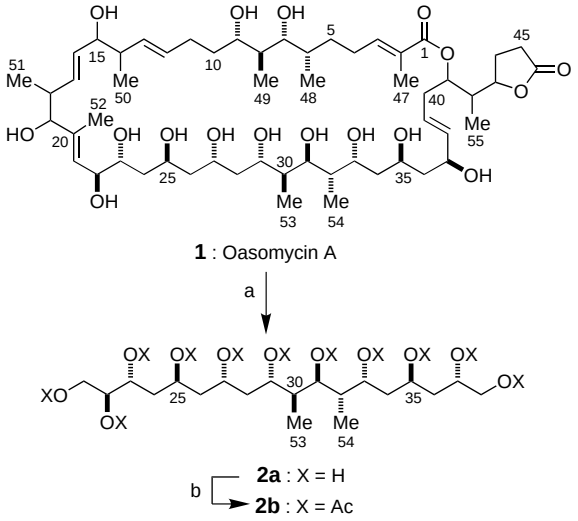
Stereochemical Assignment of the C21–C38 Portion of the Desertomycin/Oasomycin Class of Natural Products by Using Universal NMR Databases: Proof**

Choon-Hong Tan, Yoshihisa Kobayashi, and Yoshito Kishi*

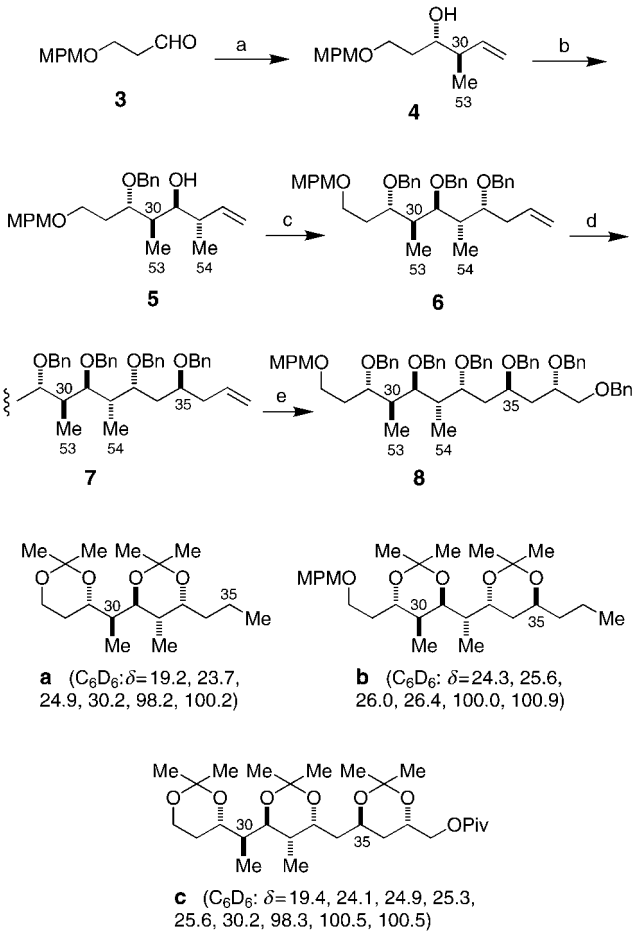
We have predicted the relative stereochemistry of the C21–C38 portion of the desertomycin/oasomycin class of natural products from three simple universal NMR databases.[1] Herein we report a stereoselective synthesis of the C21–C38 degradation product with the predicted relative stereochemistry, thereby proving our prediction.

The C21–C38 degradation product **2a** was obtained in two steps from oasomycin A (**1**; Scheme 1). For practical reasons the degradation product **2a** was isolated and fully characterized as its peracetate **2b**.[2, 3]



Scheme 1. Reagents and conditions: a) 1. O_3, MeOH, $-78\,^{\circ}C$; 2. $NaBH_4$; b) Ac_2O, Py, DMAP, 60% (3 steps). See ref. [16] for abbreviations.

Scheme 2 outlines a stereoselective synthesis of the right half of the predicted diastereomer. The C29–C32 moiety corresponds to one of the eight diastereomers used for the creation of the contiguous dipropionate NMR database, and we have shown that this particular diastereomer can be obtained with high stereoselectivity by two consecutive Brown crotylborations.[4, 5] Indeed, the first crotylboration gave the desired *anti* enantiomer **4** with 92% *ee*, whereas the second crotylboration gave the desired diastereomer **5** in a 10:1 diastereoselectivity with >98% *ee*.[6, 7] In these reactions the relative stereochemistry at C29/C30 and C31/C32 was set



Scheme 2. Reagents and conditions: a) *t*BuOK, (*E*)-2-butene, *n*BuLi, (+)-$(Ipc)_2$BOMe, $BF_3\cdot OEt_2$, THF, $-78\,^{\circ}C$, 62%; b) 1. BnBr, NaH, nBu_4NI, DMF, RT; 2. OsO_4, NMO, acetone/H_2O, RT; 3. $Pb(OAc)_4$, benzene, RT; 4. *t*BuOK, (*E*)-2-butene, *n*BuLi, (−)-$(Ipc)_2$BOMe, $BF_3\cdot OEt_2$, THF, $-78\,^{\circ}C$, 60% (4 steps); c) 1. BnBr, NaH, nBu_4NI, DMF, RT; 2. OsO_4, NMO, acetone/H_2O, RT; 3. $Pb(OAc)_4$, benzene, RT; 4. (+)-$(Ipc)_2$BOMe, $CH_2{=}CHCH_2MgBr$, THF, $-78\,^{\circ}C$; 5. BnBr, NaH, nBu_4NI, DMF, RT, 73% (5 steps); d) 1. OsO_4, NMO, acetone/H_2O, RT; 2. $Pb(OAc)_4$, benzene, RT; 3. (−)-$(Ipc)_2$BOMe, $CH_2{=}CHCH_2MgBr$, THF, $-78\,^{\circ}C$; 4. BnBr, NaH, nBu_4NI, DMF, RT, 67% (4 steps); e) 1. OsO_4, Corey (*S,S*)-ligand, CH_2Cl_2, $-90\,^{\circ}C$, 87%; 2. BnBr, NaH, nBu_4NI, DMF, RT, 88%. See ref. [16] for abbreviations.

through the *E* configuration of butene, whereas the absolute configuration was set by the configuration of $(Ipc)_2$BOMe. The C33 and C35 stereogenic centers were then introduced through two consecutive Brown allylations with diastereoselectivities of >15:1 and 15:1, respectively.[4, 7] In these transformations the chirality of the $(Ipc)_2$BOMe used determined the absolute configuration of the newly introduced stereogenic center, and the stereochemistry of the major product in each step was assigned on the basis of literature precedents. This assignment was further confirmed through ^{13}C NMR analysis[8] of the 1,3-acetonides **a** and **b**, derived from **6** and **7**, respectively (Scheme 2, compare the chemical shifts of the carbon atoms given for the acetonide moieties).

The asymmetric dihydroxylation of **7** in the presence of the Corey (*S,S*)-ligand,[9] followed by benzylation, furnished the right-half segment **8** as an 8:1 mixture of two diastereomers.[7] The stereochemistry of the major product was assigned from

[*] Prof. Dr. Y. Kishi, Dr. C.-H. Tan, Dr. Y. Kobayashi
Department of Chemistry and Chemical Biology
Harvard University
Cambridge, MA 02138 (USA)
Fax: (+1) 617-495-5150
E-mail: kishi@chemistry.harvard.edu

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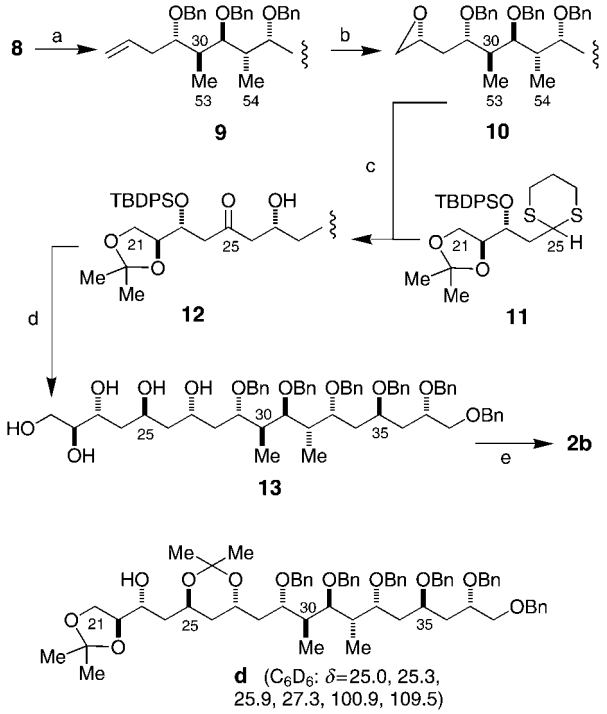
literature precedents, which was further supported by the observation that the dihydroxylation carried out with the Corey (*R*,*R*)-ligand yielded a 1:>15 mixture of the two diastereomers. This stereochemical assignment was confirmed through ^{13}C NMR analysis of the 1,3-acetonide **c**, derived from **8** (Scheme 2).

After completion of the synthesis of the right-hand side of the molecule, the left terminus of **8** was transformed to the olefinic group in three standard synthetic steps. Asymmetric dihydroxylation of the olefin **9** was conducted again in the presence of the Corey (*R*,*R*)-ligand[9] to yield the desired diol (stereoselectivity >15:1).[10] The diol was converted into the α-epoxide **10**, which was treated with the anion generated from the dithiane **11**[11] to give **12** in 79% yield. After deprotection of the dithiane, **12** was subjected to reduction with $Me_4NBH(OAc)_3$.[12] As scrambling of the *tert*-butyldiphenylsilyloxy and acetonide groups was observed under the reduction condition employed, the product was isolated and characterized after the deprotection. In this way the stereoselectivity of the reduction was estimated to be approximately 10:1.[7] The stereochemistry of the major diastereomer produced in the $Me_4NBH(OAc)_3$ reduction was assigned to be an *anti*-diol on the basis of literature precedents,[12] and this assignment was confirmed through the ^{13}C NMR analysis of acetonide **d** derived from **13** (Scheme 3).[13]

Debenzylation and then acetylation of **13** furnished the synthetic peracetate **2b**. A comparison of the spectroscopic (^1H NMR (Figure 1), ^{13}C NMR, and MS)[14] and chromatographic data of the synthetic peracetate with the peracetate



Scheme 3. Reagents and conditions: a) 1. DDQ, CH_2Cl_2/H_2O, RT; 2. DMP, CH_2Cl_2, RT; 3. CH_3PPh_3Br, *n*BuLi, THF, 84% (3 steps); b) 1. OsO_4, Corey (*R*,*R*)-ligand, CH_2Cl_2, −90 °C, 85%; 2. Ts-imidazole, NaH, THF, 73%; c) 1. **11**, *n*BuLi, THF, −20 °C, 2 h; then **10**, 14 h, 79%; 2. $Hg(ClO_4)_2 \cdot 3H_2O$, THF/H_2O, 86%; d) 1. $Me_4NBH(OAc)_3$, AcOH, acetone, 91%; 2. aq HF, MeCN, 76%; e) 1. H_2, Pd/C, MeOH, RT; 2. Ac_2O, Py, DMAP, 60% (2 steps). See ref. [16] for abbreviations.

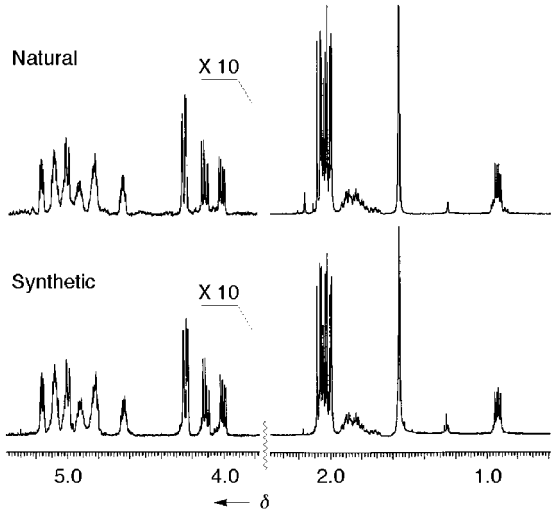
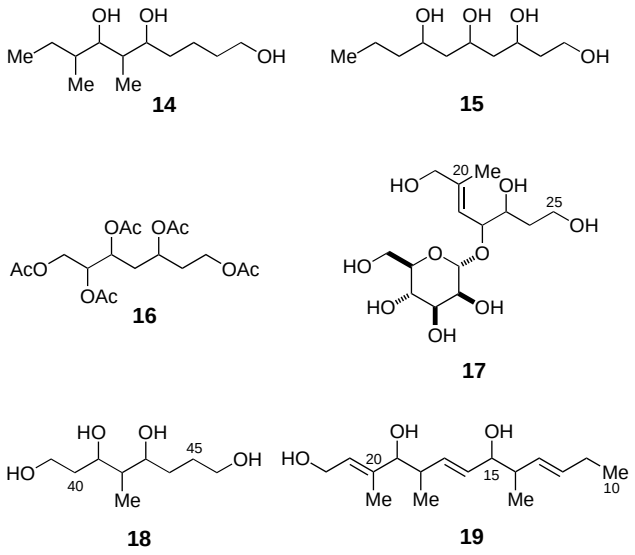


Figure 1. Proton NMR spectra (500 MHz, $CDCl_3$) of the C21–C38 degradation product **2b** of oasomycins. The signal intensity in the $\delta = 4-5$ region is ten times that of the $\delta = 1-2$ region.

derived from oasomycin A has unambiguously demonstrated their identity, thereby proving the predicted relative stereochemistry for the C21–C38 portion of the desertomycin/oasomycin class of natural products. In addition, its absolute configuration was concluded to be the one shown in structure **1** (Scheme 1) on the basis of the sign of its $[\alpha]_D^{20}$ value.[14] Related to this, it is worthwhile mentioning a possibility that the assignment of the absolute configuration could be achieved through an NMR database such as **17**[15] (Scheme 4).



Scheme 4. Chemical structures of **14**–**19**.

In conclusion, using only three simple universal NMR databases **14**–**16** (Scheme 4), we have predicted the stereochemistry of the C21–C38 portion of the desertomycin/oasomycin class of natural products and have proven the predicted stereochemistry by a stereoselective synthesis of the C21–C38 degradation product. We are currently creating two

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additional databases **18** and **19** (Scheme 4) to establish the complete structure of the desertomycin/oasomycin class of natural products.

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[1] Y. Kobayashi, C.-H. Tan, Y. Kishi, *Angew. Chem.* **2000**, *112*, 4449; *Angew. Chem. Int. Ed.* **2000**, *39*, 4279.

[2] The degradation product **2b** was also obtained from oasomycin B in five steps: 1) O_3/MeOH/ $-78\,^{\circ}C$; 2) $NaBH_4$/MeOH/RT; 3) Ac_2O/Py; 4) EtSH/conc. HCl; 5) Ac_2O/Py.

[3] We thank Dr. Gerhard Kretzschmar for samples of oasomycins A and B.

[4] a) H. C. Brown, K. S. Bhat, *J. Am. Chem. Soc.* **1986**, *108*, 5919; b) H. C. Brown, K. S. Bhat, R. S. Randad, *J. Org. Chem.* **1989**, *54*, 1570.

[5] Y. Kobayashi, J. Lee, K. Tezuka, Y. Kishi, *Org. Lett.* **1999**, *1*, 2177.

[6] The enantiomeric excess was estimated from the ^{19}F NMR spectrum of its (*R*)-Mosher ester.

[7] The minor product was removed by column chromatography on silica gel.

[8] a) S. D. Rychnovsky, D. J. Skalitzky, *Tetrahedron Lett.* **1990**, *31*, 945; b) D. A. Evans, D. L. Reiger, J. R. Gage, *Tetrahedron Lett.* **1990**, *31*, 7099.

[9] E. J. Corey, P. D. Jardine, S. Virgil, P.-W. Yuen, R. D. Connell, *J. Am. Chem. Soc.* **1989**, *111*, 9243.

[10] Dihydroxylation of **9** in the presence of the Corey (*S*,*S*)-ligand gave a 1:7 mixture of the two diols.

[11] The dithiane **11** was prepared from L-(+)-arabinose. By using Gray's procedure (M. Y. H. Wong, G. R. Gray, *J. Am. Chem. Soc.* **1978**, *100*, 3548), L-(+)-arabinose was transformed to the diethylthioacetal, corresponding to structure **4** in Gray's paper. This diethylthioacetal was then subjected to the following three steps: 1) TBDPSCl, imidazole, DMF, RT; 2) HgO, $HgCl_2$, acetone/H_2O (10/1), RT; 3) 1,3-propanedithiol, $BF_3 \cdot OEt_2$, CH_2Cl_2, $0\,^{\circ}C$ (26% overall yield from L-(+)-arabinose).

[12] D. A. Evans, K. T. Chapman, E. M. Carreira, *J. Am. Chem. Soc.* **1988**, *110*, 3560.

[13] Acetonization ($MeC(OMe)_2Me$, acetone, CSA) of **13** yielded an appromixately 1:1:1 mixture of the acetonides. The acetonide **d** was isolated in a pure form by chromatography on silica gel.

[14] **2b** (synthetic): ^1H NMR (500 MHz, $CDCl_3$): see Figure 1; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 9.4$, 10.7, 20.8–21.2 (overlapped), 34.8, 35.5, 36.6, 37.0, 37.3, 37.6, 39.1, 61.9, 65.1, 65.6, 67.1, 67.2, 67.6, 67.9, 71.5, 71.6, 71.8, 77.2, 169.9–170.5 (overlapped); $[\alpha]_D^{20} = +5.7$ ($c = 0.23$ in MeOH). **2b** (natural): ^1H NMR (500 MHz, $CDCl_3$): see Figure 1; ^{13}C NMR (100 MHz, $CDCl_3$): identical to synthetic **2b**; $[\alpha]_D^{20} = +7.8$ ($c = 0.25$ in MeOH).

[15] Oasomycins A and B are known to exhibit significant differences in the chemical shifts of the carbon atoms and protons at the C20–C23 region; see the structures in Scheme 1 and the references quoted in A. Bax, A. Aszalos, Z. Dinya, K. Sudo, *J. Am. Chem. Soc.* **1986**, *108*, 8056 and S. Grabley, G. Kretzschmar, M. Mayer, S. Philipps, R. Thiericke, J. Wink, A. Zeeck, *Liebigs Ann. Chem.* **1993**, 573.

[16] Abbreviations: Ac = acetyl; Bu = butyl; Bn = benzyl; CSA = 10-camphorsulfonic acid; DMAP = 4-dimethylaminopyridine; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DMF = *N*,*N*-dimethylformamide; DMP = Dess–Martin periodinane; DMSO = dimethylsulfoxide; Ipc = isopinocamphenyl; MPM = 4-methoxyphenylmethyl; NMO = *N*-methylmorpholine *N*-oxide; Piv = pivaloyl = trimethylacetyl; Py = pyridine; TBS = *tert*-butyldimethylsilyl; TBDPS = *tert*-butyldiphenylsilyl; THF = tetrahydrofuran; Ts = toluene-4-sulfonyl.

Tuning the Regiospecificity of Cleavage in Fe^{III} Catecholate Complexes: Tridentate Facial versus Meridional Ligands**

Du-Hwan Jo and Lawrence Que, Jr.*

Bacterial catechol dioxygenases are a component of nature's strategy for degrading aromatic molecules to aliphatic products in the environment.[1] These enzymes catalyze the oxidative cleavage of catechols, which leads to the scission of the C1–C2 (intradiol) or C2–C3 (extradiol) bond. Intradiol-cleaving enzymes have an iron(III) active site, while extradiol-cleaving enzymes require Fe^{II} or Mn^{II}.[1, 2] To date the factors that determine the regiospecificity of cleavage are not well understood. Most biomimetic studies have focused on iron(III) catecholate complexes with tetradentate ligands, all of which performed only intradiol cleavage.[3] However, the few examples of iron(III) catecholate complexes having tridentate ligands result in at least some extradiol cleavage products.[4] To further investigate the factors that determine the cleavage site, we characterized a series of mononuclear iron(III) catecholate complexes [(L)Fe(DBC)Cl] [L = Me_3-TACN (**1**), TPY (**2**), BnBPA (**3**)],[5] containing tridentate ligands that can coordinate the metal center in a facial or meridional fashion. Their reactivity towards O_2 provides insight into the factors that tune the regiospecificity of cleavage.

The reactions of [(L)$FeCl_3$], $DBCH_2$, and $NaOCH_3$ in a 1:1:2 ratio in CH_2Cl_2 under N_2 afforded complexes **1**–**3** as purple-black solids, which were recrystallized from THF/hexane, acetone, and DMF/Et_2O, respectively. All of these complexes have high-spin iron(III) centers and exhibit two intense catecholate-to-iron(III) charge transfer bands in the spectral region of 400–1000 nm, similar to [(TPA)-Fe^{III}(DBC)]BPh_4 (**4**).[3c] The crystal structures of **1** and **2** (Figure 1) reveal a distorted octahedral geometry with a facial (**1**) or meridional (**2**) tridentate ligand, a catecholate dianion, and a chloride ligand at the sixth coordination site.[6] The Fe–N and Fe–O bond lengths in both complexes are typical of high-spin iron(III) complexes. The fairly long Fe–Cl bond lengths (average 2.385(2) Å for **1** and 2.325(1) Å for **2**) suggest that the chloride ligand should be highly labile in solution.

Complexes **1**–**3** react with O_2 in the presence of one equivalent of AgOTf to afford oxidative cleavage products of DBC. The addition of silver salt removes the chloride ligand to generate an empty coordination site on the metal center and enhances the reactivity of the complex toward O_2.[7] Complex **1**, with the *fac*-Me_3TACN ligand, affords only

[*] Prof. Dr. L. Que, Jr., Dr. D.-H. Jo
Department of Chemistry and Center for Metals in Biocatalysis
University of Minnesota, Minneapolis, MN 55455 (USA)
Fax: (+1) 612-624-7029
E-mail: que@chem.umn.edu

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