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Stereoselective Synthesis of the Cytotoxic 14-Membered Macrolide Aspergillide A

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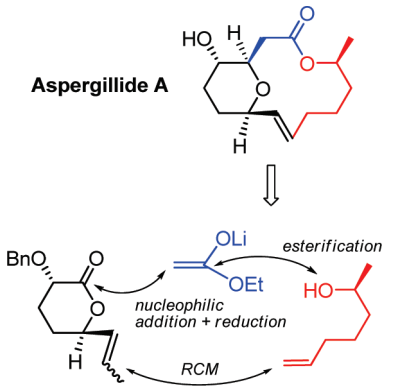

A stereoselective synthesis of the cytotoxic 14-membered macrolide aspergillide A has been performed. The preparation of a *cis*-2,6-disubstituted tetrahydropyran ring via stereoselective reduction of an intermediate cyclic hemiacetal was one key feature of the synthesis. The macrocyclic lactone ring was created by means of a ring-closing metathesis (RCM), whereby the new C=C bond displayed exclusively the undesired *Z* configuration. Conversion to the required *E* configuration was achieved via photochemical isomerization.

The aspergillides A, B, and C (**1**−**3**, see comments below) are three 14-membered macrolides isolated from a strain of the marine-derived fungus *Aspergillus ostianus* cultivated in a bromine-modified medium.[1,2] The compounds showed cytotoxic activity in the micromolar range against mouse lymphocytic leukemia cells (L1210). Their stereostructures show some unusual features. For instance, only two recent examples have been reported of naturally occurring, 14-membered macrolides that possess a tetrahydropyran ring not forming part of a hemiacetal or acetal moiety.[3,4] This and the aforementioned bioactivities prompted us and other groups to initiate total syntheses of these compounds.

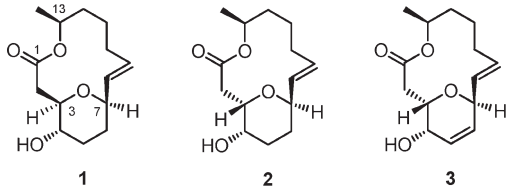

FIGURE 1. Correct stereostructures of aspergillides A (**1**), B (**2**), and C (**3**).

In the beginning of 2009, Uenishi et al. published their synthesis of a compound with structure **2**, then assumed it corresponded to aspergillide A.[5] However, these authors found that their synthetic compound had spectral properties identical with those reported for aspergillide B. The latter compound was thus assigned structure **2**, which led to the need of a revised structure for aspergillide A. Still more recently, Kuwahara et al. published a total synthesis of aspergillide C and confirmed it to have structure **3** (Figure 1).[6] Shortly afterward, we published our own synthesis of aspergillide B (**2**),[7] thus confirming the findings of Uenishi and his group. Finally, the group that isolated the natural compounds was able to perform X-ray diffraction analyses[8] of suitable derivatives of aspergillides A and B. Their and the previous synthetic studies led to the definitive assignment of **1** and **2**, respectively, as the correct structures of these two natural compounds.[9]

In the present paper, we wish to publish the first total synthesis of aspergillide A, now known to be **1**. The retrosynthesis, depicted in Scheme 1, relies in part on that used for aspergillide B (**2**).[7] Indeed, the only difference between **1** and **2** is the configuration at C-3. However, this apparently minor issue crucially affects the retrosynthetic concept as it involves

(1) Kito, K.; Ookura, R.; Yoshida, S.; Namikoshi, M.; Ooi, T.; Kusumi, T. *Org. Lett.* **2008**, *10*, 225–228.

(2) These compounds should not be confused with a group of other structurally unrelated metabolites of the same name isolated from *Aspergillus terreus*. See: Golding, B. T.; Rickards, R. W.; Vanek, Z. *J. Chem. Soc., Perkin Trans. I* **1975**, 1961–1963.

(3) Neopeltolide (14-membered macrolide containing a *cis*-2,6-disubstituted tetrahydropyran ring): Wright, A. E.; Botelho, J. C.; Guzman, E.; Harmody, D.; Linley, P.; McCarthy, P. J.; Pitts, T. P.; Pomponi, S. A.; Reed, J. K. *J. Nat. Prod.* **2007**, *70*, 412–416. The structure reported in this paper has been later corrected as a consequence of synthetic efforts of several groups. For a review on this compound, see: Gallon, J.; Reymond, S.; Cossy, J. *C. R. Chim.* **2008**, *11*, 1463–1476.

(4) Pochonin J (benzofused 14-membered macrolide containing a *trans*-2,6-disubstituted tetrahydropyran ring): Shinonaga, H.; Kawamura, Y.; Ikeda, A.; Aoki, M.; Sakai, N.; Fujimoto, N.; Kawashima, A. *Tetrahedron Lett.* **2009**, *50*, 108–110.

(5) Hande, S. M.; Uenishi, J. *Tetrahedron Lett.* **2009**, *50*, 189–192.

(6) Nagasawa, T.; Kuwahara, S. *Org. Lett.* **2009**, *11*, 761–764. For a more recent synthesis, see: Panarese, J. D.; Waters, S. P. *Org. Lett.* **2009**, *11*, 5086–5088.

(7) Díaz-Oltra, S.; Angulo-Pachón, C. A.; Kneeteman, M. N.; Murga, J.; Carda, M.; Marco, J. A. *Tetrahedron Lett.* **2009**, *50*, 3783–3785. When we started our work, the synthesis of Hande and Uenishi had not yet been reported. Our initial synthetic target therefore was aspergillide A, still believed to be **2**.

(8) Ookura, R.; Kito, K.; Saito, Y.; Kusumi, T.; Ooi, T. *Chem. Lett.* **2009**, *38*, 384.

(9) Two more recent syntheses of aspergillide B have been reported: (a) Liu, J.; Xu, K.; He, J.-M.; Zhang, L.; Pan, X.-F.; She, X.-G. *J. Org. Chem.* **2009**, *74*, 5063–5066. (b) Nagasawa, T.; Kuwahara, S. *Biosci. Biotechnol. Biochem.* **2009**, *73*, 1893–1894.

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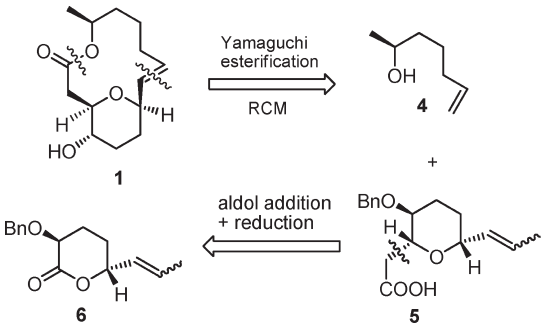
SCHEME 1. Retrosynthetic Analysis of Aspergillide A (1)



the methodology needed to create the relative configuration of the stereocenters C-3/C-7.[10−12]

Retrosynthetic opening of the lactone ring by means of ring-closing metathesis (RCM)[13] and hydrolytic cleavage of the ester moiety gives rise to the known alcohol **4**[14] as well as to acid **5**. As in our recently published synthesis of aspergillide B, we planned to create the tetrahydropyran ring[10] of **5** through a stereocontrolled Mukaiyama-type C-glycosidation[15] of a suitable lactol derivative prepared through reduction of the δ-lactone **6**.[7] In contrast to the previous synthesis, however, the glycosidation has now to be performed under conditions conducive to the formation of a *cis*-2,6-disubstituted tetrahydropyran system.

Our initial experiments based on the experience gained in the synthesis of **2**[7] were disappointing. All attempts at obtaining **5** or a similar derivative with use of a Mukaiyama-type C-glycosidation under various conditions were not satisfactory. We always obtained mixtures of *cis*-2,6- and *trans*-2,6-disubstituted tetrahydropyran where the desired *cis* isomer was never the major compound.[16] We were finally successful with a modified methodology (Scheme 2). Addition of the lithium enolate of ethyl acetate to lactone **6** at low temperature gave lactol **7** as a mixture of stereoisomers at the olefinic bond and at the hemiketal carbon. Treatment of this mixture with $Et_3SiH/BF_3 \cdot Et_2O$[11a,b] provided **8**, which displayed an exclusively *cis* relationship at the stereocenter pair C-3/C-7 (aspergillide numbering), as demonstrated by the observation of a NOE between H-3 and H-7 (see the Supporting Information). As the precursor lactone **6**, **8** was also a ca. 9:1 *E*/*Z* mixture. Alkaline hydrolysis of **8** gave the desired acid **5** in almost quantitative yield.

Mindful of our synthesis of **2**,[7] we first submitted **5** to cross metathesis[17] with alcohol **4** in the presence of Grubbs second-generation catalyst **Ru-II** to yield **9** in 41% yield as a ca. 7:3 *E*/*Z* mixture. The subsequent macrolactonization, performed according to the Yamaguchi procedure,[18] had an unexpected outcome, however. Only the minor *Z* isomer of **9** underwent cyclization to lactone (*Z*)-**10** in 28% yield (based on the whole starting material). Apparently, the major *E* isomer decomposed under these conditions and could not be isolated. Variations in the reaction conditions did not lead to success, either. Attempts at macrolactonization under Shiina,[19] Trost,[20] or Keck[21] conditions were also fruitless. The starting hydroxy acid **9** was the only defined compound isolated from the reaction mixture, with partial decomposition also taking place.

In view of this, we decided to change the order of the steps needed for the creation of the macrocyclic ring. Esterification of **4** and **5** under Yamaguchi conditions[17] provided compound **11**, still as an *E*/*Z* mixture. However, when subjected to ring-closing metathesis, ester **11** gave exclusively lactone (*Z*)-**10** in a

(10) For reviews on various synthetic methods for the preparation of tetrahydropyran derivatives, see: (a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309–3362. (b) Kotsuki, H. *Synlett* **1992**, 97–106. (c) Clarke, P. A.; Santos, S. *Eur. J. Org. Chem.* **2006**, 2045–2053. (d) Piccialli, V. *Synthesis* **2007**, 2585–2607. (e) Smith, A. B. III; Fox, R. J.; Razler, T. M. *Acc. Chem. Res.* **2008**, *41*, 675–687.

(11) For examples of synthesis of *cis*-2.6-disubstituted tetrahydropyran rings, see: (a) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976–4978. (b) Evans, D. A.; Carter, P. H.; Carreira, E. M.; Charette, A. B.; Prunet, J. A.; Lautens, M. *J. Am. Chem. Soc.* **1999**, *121*, 7540–7552. (c) Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420–8421. (d) Berberich, S. M.; Cherney, R. J.; Colucci, J.; Courillon, C.; Geraci, L. S.; Kirkland, T. A.; Marx, M. A.; Schneider, M. F.; Martin, S. F. *Tetrahedron* **2003**, *59*, 6819–6832. (e) Pattenden, G.; González, M. A.; Little, P. B.; Millan, D. S.; Plowright, A. T.; Tornos, J. A.; Ye, T. *Org. Biomol. Chem.* **2003**, *1*, 4173–4208. (f) Das, S.; Li, L.-S.; Sinha, S. C. *Org. Lett.* **2004**, *6*, 123–126. (g) Kang, E. J.; Cho, E. J.; Ji, M. K.; Lee, Y. E.; Shin, D. M.; Choi, S. Y.; Chung, Y. K.; Kim, J. S.; Kim, H.-J.; Lee, S.-G.; Lah, M. S.; Lee, E. *J. Org. Chem.* **2005**, *70*, 6321–6329. (h) Li, D.-R.; Zhang, D.-H.; Sun, C.-Y.; Zhang, J.-W.; Yang, L.; Chen, J.; Liu, B.; Su, C.; Zhou, W.-S.; Lin, G.-Q. *Chem.—Eur. J.* **2006**, *12*, 1185–1204. (i) Troast, D. M.; Yuan, J.; Porco, J. A., Jr. *Adv. Synth. Catal.* **2008**, *350*, 1701–1711.

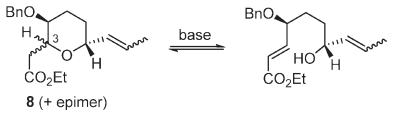
(12) For examples of synthesis of *trans*-2,6-disubstituted tetrahydropyran rings, see ref 11a and: (a) Horita, K.; Oikawa, Y.; Yonemitsu, O. *Chem. Pharm. Bull.* **1989**, *37*, 1698–1704. (b) Micalizio, G. C.; Pinchuk, A. N.; Roush, W. R. *J. Org. Chem.* **2000**, *65*, 8730–8736. (c) Fettes, A.; Carreira, E. M. *J. Org. Chem.* **2003**, *68*, 9274–9283. (d) Williams, D. R.; Patnaik, S.; Plummer, S. V. *Org. Lett.* **2003**, *5*, 5035–5038. (e) De Vicente, J.; Huckins, J. R.; Rychnovsky, S. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 7258–7262.

(13) (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012–3043. (b) Jafarpour, L.; Nolan, S. P. *Adv. Organomet. Chem.* **2000**, *46*, 181–222. (c) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29. (d) Love, J. A. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 2, pp 296−322. (e) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117–7140. (f) Astruc, D. *New J. Chem.* **2005**, *29*, 42–56. (g) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243–251.

(14) Dixon, D. J.; Ley, S. V.; Tate, E. W. *J. Chem. Soc., Perkin Trans. I* **2000**, 2385–2394.

(15) (a) Mukaiyama, T. *Aldrichim. Acta* **1996**, *29*, 59–76. (b) Mukaiyama, T.; Matsuo, J.-I. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 1, Chapter 3. (c) Mitchell, T. A.; Zhao, C.; Romo, D. *J. Org. Chem.* **2008**, *73*, 9544–9551. For a review on synthesis of C-glycosides, see: Du, Y.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913–9959.

(16) With respect to the reaction conditions used in our previous synthesis of aspergillide B,[7] where the trans (major) to cis (minor) ratio was ca. 2.6:1, changes in temperature, solvent, and Lewis acid were investigated without improvements in the cis−trans ratio. Furthermore, the enolsilanes of acetic acid and ethyl acetate were tried in addition to *tert*-butyl thioacetate but the cis−trans ratio was not ameliorated in this way. Finally, we tried to convert the undesired C-3 epimer of **8** into **8** via a base-catalyzed retro-Michael/Michael sequence (equilibration). Again, variable mixtures were obtained with no synthetically satisfactory percentages of the desired **8**.



(17) (a) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900–1923. (b) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370. (c) Vernall, A. J.; Abell, A. D. *Aldrichim. Acta* **2003**, *36*, 93–105. (d) Schrodi, Y.; Pederson, R. L. *Aldrichim. Acta* **2007**, *40*, 45–52.

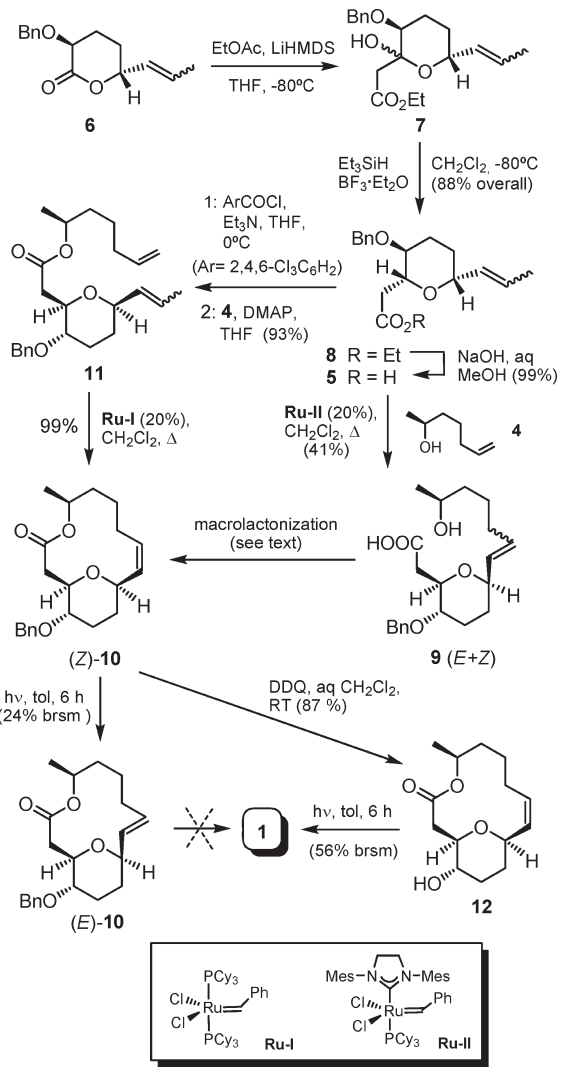
(18) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

(19) Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J. Org. Chem.* **2004**, *69*, 1822–1830. For an application, see: Wu, Y.-K.; Yang, Y.-Q. *J. Org. Chem.* **2006**, *71*, 4296–4301.

(20) Trost, B. M.; Chisholm, J. D. *Org. Lett.* **2002**, *4*, 3743–3745. For an application, see: Kim, C. H.; An, H. J.; Shin, W. K.; Yu, W.; Woo, S. K.; Jung, S. K.; Lee, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 8019–8021.

(21) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394–2395. For an application, see: Hanessian, S.; Ma, J.-G.; Wang, W.-G. *J. Am. Chem. Soc.* **2001**, *123*, 10200–10206.

SCHEME 2. Stereoselective Synthesis of Aspergillide A (1)[a]



[a]Acronyms and abbreviations: DMAP, 4-(*N*,*N*-dimethylaminopyridine); DDQ, 2,3-dichloro-5,6-dicyano-*p*-benzoquinone; Cy, cyclohexyl; Mes, mesityl (2,4,6-trimethylphenyl); tol, toluene.

very high yield. Furthermore, both the first- and the second-generation ruthenium catalysts **Ru-I** and **Ru-II** yielded (*Z*)-**10** as the sole reaction product, with **Ru-I** giving higher yields (99% vs 67%, see the Experimental Section).

These facts deserve some comment. The markedly high stereoselectivity is worth mentioning since the stereochemical outcome of RCM reactions which give rise to medium-sized or large rings (≥10 atoms)[22] is not always predictable with full certainty. In the present case, molecular mechanics calculations showed that (*Z*)-**10** is much more stable than (*E*)-**10**.[23] This suggests that the formation of (*Z*)-**10** in the RCM process is thermodynamically controlled.[22] However, even though the macrolide ring of **1** is formally 14-membered from the point of view of the atom periphery and thus relatively flexible, the presence of the tetrahydropyran ring may impose certain conformational restraints which make the formation of (*E*)-**10** kinetically disfavored. Thus, the formation of (*Z*)-**10** in the RCM may also be kinetically controlled. Indeed, compound (*Z*)-**10** is obtained in very high yield when using catalyst **Ru-I**, which is assumed to work under kinetic conditions.[13] The more active, second-generation catalyst **Ru-II**, however, is known to cause *E*/*Z* isomerizations, thus approaching thermodynamic (equilibrium) conditions. Thus, if compound (*E*)-**10** shows some instability under the RCM conditions, this could explain the eroded yield observed when using catalyst **Ru-II**.

Since only the isomer with the *Z*-configured olefinic bond was available with good yield, we investigated ways to invert its configuration. After some experimentation,[24] we found that irradiation of a solution of lactone (*Z*)-**10** in dry, deoxygenated toluene gave rise to a photostationary equilibrium in which 30% of the *Z* isomer was converted into (*E*)-**10** (24% isolated yield, based on recovered starting material).[25,26] Unfortunately, attempts at cleavage of the benzyl group in (*E*)-**10** under several conditions[27] were unsuccessful. Again, an inversion in the order of steps provided the solution. Cleavage of the benzyl group in (*Z*)-**10** was performed through treatment with DDQ in wet CH_2Cl_2.[28] This yielded the *Z* lactone **12**, which was subjected as above to photochemical isomerization of the C=C bond. This afforded a mixture of **12** and its *E* isomer (56% isolated yield, based on recovered starting material), the spectral data of which matched those of natural aspergillide A (**1**).[1]

In summary, the synthesis of the cytotoxic, 14-membered macrolide aspergillide A in a stereoselective way has been reported for the first time. This confirms its stereostructure and establishes as well its absolute configuration.

Experimental Section

General Features. See the Supporting Information.

(2*S*)-Hept-6-en-2-yl 2-[(2*R*,3*S*,6*R*)-3-(Benzyloxy)-6-(prop-1*E*,*Z*-enyl)tetrahydro-2*H*-pyran-2-yl]acetate (11). A solution of acid **5** (174 mg, 0.6 mmol) in dry THF (15 mL) was cooled to 0 °C under N_2. Then, triethylamine (210 μL, 1.5 mmol) and 2,4,6-trichlorobenzoyl chloride (188 μL, 1.2 mmol) were added dropwise, followed by stirring at room temperature for 2 h. Alcohol **4** (82 mg, 0.72 mmol) and DMAP (183 mg, 1.5 mmol) were

(22) For reviews on the uses of this reaction for the synthesis of macrocycles, see: (a) Prunet, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 2826–2830. (b) Gradillas, A.; Pérez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086–6101. (c) Majumdar, K. C.; Rahaman, H.; Roy, B. *Curr. Org. Chem.* **2007**, *11*, 1339–1365.

(23) The structures of (*E*)- and (*Z*)-**10** were first optimized with the aid of semiempirical methods (PM3). Energies were then refined by means of HF/6-31G* calculations. These were found to predict a higher thermodynamic stability for lactone (*Z*)-**10** as compared with (*E*)-**10** by an energy difference of about 15 kcal/mol.

(24) (a) I_2/*hν* (no reaction): Nazaré, M.; Waldmann, H. *Chem.—Eur. J.* **2001**, *7*, 3363–3376. (b) PhSH/AIBN, C_6H_6, Δ (dec): Paquette, L. A.; Chang, S.-K. *Org. Lett.* **2005**, *7*, 3111–3114.

(25) The mutual coupling constant of the olefinic protons in (*Z*)-**10** (11 Hz) and (*E*)-**10** (15.2 Hz) is clearly indicative of the configuration of the C=C bond.

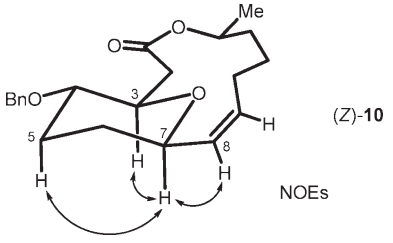
(26) The aromatic solvent toluene acts here as a sensitizer: Inoue, Y.; Yamasaki, N.; Tai, A.; Daino, Y.; Yamada, T.; Hakushi, T. *J. Chem. Soc., Perkin Trans. II* **1990**, 1389–1394. See also: Mori, T.; Inoue, Y. In *CRC Handbook of Organic Photochemistry and Photobiology*; Horspool, W., Lenci, F., Eds.; CRC Press: Boca Raton, FL, 2004; Chapter 16.

(27) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 4th ed.; John Wiley and Sons: Hoboken, NJ, 2007; pp 106−120.

(28) For cleavage of *p*-methoxybenzyl ethers under these conditions, see: Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021–3028. For uses in the cleavage of benzyl ethers, see: (a) Ikemoto, N.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 9657–9659. (b) Paterson, I.; Smith, J. D.; Ward, R. A. *Tetrahedron* **1995**, *51*, 9413–9436. (c) Blakemore, P. R.; Browder, C. C.; Hong, J.; Lincoln, C. M.; Nagornyy, P. A.; Robarge, L. A.; Wardrop, D. J.; White, J. D. *J. Org. Chem.* **2005**, *70*, 5449–5460.

dissolved in dry THF (9 mL) and added via syringe to the reaction mixture, with further stirring for 16 h at the same temperature. Workup (extraction with Et_2O) and column chromatography on silica gel (hexanes−EtOAc, 19:1) furnished **11** (215 mg, 93%) as a ca. 9:1 *E*/*Z* mixture: colorless oil; ^{1}H NMR (signals from the major *E* isomer) δ 7.35−7.25 (5H, br m), 5.80−5.70 (1H, m), 5.70−5.60 (1H, m), 5.44 (1H, ddq, J = 15.5, 5.8, 1.8 Hz), 5.00 (1H, dq, J = 17, 2 Hz), 4.94 (2H, m), 4.62 (1H, d, J = 11.6 Hz), 4.44 (1H, d, J = 11.6 Hz), 3.80 (1H, m), 3.76 (1H, td, J = 9, 4 Hz), 3.19 (1H, m), 2.86 (1H, dd, J = 14.7, 3.7 Hz), 2.40 (1H, dd, J = 14.7, 8.3 Hz), 2.28 (1H, m), 2.15−2.00 (2H, m), 1.80−1.75 (1H, m), 1.66 (3H, br d, $J \approx 6$ Hz), 1.60−1.35 (6H, br m), 1.18 (3H, d, J = 6.5 Hz); ^{13}C NMR (signals from the major *E* isomer) δ 171.1, 138.2 (C), 138.4, 131.3, 128.4 (×2), 127.7 (×2), 127.5, 126.6, 77.6 (×2), 76.6, 70.6 (CH), 114.5, 70.5, 38.7, 35.3, 33.4, 30.9, 29.0, 24.5 (CH_2), 19.9, 17.7 (CH_3); IR ν_{max} 1732 (C=O) cm^{-1}; HR ESMS *m*/*z* 409.2351 (M + Na$^+$), calcd for $C_{24}H_{34}O_4Na$ 409.2355.

(1*R*,5*S*,11*R*,14*S*)-14-(Benzyloxy)-5-methyl-4,15-dioxabicyclo[9.3.1]pentadec-9(*Z*)-en-3-one (*Z*-10). Grubbs ruthenium catalyst **Ru-I** (82 mg, ca. 0.1 mmol) was dissolved under N_2 in dry, deoxygenated CH_2Cl_2 (500 mL). After the solution was heated to reflux, diene **11** (193 mg, 0.5 mmol) dissolved in dry, deoxygenated CH_2Cl_2 (30 mL) was added slowly via syringe (within 1 h) to the reagent solution. The reaction mixture was then stirred at reflux for an additional 6 h. After cooling to room temperature, the reaction was quenched through addition of DMSO[29] (0.4 mL) followed by stirring overnight. Removal of all volatiles under reduced pressure and column chromatography of the residue on silica gel (hexanes−EtOAc, 19:1) yielded (*Z*)-**10** (172 mg, 99%) as a single stereoisomer (when the reaction was performed with catalyst **Ru-II**, the yield was 67%): colorless oil; $[\alpha]_D$ +67.5 (*c* 1.13; $CHCl_3$); ^{1}H NMR δ 7.35−7.25 (5H, br m), 5.63 (1H, tdd, J = 11, 5.2, 2 Hz), 5.18 (1H, dd, J = 11, 2.5 Hz), 5.04 (1H, m), 4.65 (1H, d, J = 11.7 Hz), 4.44 (1H, d, J = 11.7 Hz), 4.06 (1H, br d, J = 11 Hz), 3.74 (1H, td, J = 10.2, 2.5 Hz), 3.16 (1H, m), 2.90 (1H, dd, J = 11.7, 2.5 Hz), 2.28 (3H, m), 1.85−1.80 (1H, m), 1.70−1.40 (7H, br m), 1.24 (3H, d, J = 6.5 Hz); ^{13}C NMR δ 173.3, 138.3 (C), 135.4, 128.3 (×2), 128.1, 127.6, 127.5 (×2), 80.0, 76.5, 75.0, 69.6 (CH), 70.5, 39.2, 34.4, 31.7, 29.4, 28.0, 25.9 (CH_2), 20.9 (CH_3); IR ν_{max} 1720 (C=O) cm^{-1}; HR ESMS *m*/*z* 367.1884 (M + Na$^+$), calcd for $C_{21}H_{28}O_4Na$ 367.1885. Its key stereochemical features were supported by NOE masurements:



(*Z*)-**10**

(1*R*,5*S*,11*R*,14*S*)-14-Hydroxy-5-methyl-4,15-dioxabicyclo[9.3.1]pentadec-9(*Z*)-en-3-one (12). A solution of lactone (*Z*)-**10** (69 mg, 0.2 mmol) was dissolved under N_2 in CH_2Cl_2 (15 mL) and treated at room temperature with DDQ (454 mg, 2 mmol) and pH 7 phosphate buffer solution (1.5 mL). The reaction mixture was then stirred at room temperature for 16 h. Workup (extraction with CH_2Cl_2) was followed by column chromatography on silica gel. Elution with hexanes−EtOAc (19:1) gave recovered (*Z*)-**10** (23 mg) whereas elution with hexanes−EtOAc (4:1) afforded lactone **12** (29.5 mg, 87% based on recovered starting material): colorless oil; $[\alpha]_D$ +42.9 (*c* 0.77; $CHCl_3$); ^{1}H NMR δ 5.65 (1H, dddd, J = 10.5, 8.5, 6, 2.5 Hz), 5.20 (1H, dd, J = 10.5, 2 Hz), 5.04 (1H, m), 4.08 (1H, br d, $J \approx 9.3$ Hz), 3.58 (1H, td, J = 11.8, 2.5 Hz), 3.38 (1H, m), 2.85 (1H, dd, J = 11.8, 2.5 Hz), 2.36 (1H, t, J = 11.8 Hz), 2.28 (1H, br q, J = ∼10 Hz), 2.16 (1H, m), 1.80 (1H, m), 1.70−1.40 (7H, br m), 1.27 (3H, d, J = 6.5 Hz) (OH proton not visible); ^{13}C NMR δ 173.5 (C), 135.7, 128.1, 81.6, 74.9, 70.2, 69.9 (CH), 39.1, 34.5, 33.7, 32.0, 28.1, 25.9 (CH_2), 20.9 (CH_3); IR ν_{max} 3440 (br, OH), 1720 (C=O) cm^{-1}; HR ESMS *m*/*z* 277.1414 (M + Na$^+$), calcd for $C_{14}H_{22}O_4Na$ 277.1416.

(1*R*,5*S*,11*R*,14*S*)-14-Benzyloxy-5-methyl-4,15-dioxabicyclo[9.3.1]pentadec-9(*E*)-en-3-one (*E*-10). A solution of compound (*Z*)-**10** (34.5 mg, ∼0.1 mmol) in deoxygenated toluene-d_8 (1.5 mL) was placed in a quartz NMR tube. The solution was then irradiated under N_2 bubbling using a medium-pressure 125 W Hg lamp (refrigerated to −20 °C). Periodic checking by means of ^{1}H NMR revealed that the maximum conversion (about 30%) was achieved after ca. 6 h (further irradiation caused progressive decomposition). Removal of the solvent under reduced pressure was followed by column chromatography of the residue on silica gel. Elution with hexanes−EtOAc (19:1) gave recovered (*Z*)-**10** (11.5 mg) whereas elution with hexanes−EtOAc (9:1) gave (*E*)-**10** (5.5 mg, 24% based on recovered starting material): colorless oil; $[\alpha]_D$ −28.2 (*c* 0.13; $CHCl_3$); ^{1}H NMR δ 7.40−7.30 (5H, m), 5.82 (1H, ddd, J = 15.2, 8.3, 1.5 Hz), 5.75 (1H, ddd, J = 15.2, 8.8, 3.5 Hz), 5.00 (1H, m), 4.62, 4.58 (2H, AB system, J = 11.2 Hz), 4.48 (1H, dd, J = 12.5, 4 Hz), 4.30 (1H, br t, $J \approx 6$ Hz), 3.28 (1H, m), 2.63 (1H, dd, J = 15.5, 12.5 Hz), 2.35−2.25 (3H, m), 2.15 (1H, m), 2.00−1.90 (2H, m), 1.85−1.80 (2H, m), 1.60−1.50 (2H, m), 1.40 (1H, m), 1.22 (3H, d, J = 6.5 Hz); ^{13}C NMR δ 170.3, 136.6 (C), 136.6, 132.6, 128.4 (×2), 127.5 (×3), 73.6, 71.4, 70.9, 70.1 (CH), 71.3, 41.1, 32.3, 31.1, 23.9, 23.0, 20.1 (CH_2), 18.7 (CH_3); IR ν_{max} 1727 (C=O) cm^{-1}; HR ESMS *m*/*z* 367.1888 (M + Na$^+$), calcd for $C_{21}H_{28}O_4Na$ 367.1885.

(1*R*,5*S*,11*R*,14*S*)-14-Hydroxy-5-methyl-4,15-dioxabicyclo[9.3.1]pentadec-9(*E*)-en-3-one (aspergillide A, 1). A solution of compound **12** (25.5 mg, 0.1 mmol) in deoxygenated toluene-d_8 (1.5 mL) was placed in a quartz NMR tube. The solution was then irradiated under N_2 bubbling using a medium-pressure 125 W Hg lamp (refrigerated to −20 °C). Periodic checking by means of ^{1}H NMR revealed that the maximum conversion (about 40%) was achieved after ca. 6 h (further irradiation caused progressive decomposition). Removal of the solvent under reduced pressure was followed by column chromatography of the residue on silica gel. Elution with hexanes−EtOAc (4:1) gave recovered **12** (12 mg) whereas elution with hexanes−EtOAc (1:1) gave **1** (7.6 mg, 56% based on recovered starting material): colorless oil; $[\alpha]_D$ −51.7 (*c* 0.33; $CHCl_3$), lit.[1] $[\alpha]_D$ −59.5 (*c* 0.45; $CHCl_3$); ^{1}H NMR δ 5.82 (1H, ddd, J = 15.2, 8.3, 1.5 Hz), 5.75 (1H, ddd, J = 15.2, 9.3, 3 Hz), 4.98 (1H, m), 4.30−4.25 (2H, m), 3.60 (1H, m), 2.66 (1H, dd, J = 15.3, 13 Hz), 2.42 (1H, dd, J = 15.3, 4.4 Hz), 2.35−2.10 (3H, br m), 2.00−1.90 (2H, m), 1.85 (1H, m), 1.75 (1H, m), 1.60−1.50 (2H, m), 1.45 (1H, m), 1.23 (3H, d, J = 6.5 Hz) (OH proton not detected); ^{13}C NMR δ 170.0 (C), 137.2, 132.2, 74.1, 71.6, 71.3, 66.9 (CH), 40.6, 32.3, 31.2, 23.8, 22.1, 21.9 (CH_2), 18.7 (CH_3); IR ν_{max} 3450 (br, OH), 1724 (C=O) cm^{-1}; HR ESMS *m*/*z* 277.1417 (M + Na$^+$), calcd for $C_{14}H_{22}O_4Na$ 277.1416. The physical properties of synthetic **1** match those reported for aspergillide A.[1]

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Supporting Information Available: Description of general features and graphical ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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