifluoroacetamide **26**. Preparation of the vinyl iodide required a further three steps: hydrogenation of the benzyl ether over $Pd(OH)_2$, then Swern oxidation followed by one-carbon homologation according to the Takai procedure.[20] This provided **27** as a 4:1 ratio of isomers in overall 64 % yield (four steps), favoring the *E* geometry. Subsequent elimination of the trifluoroacetamide group was effected by using DBU to afford **4** in 95 % yield with no epimerization of the C-34 methyl substituent.

With all three fragments successfully prepared, the initial coupling between **2** and **3** was investigated. Swern oxidation of **18** produced aldehyde **2**, which was found to be unstable and hence was not purified, but used crude in the subsequent coupling step (Scheme 5). Thus, treatment of **10** with butyllithium produced the lithiated alkyne species **27**, which was then quenched by the addition of crude **2** to afford propargylic alcohol **28** in good yield (72 %). However, the reaction proceeded with poor diastereoselection, which was subsequently shown to favor the undesired *R* epimer at the newly formed C-16 stereocenter. Attempts to optimize this coupling proved unsuccessful and ultimately an oxidation–reduction protocol was adopted. Consequently, hydrogenation of the alkyne **28** over Raney nickel allowed complete separation of the desired *S* epimer **29**. The remaining material was then recycled by TPAP oxidation,[21] followed by reduction with L-Selectride; this route gave a 4:1 ratio of products favoring **29**, in 64 % yield over three steps. With the final stereogenic center installed, **29** was prepared for coupling with **4**. Thus silylation of the secondary alcohol then hydrogenation over $Pd(OH)_2$, allowed Dess–Martin oxidation to the aldehyde,[22] followed by one-carbon homologation using the Colvin–Gilbert–Seyferth reagent to afford the terminal alkyne **30** in 62 % yield.[23]

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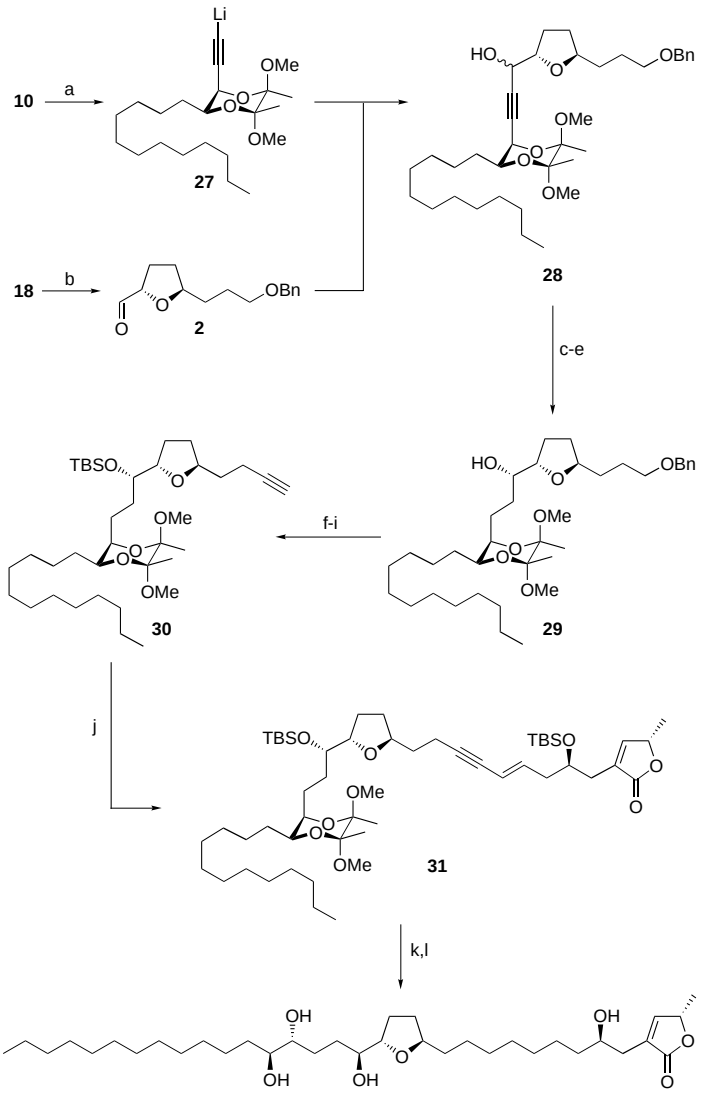

Scheme 5. Coupling reactions and synthesis of **1**. a) *n*BuLi, THF, 30 min, $-78\,^{\circ}C \rightarrow 0\,^{\circ}C$; $-78\,^{\circ}C$ then **2;** b) DMSO, $(COCl)_2$, CH_2Cl_2, $-78\,^{\circ}C$; NEt_3, $-78\,^{\circ}C \rightarrow 0\,^{\circ}C$ (72%; two steps); c) RaNi, H_2, EtOH, 30 min, 20 °C (91%); d) TPAP (7 mol%), NMO, NEt_3, CH_2Cl_2, 45 min, 0 °C; e) L-Selectride, THF, $-100\,^{\circ}C$ (70%; two steps); f) TBSCl, DMF, imidazole, 14 h, 45 °C; g) $Pd(OH)_2$ (20 mol%), H_2, EtOH, 10 h, 20 °C (87%; two steps); h) DMP, CH_2Cl_2, 45 min, $0\,^{\circ}C \rightarrow 20\,^{\circ}C$; i) diethyl methyldiazophosphonate, *t*BuOK, THF, $-78\,^{\circ}C$, 16 h; 20 °C 4 h, (71%; two steps); j) $[Pd(PPh_3)_2Cl_2]$ (10 mol%), CuI (30 mol%), NEt_3, 2 h, 20 °C (86%); k) $[Rh(PPh_3)_3Cl]$, H_2, THF, 10 h, 20 °C (76%); l) TFA/H_2O 9/1, 1 min; repeat (82%). TPAP = tetrapropyl ammonium perruthenate, NMO = 4-methyl-morpholine-*N*-oxide, DMP = Dess–Martin periodinanne, TFA = trifluoroacetic acid.

Sonogashira cross coupling of **30** with the vinyl iodide **4** proceeded smoothly in the presence of catalytic $[Pd(PPh_3)_2Cl_2]$ and CuI in triethylamine, in 86% yield.[24] Selective hydrogenation of the resultant enyne **31** was achieved in 76% yield by using Wilkinson's catalyst. Final desilylation and removal of the butane diacetal (BDA) group could be carried out in one step using aqueous trifluoroacetic acid. Purification by silica gel chromatography afforded **1** as a white amorphous solid in 82% yield. The spectroscopic data for synthetic **1** (^1H NMR, ^{13}C NMR, IR, MS, m.p. and specific rotation)[25] were in excellent agreement with those reported for naturally occurring Muricatetrocin C.[7]

In summary the first stereoselective synthesis of **1** has been achieved by implementing new methods for each of the three coupling fragments. Thus our *anti*-diol building block, (*R*′,*R*′,*R*,*S*)-2,3-BDA-protected butane tetrol **8** has found further utility in total synthesis, the recently developed anomeric O–C rearrangement methodology has been used to install the 2,5-*trans*-disubstituted THF moiety **3** and a new approach to the (*S*)-hydroxy-butenolide terminus **4** that employs a highly diastereoselective HDA reaction has been developed. Further studies aimed at expanding our synthetic approach to other members of this family of bioactive natural products are currently underway.

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[25] Spectroscopic data for synthetic **1**, a white amorphous solid: M.p. 65–67 °C (lit. [7] 65–66 °C); $[\alpha]_D^{20} = +5.8$ ($c = 0.38$ in CH_2Cl_2, lit. [7] +6.3 in CH_2Cl_2); ^{1}H NMR (600 MHz; $CDCl_3$): $\delta = 7.18$ (d, 1H, $J = 1.1$ Hz; H-33), 5.06 (qd, 1H, $J = 6.8$, 1.1 Hz; H-34), 3.89–3.87 (m, 1H, H-12), 3.87–3.83 (m, 1H, H-4), 3.82 (q, 1H, $J = 7.2$ Hz, H-15), 3.63–3.60 (m, 2H; H-19, H-20), 3.47–3.43 (m, 1H; H-16), 2.90 (s (br), 2H; OH), 2.53 (dt, 1H, $J = 15.1$, 1.6 Hz; H-3), 2.40 (dd, 1H, $J = 15.1$, 8.3 Hz; H-3), 2.04–2.01 (m, 1H; H-13), 2.00–1.97 (m, 1H; H-14), 1.70–1.40 (m, 6H; H_2-21, H_2-18, H_2-17), 1.60–1.40 (m, 3H; H-13, H_2-11), 1.62–1.55 (m, 1H; H-14) 1.50–1.40 (m, 2H; H_2-5), 1.43 (d, 3H, $J = 6.8$ Hz; H_3-35), 1.40–1.20 (m, 32H; H_2-6 → H_2-10, H_2-22 → H_2-31, 2 × OH), 0.88 (t, 3H; $J = 6.9$ Hz, H_3-32); ^{13}C NMR (150 MHz; $CDCl_3$): $\delta =$ 174.5 (C-1), 151.7 (C-33), 131.2 (C-2), 81.7 (C-15), 79.3 (C-12), 77.9 (C-34), 74.7, 74.4 (C-20, C-19), 74.3 (C-16), 70.0 (C-4), 37.4 (C-5), 33.5–22.7 (C-6 → C-11, C-17, C-18, C-21 → C-31), 33.4 (C-3), 32.4 (C-13), 28.4 (C-14), 19.1 (C-35), 14.1 (C-32); IR ($CDCl_3$): $\tilde{\nu}_{max} = 3422$ (br OH), 2928, 2855 (C–H), 1733 (C=O) and 1675 (C=C) cm^{-1}; HRMS $[M+Na]^+$ found: m/z: 619.4522, $C_{35}H_{64}O_7Na$ required: m/z: 619.4544.

Development of a Diversity-Based Approach for the Discovery of Stereoselective Polymerization Catalysts: Identification of a Catalyst for the Synthesis of Syndiotactic Polypropylene**

Jun Tian and Geoffrey W. Coates*

The discovery of efficient and selective catalysts for organic and polymer synthesis will be a crucial requirement for the sustained growth of the chemical industry as economic and environmental constraints become more restrictive in the new millennium. Increasingly important will be the stereoselective catalysts that provide key enantiomerically pure building blocks to the pharmaceutical industry[1] as well as stereoregular macromolecules to the polymer industry.[2] Due to the complicated mechanistic nature of many transition metal based catalysts, structure–activity relationships are often unpredictable leaving empirical exploration and serendipity the most common routes to discovery. Although impressive catalyst breakthroughs have been made, more efficient strategies clearly must be implemented to aid the pursuit of new catalysts. Perhaps the most widely heralded approach that is proposed to influence the discovery and optimization of new catalysts is combinatorial chemistry.[3–5] Combinatorial methods have significantly hastened the discovery of new drugs through the rapid synthesis and efficient screening of diverse sets (libraries) of organic molecules.[6–8] It seems reasonable that a similar strategy might impact catalyst discovery and optimization if metal complex libraries can be rapidly synthesized and their desired properties tested.[9] Although the combinatorial approach is often viewed by some with skepticism, it should be stressed that the more rapidly new classes of highly selective catalysts are discovered, the faster traditional chemists can initiate studies to elucidate their detailed mechanisms of operation. Large collections of structure–activity data will not only provide a solid information base upon which mechanistic hypotheses can be proposed and supported, but will also facilitate the development of new catalyst systems. Herein we report a combinatorial approach for the discovery of stereoselective polymerization catalysts. Using this method, we identified a new catalyst system for the syndiospecific polymerization of propylene.

The development of new polymerization catalysts can be subdivided into three main steps: ligand preparation, complex synthesis, and screening of the behavior of these complexes for a specific reaction. Depending on the catalyst system under investigation, any one of these can be the rate-determining step that limits improvement. The synthesis and testing of catalyst libraries can occur primarily in two formats, parallel (spatially separate reaction vessels) and pooled (combined in one reaction vessel) libraries.[10, 11] Although each format has its advantages, the use of combinatorial methods for developing enantioselective catalysts for small-molecule transformations has thus far relied on the parallel synthesis of ligands and complexes, followed by the serial screening for enantioselectivity using chiral chromatography.[12, 13] Due to the time-consuming nature of sequentially screening the enantioselectivities of the products of a parallel library, one might wonder why the screening of a pooled, bead-bound stereoselective catalyst library has not been reported. Exchange of products between different beads and/or the reaction solution occurs, therefore only an average stereoselectivity of the library can be determined (Scheme 1).[14]

Interestingly, the situation changes in the case of stereoselective polymerization catalysts (Scheme 1). Unlike the asymmetric transformation of small molecules where the stereochemical events of the reaction are unconnected, the polymer itself serves as a stereochemical recording of the events of the polymerization catalyst. Assuming that the catalyst species do not interact with one another, then a group of complexes for stereoselective polymerization can be

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