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Convergent Total Synthesis of Asimicin via Decarbonylative Radical Dimerization

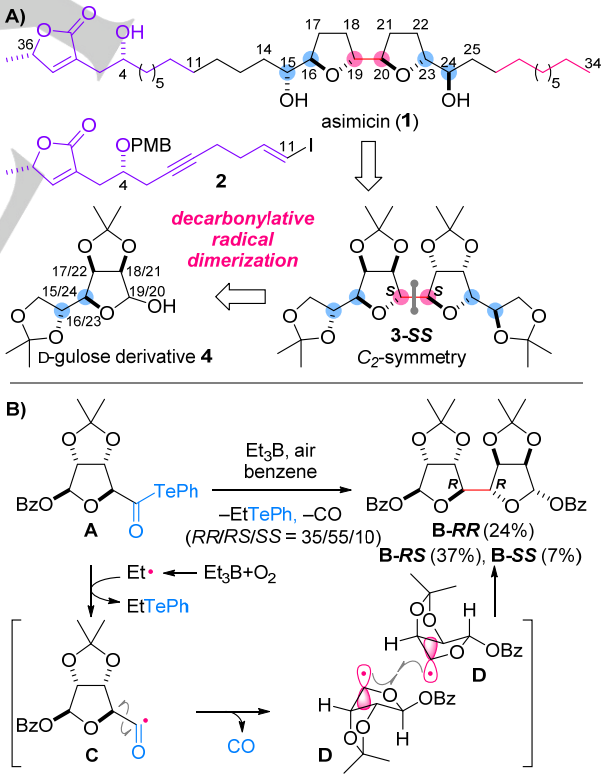
Takahiro Kawamata, Akinori Yamaguchi, Masanori Nagatomo, and Masayuki Inoue*

Abstract: Asimicin (**1**) exhibits potent antitumor activity and comprises a central C_2-symmetric bis-tetrahydrofuran and two aliphatic side-chains, one of which terminates with (*S*)-methyl-2(5*H*)-furanone. Herein we report a convergent total synthesis of **1** in 17 steps from D-gulose derivative **4**. Decarbonylative radical-radial homo-coupling of α-alkoxyacyl telluride **12a** efficiently produced the C_2-symmetric core **3-*SS***, which was transformed into **1** through stepwise attachment of the two side-chains and functional group manipulations.

Asimicin (**1**, Scheme 1A) is a bioactive component isolated from the bark and seeds of the pawpaw tree, *Asimina trilobal* Dunal (Annonaceae),[1] and belongs to an annonaceous acetogenin family that includes 500 members.[2] Compound **1** displays nanomolar cytotoxicity against various cancer cell lines as well as potent pesticidal and antileishmanial activities. Accordingly, **1** and its congeners represent promising starting points for the development of new pharmaceuticals and agrochemicals.[3] The diverse activities originate from the selective function of **1** as an inhibitor of the NADH dehydrogenase complex (also known as Complex I),[4] which performs electron transport processes for generating ATP in mitochondria.

The structure of **1** contains three types of distinct domains: the C_2-symmetric bis-tetrahydrofuran (THF) core (C15–24), two *n*-decane chains (C5–14 and C25–34), and a C5-attached (*S*)-methyl-2(5*H*)-furanone substructure. Six of the eight stereogenic centers of **1** are located in the central bis-THF (C15, 16, 19, 20, 23, and 24), and the other two are localized in the terminal furanone (C4 and 36). Because of its biologically important activities and characteristic architecture, the chemical construction of **1** and its artificial analogues has attracted a great deal of attention from the synthetic community,[5] culminating in seven elegant total syntheses[6] and detailed structure-activity relationship (SAR) studies of **1**.[7] The SAR studies uncovered that the six stereochemistries of the bis-THF core and the length of the two side-chains are both crucial for the potent activities of **1**.[8] Here we report the development of a new strategy for an efficient total synthesis of **1**. The C_2-symmetric bis-THF substructure of **1** with the six stereocenters was assembled by a one-step radical dimerization reaction of a sugar derivative, and then elaborated into **1** via desymmetrizing carbon chain extensions.[6c,g,h]

We recently reported the direct construction of bis-THF structures via decarbonylative homo-radical-radical coupling reactions of monosaccharide derivatives (Scheme 1B).[9] For instance, when D-ribose-derived α-alkoxyacyl telluride **A** was treated with Et_3B and O_2 at room temperature, three dimeric structures, **B-*RR***, **B-*RS***, and **B-*SS***, with eight contiguous stereocenters were produced in 68% combined yield. In this reaction, the ethyl radical generated from Et_3B/O_2[10] homolytically cleaves the weak C–Te bond of **A** to form acyl radical **C**. Rapid decarbonylation of **C** proceeds to give α-alkoxy carbon radical **D**,[11] and subsequent radical-radical coupling leads to **B-*RR*/*RS*/*SS***. The stereochemical information at the α-alkoxy carbon was lost upon the formation of radical **D**, and redefined upon dimerization. Comparison of the observed ratio of **B-*RR*/*RS*/*SS*** (35:55:10) with the statistical distribution (25:50:25) revealed modest *R*-selectivity, presumably because the acetonide moiety sterically blocks the approach of the coupling partner from the same face. Most importantly, C_2-symmetric bis-THF **B-*RR*** was immediately assembled from the simple carbohydrate derivative without damaging the preexisting oxygen functionalities.[12]



Scheme 1. A) Structure and synthetic plan of asimicin (**1**). B) Decarbonylative radical dimerization (Ref. [9]). Bz = benzoyl, PMB = *p*-methoxybenzyl.

We envisioned implementing this powerful, yet mild, radical dimerization for expeditious access to the central C_2-symmetric bis-THF substructure of asimicin (**1**) (Scheme 1A). Thus, **1** was retrosynthetically simplified into C_2-symmetric dimer **3-*SS***. The

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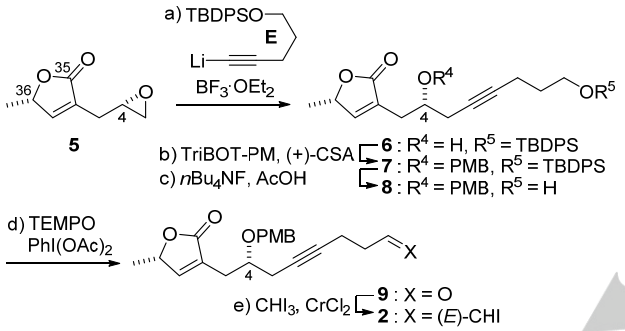
corresponding monomer of **3-*SS*** was traced back to commercially available 2,3:5,6-di-*O*-isopropylidene-D-gulofuranose (**4**),[13] as the C15/24- and C16/23-stereochemistry of **4** (indicated by the cyan circles) directly match those of **1**. The bulky acetonide at the C17/22- and C18/21-*syn*-1,2-diol of **1** was expected to function as a stereocontrolling element for installing the correct C19,20-stereochemistry of **3-*SS*** (indicated by the pink circles). Since **3-*SS*** possesses the six requisite stereocenters of **1**, assembly of the entire skeleton of **1** from **3-*SS*** would only require introduction of the two different carbon chains, reductive removal of the C17,18,21,22-oxygen functional groups, and elongation of the (*S*)-methyl-2(5*H*)-furanone fragment **2**. Compound **2** was designed to have the vinyl iodide structure as a handle for the palladium-catalyzed cross-coupling reaction with the rest of the structure at the last stage of the synthesis.



Scheme 2. Preparation of the (*S*)-methyl-2(5*H*)-furanone fragment **2**. Reagents and conditions: a) *tert*-butyl(pent-4-yn-1-yloxy)diphenylsilane, *n*BuLi, $BF_3{\cdot}OEt_2$, THF, –78 °C, 75%; b) 2,4,6-tris(*p*-methoxybenzyloxy)-1,3,5-triazine (TriBOT-PM), (+)-camphorsulfonic acid (CSA), THF, 85 °C, 81%; c) nBu$_4$NF, AcOH, THF, RT, 99%; d) 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), $PhI(OAc)_2$, CH_2Cl_2, RT, 75%; e) iodoform, $CrCl_2$, 1,4-dioxane/THF (2:1), RT, 66%. TBDPS = *tert*-butyldiphenylsilyl.

The 2(5*H*)-furanone fragment **2** was synthesized in five steps from known epoxide **5**,[14] whose C4,36-stereocenters correspond to those of **1** (Scheme 2). Addition of lithium acetylide **E** to the C4-epoxide of **5** in the presence of $BF_3{\cdot}OEt_2$ proceeded chemoselectively over the C35-lactone, giving rise to alkyne **6**.[15] Because strong acid or base could induce C36-enolization/epimerization of furanone **6**, *p*-methoxybenzyl protection of the resultant secondary hydroxy group of **6** was performed under mild conditions (CSA and TriBOT-PM) to produce PMB ether **7**.[16] The TBDPS group of **7** was then removed using nBu$_4$NF to afford **8**. After oxidation of the liberated primary alcohol of **8** with TEMPO and $PhI(OAc)_2$,[17] aldehyde **9** was treated with a reagent combination of iodoform and $CrCl_2$ to furnish the requisite alkenyl iodide **2**.[18]

Next, we explored the homo-radical-radical coupling reaction for constructing the bis-THF structure **3-*SS*** (Scheme 3). First, α-alkoxy acyl telluride **12a**, the coupling substrate, was derivatized from acetonide-protected D-gulose **4**. Hemiacetal **4** was treated with vinyl magnesium bromide to attach the two-carbon unit at the anomeric position. Then, TsCl and pyridine at 100 °C induced site-selective tosylation of the C19-allylic alcohol over the C16-secondary alcohol and subsequent S_N2-displacement of the C19-tosylate by the C16-alcohol, generating the THF structure **10a** (43%) and its C19-epimer **10b** (21%). The major C19'α-isomer **10a** was transformed into the carboxylic acid **11a** by ozonolysis of the terminal olefin and subsequent $NaClO_2$ oxidation of the resultant aldehyde. Then, **11a** was condensed with isobutyl chloroformate using *N*-methylmorpholine to form the activated ester, which was subjected to a reagent combination of $(PhTe)_2$ and iBu$_2$AlH to provide α-alkoxy acyl telluride **12a**.[19] To investigate the role of the C19-stereochemistry in the radical dimerization, the minor C19'β-isomer **10b** was also converted to the corresponding acyl telluride **12b** via the same three-step sequence.

Despite the stability of intermediates **12a** and **12b** against air, light, and silica gel, both of the compounds underwent homo-coupling by the action of Et_3B and O_2. Namely, upon treatment of α-alkoxy acyl telluride **12a** with Et_3B (5 equiv) in CH_2Cl_2 (0.2 M) under air at room temperature for 20 minutes, **12a** sequentially underwent C–Te bond homolysis, CO-ejection from the acyl radical, and a radical-radical coupling reaction of the resultant **F**, affording the desired C_2-symmetric dimer **3-*SS*** and its stereoisomer **3-*SR*** in 27% and 25% yields, respectively. The reaction displayed the desired *SS*-stereoselectivity (**3-*SS*/*SR*/*RR*** = 52:48:0) compared with the statistical ratio (25:50:25), presumably due to the preferred C–C bond formation from the opposite face of the bulky acetonide group of α-alkoxy radical **F**.[9,20] Most importantly, the single-step installation of the two new C19,20-stereocenters of **3-*SS*** under mild conditions clearly showed the exceptional efficacy of the present method for assembling the bridged bis-THF structures. In contrast, C19-epimeric **12b** was an inferior radical precursor: treatment of **12b** under the same conditions resulted in the formation of **3-*SS*** and **3-*SR*** in a similar ratio, but in lower yields (15% and 11%, respectively). Since both **12a** and **12b** lost their C19-stereochemistry and went through the same α-alkoxy radical **F** upon dimerization, the better yield from **12a** was attributed to higher efficiency of the formation of **F** from the C19'α-isomer **12a** than from the C19'β-isomer **12b**.

To rationalize the reactivity and selectivity of the radical-radical coupling reactions, DFT calculations were performed at the UM06-2X/6-31+G(d) level of theory (298 K, 1 atm)[21] using the Gaussian 09[22] and Reaction Plus Pro programs (Scheme 4).[23] Specifically, we evaluated the energy levels of C19'α-acyl radical **Ga** and C19'β-acyl radical **Gb**, the corresponding transition states **TSa** and **TSb**, and the resultant α-alkoxy carbon radical **F** and CO. The activation energy (Δ*G*) from **Ga** to **TSa** and that from **Gb** to **TSb** was calculated to be 6.38 kcal/mol and 7.90 kcal/mol, respectively. While the low energy barrier for **TSa** coincides with the facile decarbonylation reaction of the present dimerization,[24] the energy difference of the two barriers (ΔΔ*G* = 1.52 kcal/mol) corroborates the higher efficiency of the α-alkoxy radical formation from **12a** rather than from **12b**. Moreover, **F** and carbon monoxide (*G* = -5.92 kcal/mol) were revealed to be notably more stable than **Ga** (*G* = 0 kcal/mol) or **Gb** (*G* = +1.29 kcal/mol), indicating the higher concentration of dimerizing **F** compared with the acyl radical in the reaction mixture. This finding also corresponds to the absence of product formation by the acyl radicals in the present reactions.

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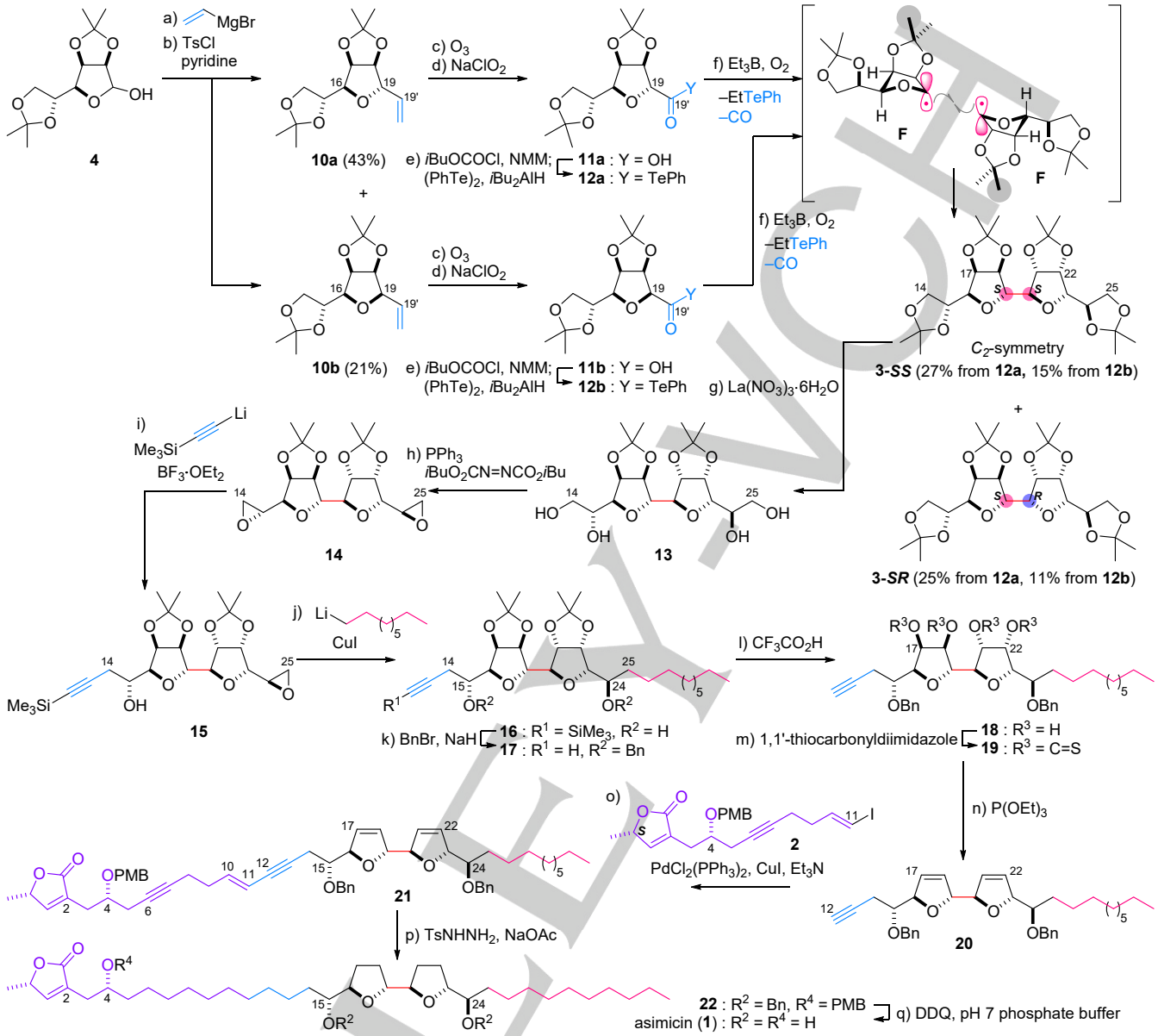

Scheme 3. Total synthesis of asimicin. Reagents and conditions: a) vinylMgBr, THF, –78 °C to RT; b) *p*-toluenesulfonyl chloride (TsCl), pyridine, 100 °C, **10a**: 43% (2 steps), **10b**: 21% (2 steps); c) O_3, CH_2Cl_2/MeOH/pyridine (10:1:1), –78 °C then Me_2S, RT; d) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH/H_2O (1:1), RT; e) *i*BuOCOCl, *N*-methylmorpholine (NMM), THF, 0 °C; $(PhTe)_2$, iBu_2AlH, THF, RT, **12a**: 53% (3 steps) from **10a**, **12b**: 55% (3 steps) from **10b**; f) **12a** or **12b** (1 equiv), Et_3B (5 equiv), CH_2Cl_2 (0.2 M), under air, RT, **3-*SS***: 27%, **3-*SR***: 25% from **12a**, **3-*SS***: 15%, **3-*SR***: 11% from **12b**; g) $La(NO_3)_3·6H_2O$, MeCN, 60 °C, 89%; h) PPh_3, $iBuO_2CN=NCO_2iBu$, 110 °C, 68%; i) ethynyltrimethylsilane, *n*BuLi, $BF_3·OEt_2$, THF, –78 °C, 77%; j) 1-bromononane, *t*BuLi, CuI, –78 to 0 °C, 84%; k) benzyl bromide (BnBr), NaH, THF, RT, 84%; l) CF_3CO_2H/H_2O/THF (3:2:5), 70 °C; m) 1,1'-thiocarbonyldiimidazole, toluene, 55 °C, 67% (2 steps); n) $P(OEt)_3$, 130 °C, 73%; o) **2**, $PdCl_2(PPh_3)_2$ (10 mol%), CuI (30 mol%), Et_3N, RT, 67%; p) $TsNHNH_2$, 1.6 M aqueous NaOAc/1,2-dimethoxyethane (5:6), 100 °C, 72%; q) 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ), 1,2-dichloroethane/pH 7 phosphate buffer (25:4), 50 °C, 98%.

Further analyses disclosed that the energy difference between **TSa** and **TSb** reflects both steric and stereoelectronic interactions arising from their distinct three-dimensional structures. The leaving carbon monoxide of **TSb** has unfavorable contacts with the two atoms (indicated by the purple dotted lines) within the sum of the van der Waals radii (2.9 Å) (Scheme 4).[25] On the other hand, there is no such close contact in **TSa**, indicating its sterically favored character. Next, the orbital interactions of adjacent covalent bonds and lone pairs with the dissociating C19−C19' bond of **TSa** and **TSb** were estimated by natural bond orbital (NBO) analysis (Table 1).[26] The antibonding orbital (BD*) of the C19−C19' bond and the axial-oriented lone pair (LP) of C19O of **TSa** are coplanar, thereby overlapping with a stabilization energy of 4.78 kcal/mol. Moreover, the bonding orbital (BD) of the same C19−C19' bond interacts with the BD* of the antiperiplanar C18−O bond to gain

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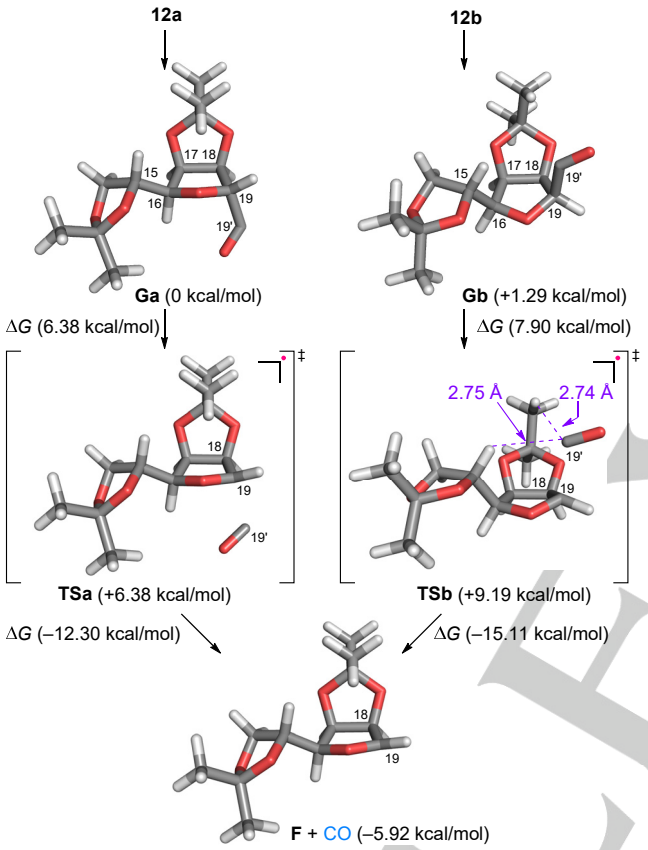
an energy of 6.14 kcal/mol.[27] Similar to **TSa**, **TSb** has two orbital interactions between LP (C19O) and BD* (C19−C19'), and between BD (C19−C19') and BD* (C18−O). The stabilizing energy of the former, however, is much smaller than that of **TSa** (1.84 kcal/mol vs. 4.78 kcal/mol), presumably because neither of the two lone pairs of C19O is coplanar with the C19−C19' bond. Consequently, this unfavorable stereoelectronic effect contributes to heighten the barrier from **Gb** to **TSb**. Taken together, **TSa** is preferable over **TSb** in terms of the steric and orbital interactions, and thus the C19'α-isomer **12a** more efficiently generates **F**, which dimerizes into **3-*SS*** and **3-*SR***.



Scheme 4. Rationale of the C19-stereochemical effect on the formation of **F**.[a]
[a] Values in parentheses are relative free energies: Δ*G*, 298 K, 1 atm.

Table 1. NBO analysis of stabilizing orbital interactions in **TSa** and **TSb**.[a]

TS	donor	acceptor	energy (kcal/mol)
TSa	LP (C19O)	BD* (C19–C19')	4.78
	BD (C19–C19')	BD* (C18–O)	6.14
TSb	LP (C19O)	BD* (C19–C19')	1.84
	BD (C19–C19')	BD* (C18–O)	4.88

[a] LP, BD, and BD* represent lone pair, bonding orbital, and antibonding orbital, respectively.

Having stereoselectively constructed the C_2-symmetric core **3-*SS***, the stage was now set for extension of the different carbon chains at the C14- and C25-positions (Scheme 3). Prior to these transformations, the reactive bis-epoxide **14** was prepared from **3-*SS*** through two pairwise functionalizations.[28] Namely, treatment of tetra-acetonide **3-*SS*** with $La(NO_3)_3{\cdot}6H_2O$ in MeCN regioselectively removed the two less-hindered acetals to afford tetraol **13**,[29] which was converted to bis-epoxide **14** under Mitsunobu reaction conditions.[30] The subsequent step involved C14-monofunctionalization in the presence of the homotopic C25-position of C_2-symmetric **14**. This desymmetrizing reaction turned out to be quite challenging because various nucleophiles such as organocuprates simultaneously functionalized both C14 and C25 to generate the C_2-symmetric compound (Table S2). After screening the reagents and conditions, a combination of trimethylsilylethynyllithium (10 equiv) and $BF_3{\cdot}OEt_2$ (10 equiv) in THF at -78 °C was found to distinguish bis-epoxide **14** and in situ formed mono-alkynylated intermediate, leading to mono-functionalized **15** in 77% yield.[15] The lower rate observed for the second nucleophilic addition is not easily explained, but the steric proximity of the two epoxide units and the unique reactivity of the alkynyl borane could cooperatively contribute to the effect. The C25-epoxide of the thus-desymmetrized **15** was attacked by organocuprate prepared from nonyllithium and CuI to produce **16** with the requisite right-hand side-chain.[31]

The last six-step sequence to convert **16** to asimicin (**1**) involved altering the oxidation/unsaturation levels and coupling the 2(5*H*)-furanone fragment **2**. The four pairwise functionalizations were first applied to protect the C14,25-diol and construct the C17,22-bis-olefin. Treatment of diol **16** with benzyl bromide and NaH gave bis-benzyl ether **17** with concomitant detachment of the terminal trimethylsilyl group. Bis-isopropylideneglycol **17** was subjected to CF_3CO_2H in aqueous THF to furnish bis-1,2-*syn*-diol **18**, which was transformed to **19** using 1,1'-thiocarbonyldiimidazole. Bis-olefin **20** was in turn generated from bis-thiocarbonate ester **19** via deoxygenation employing triethyl phosphite at 130 °C.[32] The left-hand side-chain was then extended by a Sonogashira coupling reaction between alkyne **20** and alkenyl iodide **2** under Pd^0/Cu^I catalysis,[33] leading to **21**. Regioselective diimide reduction of the five unsaturated bonds of **21** produced protected asimicin **22** without touching the carbonyl conjugated C2-olefin.[34] Lastly, DDQ oxidation at 50 °C in the presence of pH 7 buffer deprotected **22** with the two benzyl and one PMB groups, delivering the targeted asimicin (**1**).[35] The ^{1}H NMR, ^{13}C NMR, $[\alpha]_D$, and HRMS data of fully synthetic **1** were identical to those of naturally occurring **1** (Table S3).[1]

In conclusion, we accomplished a convergent total synthesis of asimicin (**1**) from the commercially available D-gulose derivative **4** in 17 steps. Salient features of our synthesis include: (i) Et_3B/O_2-induced homo-radical-radical coupling reaction of α-alkoxy acyl telluride **12a** to construct the C_2-symmetric core **3-*SS***; (ii) C14-mono-alkynylation of C_2-symmetric bis-epoxide **14** to synthesize the desymmetrized mono-epoxide **15**; (iii) further extension of the two side-chains by the epoxide opening reaction (**15**→**16**), and the Sonogashira coupling reaction (**20**→**21**). Exploitation of the entirely or partially C_2-symmetric intermediates enabled us to employ the six pairwise functionalizations, which effectively streamlined the synthesis. Moreover, the radical dimerization reactions from **12a** and its C19-epimeric **12b** revealed the significance of their fused isopropylideneglycol structure for controlling the C19,20-stereselectivity, and the importance of the C19-stereochemistry of **12a** for generating **3-*SS*** in high yield. The DFT calculations rationalized the sterically and stereoelectronically advantageous

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nature of the radical generation from **12a** over **12b**. These results and analyses together provide new principles for designing three-dimensional structures for efficient radical reactions beyond this work. Overall, the powerful radical dimerization strategy demonstrated here has broad applications for the total syntheses of not only various bioactive acetogenins, but also diverse complex natural products and pharmaceuticals with local C_2-symmetic structures.

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Keywords: dimerization • natural products • radical reactions • tellurium • total synthesis

[1] a) J. K. Rupprecht, C.-J. Chang, J. M. Cassady, J. L. McLaughlin, K. L. Mikolajczak, D. Weisleder, *Heterocycles* **1986**, *24*, 1197; b) G.-X. Zhao, J.-F. Chao, L. Zeng, M. J. Rieser, J. L. McLaughlin, *Bioorg. Med. Chem.* **1996**, *4*, 25.

[2] For recent reviews on annonaceous acetogenins, see: a) A. Bermejo, B. Figadère, M.-C. Zafra-Polo, I. Barrachina, E. Estornell, D. Cortes, *Nat. Prod. Rep.* **2005**, *22*, 269; b) M. Mangal, M. I. Khan, S. M. Agarwal, *Anticancer Agents Med. Chem.* **2015**, *16*, 138.

[3] D. J. Newman, G. M. Cragg, *J. Nat. Prod.* **2016**, *79*, 629.

[4] M. A. Lewis, J. T. Arnason, B. J. R. Philogene, J. K. Rupprecht, J. L. McLaughlin, *Pestic. Biochem. Physiol.* **1993**, *45*, 15.

[5] For recent reviews on total synthesis of annonaceous acetogenins a) N. Li, Z. Shi, Y. Tang, J. Chen, X. Li, *Beilstein J. Org. Chem.* **2008**, *4*, No. 48; b) I. B. Spurr, R. C. D. Brown, *Molecules* **2010**, *15*, 460.

[6] a) T. R. Hoye, L. Tan, *Tetrahedron Lett.* **1995**, *36*, 1981; b) S. C. Sinha, A. Sinha, A. Yazbak, E. Keinan, *Tetrahedron Lett.* **1995**, *36*, 9257; c) J. A. Marshall, K. W. Hinkle, *J. Org. Chem.* **1997**, *62*, 5989; d) H. Avedissian, S. C. Sinha, A. Yazbak, A. Sinha, P. Neogi, S. C. Sinha, E. Keinan, *J. Org. Chem.* **2000**, *65*, 6035; e) J. A. Marshall, A. Piettre, M. A. Paige, F. Valeriote, *J. Org. Chem.* **2003**, *68*, 1771; f) J. M. Tinsley, W. R. Roush, *J. Am. Chem. Soc.* **2005**, *127*, 10818; g) J. A. Marshall, J. J. Sabatini, *Org. Lett.* **2006**, *8*, 3557. For a synthesis of 10-hydroxyasimicin, see: h) G. L. Nattrass, E. Díez, M. M. McLachlan, D. J. Dixon, S. V. Ley, *Angew. Chem. Int. Ed*. **2005**, *44*, 580; *Angew. Chem.* **2005**, *117*, 586.

[7] For reviews on structure-activity relationship studies, see: a) H. Makabe, H. Konno, H. Miyoshi, *Curr. Drug Discov. Technol.* **2008**, *5*, 213; b) N. Kojima, T. Tanaka, *Molecules* **2009**, *14*, 3621; c) C.-C. Liaw, T.-Y. Wu, F.-R. Chang, Y.-C. Wu, *Planta Med*. **2010**, *76*, 1390.

[8] a) N. H. Oberlies, C. Chang, J. L. McLaughlin, *J. Med. Chem.* **1997**, *40*, 2102; b) S. C. Sinha, Z. Chen. Z.-Z. Huang, E. Nakamaru-Ogiso, H. Pietraszkiewicz, M. Edelstein, F. Valeriote, *J. Med. Chem.* **2008**, *51*, 7045.

[9] K. Masuda, M. Nagatomo, M. Inoue, *Nat. Chem*. **2017**, *9*, 207.

[10] For a review, see: C. Ollivier, P. Renaud, *Chem. Rev*. **2001**, *101*, 3415.

[11] For decarbonylative radical addition reactions developed in our laboratory, see: a) M. Nagatomo, H. Nishiyama, H. Fujino, M. Inoue, *Angew. Chem. Int. Ed.* **2015**, *54*, 1537; *Angew. Chem*. **2015**, *127*, 1557; b) M. Nagatomo, D. Kamimura, Y. Matsui, K. Masuda, M. Inoue, *Chem. Sci*. **2015**, *6*, 2765; c) S. Matsumura, Y. Matsui, M. Nagatomo, M. Inoue, *Tetrahedron* **2016**, *72*, 4859; d) H. Fujino, M. Nagatomo, A. Paudel, S. Panthee, H. Hamamoto, K. Sekimizu, M. Inoue, *Angew. Chem. Int. Ed*. **2017**, *56*, 11865; *Angew. Chem*. **2017**, *129*, 12027; e) K. Sakata, D. Urabe, M. Inoue, *Org. Lett*. **2018**, *20*, 130. For an account see: f) M. Inoue, *Acc. Chem. Res*. **2017**, *50*, 460.

[12] For recent reviews on radical reactions in natural product synthesis, see: a) M. Yan, J. C. Lo, J. T. Edwards, P .S. Baran, *J. Am. Chem. Soc.* **2016**, *138*, 12692; b) C. R. Jamison, L. E. Overman, *Acc. Chem. Res.* **2016**, *49*, 1578; c) M. P. Plesniak, H.-M. Huang, D. J. Procter, *Nat. Rev. Chem.* **2017**, *1*, 0077; d) K. Hung, X. Hu, T. J. Maimone, *Nat. Prod. Rep*. **2018**, *35*, 174.

[13] a) R. M. Wilson, S. J. Danishefsky, *J. Org. Chem*. **2007**, *72*, 4293; b) S. Hanessian, S. Giroux, B. L. Merner, *Design and Strategy in Organic Synthesis from the Chiron Approach to Catalysis*, Wiley-VCH, Weinheim, 2013.

[14] S. Jiang, Z.-H. Liu, G. Sheng, B.-B. Zeng, X.-G. Cheng, Y.-L. Wu, Z.-J. Yao, *J. Org. Chem.* **2002**, *67*, 3404.

[15] M. Yamaguchi, I. Hirao, *Tetrahedron Lett*. **1983**, *24*, 391.

[16] K. Yamada, H. Fujita, M. Kitamura, M. Kunishima, *Synthesis* **2013**, *45*, 2989.

[17] A. De Mico, R. Margarita, L. Parlanti, A. Vescovi, G. Piancatelli, *J. Org. Chem*. **1997**, *62*, 6974.

[18] K. Takai, K. Nitta, K. Utimoto, *J. Am. Chem. Soc*. **1986**, *108*, 7408.

[19] T. Inoue, T. Takeda, N. Kambe, A. Ogawa, I. Ryu, N. Sonoda, *J. Org. Chem.* **1994**, *59*, 5824.

[20] For reviews on the stereoselectivity of reactions of α-alkoxy radicals, see: a) H. Togo, W. He, Y. Waki, M. Yokoyama, *Synlett* **1998**, 700; b) B. Giese, *Angew. Chem. Int. Ed. Engl*. **1989**, *28*, 969; *Angew. Chem*. **1989**, *101*, 993.

[21] a) Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215; b) Y, Zhao, D. G. Truhlar, *Acc. Chem. Res.* **2008**, *41*, 157.

[22] M. J. Frisch, G. W. Trucks, H. B. Schlegel, *et al. Gaussian 09 (Revision E. 02)*. C. T. Wallingford: Gaussian, Inc.; **2013**.

[23] HPC Systems Inc., http://www.hpc.co.jp/chem/react1.html

[24] For reviews on decarbonylation of acyl radicals, see: a) H. Fischer, H. Paul, *Acc. Chem. Res*. **1987**, *20*, 200; b) D. L. Boger, *Isr. J. Chem.* **1997**, *37*, 119; c) C. Chatgilialoglu, D. Crich, M. Komatsu, I. Ryu, *Chem. Rev*. **1999**, *99*, 1991.

[25] A. Bondi, *J. Phys. Chem*. **1964**, *68*, 441.

[26] a) A. E. Reed, L. A. Curtiss, F. Weinhold, *Chem. Rev*. **1988**, *88*, 899; b) F. Weinhold, C. R. Landis, *Discovering Chemistry with Natural Bond Orbitals*, John Wiley & Sons, Inc., Hoboken, **2012**.

[27] These two stabilizing orbital interactions correspond to anomeric and quasi-anomeric effects. a) B. Giese, J. Dupuis, *Tetrahedron Lett*. **1984**, *25*, 1349; b) A. L. J. Beckwith, P. J. Duggan, *Tetrahedron* **1998**, *54*, 6919; c) H. Abe, S. Shuto, A. Matsuda, *J. Am. Chem. Soc.* **2001**, *123*, 11870. For a review, see: d) J.-P. Praly, *Adv. Carbohydr. Chem. Biochem*. **2000**, *56*, 65.

[28] For reviews on pairwise functionalizations and desymmetrization reactions in natural product synthesis, see: a) C. S. Poss, S. L. Schreiber, *Acc. Chem. Res*. **1994**, *27*, 9; b) M. Inoue, D. Urabe, *Strategies and Tactics in Organic Synthesis* **2013**, *9*, 149; c) M. Wang, M. Feng, B. Tang, X. Jiang, *Tetrahedron Lett.* **2014**, *55*, 7147; d) W.-J. Bai, X. Wang, *Nat. Prod. Rep*. **2017**, *34*, 1345; e) M. A. Horwitz, J. S. Johnson, *Eur. J. Org. Chem.* **2017**, 1381.

[29] S. M. Reddy, Y. V. Reddy, Y. Venkateswarlu, *Tetrahedron Lett.* **2005**, *46*, 7439. See Table S1 for details of other attempted conditions.

[30] D. L. Hughes, *Org. React.* **1992**, *42*, 335.

[31] R. D. Acker, *Tetrahedron Lett*. **1977**, *18*, 3407.

[32] a) E. J. Corey, R. A. E. Winter, *J. Am. Chem. Soc*. **1963**, *85*, 2677. For a review, see: b) E. Block, *Org. React*, **1984**, *30*, 457.

[33] a) K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett*. **1975**, *16*, 4467. For a review, see: b) J. A. Marsden, M. M. Haley, In *Metal-Catalyzed Cross-Coupling Reactions*, (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**, Vol. 1, p. 317.

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[34] R. S. Dewey, E. E. Van Tamelen, *J. Am. Chem. Soc.* **1961**, *83*, 3729.

[35] Y. Oikawa, T. Yoshioka, O. Yonemitsu, *Tetrahedron Lett.* **1982**, *23*, 885.

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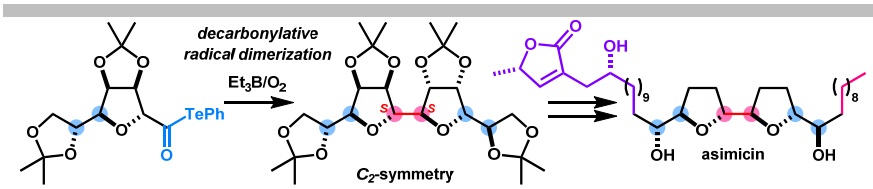

Herein we report a convergent total synthesis of the potent antitumor agent asimicin in 17 steps from a D-gulose derivative. Decarbonylative radical-radial homo-coupling of α-alkoxyacyl telluride efficiently produced the central C_2-symmetric bis-tetrahydrofuran substructure, which was transformed into asimicin through stepwise attachment of the two aliphatic side-chains.

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Convergent Total Synthesis of Asimicin via Decarbonylative Radical Dimerization

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